Supplement 1 to
Effect of a nurse-led preventive psychological intervention on symptoms of post-traumatic stress disorder among critically ill patients: A randomized clinical trial

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This supplement contains the following items:

1. Original protocol, final protocol, summary of changes

2. Original statistical analysis plan, final statistical analysis plan, summary of changes

Trial Protocol summary of changes

Protocol v1.0, 20 April 2015

Original protocol

Protocol v2.0, 25 January 2016

1) Replacement of the Centre for Epidemiological Studies Depression Scale patient follow-up questionnaire by the Hospital Anxiety and Depression Scale, as the Trial Management Group felt it would be important to understand the effect of the intervention on patients' depression and anxiety, rather than solely depression.

2) Update of power calculation. Following completion and analysis of the feasibility study and prior to the start of recruitment to the cluster-RCT, the assumptions underlying the initial pre-feasibility study power calculation were reviewed, and ratified by the Data Monitoring and Ethics Committee (DMEC), using results from the feasibility study.

3) Addition of a form to the GP letter for to enable them to inform the ICNARC CTU of any new patient significant psychological difficulties that they may be aware of.

4) Minor typographical and administrative changes.

Protocol v2.1, 2 January 2017

1) Update of power calculation. In consultation with the Independent Chairs and members of the Trial Steering Committee (TSC) and the DMEC a further review of the assumptions underlying the pre-cluster-RCT power calculation once outcome data were available for patients recruited during the five-month baseline period in both intervention and control sites.

2) Increased recruitment period from 15 months to 17 months.

3) Minor typographical and administrative changes.

Protocol v2.2, 6 March 2017

1) On the recommended by the TSC, a £5.00 gift voucher for participants receiving their follow-up questionnaire at six months post-randomisation was included to maximise response rates.

Statistical analysis plan summary of changes

Statistical analysis plan v1.0, 10 August 2017

Original statistical analysis plan

Statistical analysis plan v1.1, 27 November 2017

1) Inclusion of baseline/resource use covariates in multiple imputation (MI).
2) Addition of adherence variable to MI model.
3) Minor typographical and reference changes.

POPPI

Provision Of Psychological support to People in Intensive care

Psychological Outcomes following a nurse-led Preventative Psychological Intervention for critically ill patients (POPPI) trial

NHS REC Committee no:	**15/SC/0287**
Trial Sponsor:	**ICNARC**
Trial Sponsor reference:	**01/03/14**
Trial funder(s):	**NIHR HS&DR Programme**
Funder(s) reference:	**12/64/124**
ISRCTN registry no:	***<To be inserted>***
NIHR CRN Portfolio no:	***<To be inserted>***
CSP reference no:	**173772**
Protocol version:	**1.0**
Protocol version date:	**21 April 2015**

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NHS National Institute for Health Research

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Funding

National Institute for Health Research (NIHR) – Health Services & Delivery Research Programme (HS&DR) (Project: 12/64/124)

Contents

Abbreviations

CAM-ICU	Confusion Assessment Method for the Intensive Care Unit
CBT	Cognitive Behavioural Therapy
CBTp	Cognitive Behavioural Therapy for psychosis
CEA	Cost-effectiveness Analysis
CES-D	Centre for Epidemiological Studies Depression scale
CMP	Case Mix Programme
CRF	Case Report Form
CTSA	Clinical Trial Site Agreement
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
eCRF	Electronic Case Report Form
EQ-5D	European Quality of Life Scale
GCP	Good Clinical Practice
GLMM	Generalised linear mixed model
GP	General Practitioner
HA	Health Anxiety
HRQoL	Health Related Quality of Life
HS&DR	Health Services & Delivery Research
ICH	International Conference on Harmonisation
ICNARC	Intensive Care National Audit & Research Centre
ICU	Intensive Care Unit
IPAT	Intensive care Psychological Assessment Tool
ISF	Investigator Site File
LSHTM	London School of Hygiene & Tropical Medicine
MRC	Medical Research Council
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PI	Principal Investigator
PIAG	Patient Information Advisory Group
POPPI	Psychological Outcomes following a nurse-led Preventative Psychological Intervention for critically ill patients
PDS	Post-traumatic Stress Diagnostic Scale
PTSD	Post-traumatic Stress Disorder
R&D	Research & Development
RASS	Richmond Agitation Sedation Scale
RCT	Randomised Controlled Trial
QALY	Quality-adjusted life year
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SOP	Standard Operating Procedure
SSS	Stress Support Session

STAI	State Trait Anxiety Inventory
TMG	Trial Management Group
TSC	Trial Steering Committee
UCLH	University College London Hospitals NHS Foundation Trust

Protocol summary

1.1 Summary of trial design

Title (acronym):	Psychological Outcomes following a nurse-led Preventative Psychological Intervention for critically ill patients (POPPI)
Public Title	Provision Of Psychological support to People in Intensive care
Short Title:	POPPI
Sponsor name:	Intensive Care National Audit & Research Centre (ICNARC)
Funder name & reference:	NIHR Health Services & Delivery Research Programme, 12/64/124
Design:	Cluster-randomised controlled trial (cluster-RCT)
Aim:	To evaluate the clinical and cost-effectiveness of a complex nurse-led preventative psychological intervention in reducing patient-reported post-traumatic stress disorder (PTSD) symptom severity and other reported psychological morbidities at six months versus usual care.
Primary outcomes:	To evaluate: • Patient reported PTSD symptom severity at six months • Incremental costs, quality adjusted life years and net monetary benefit
Secondary outcomes:	To compare: • Days alive and free from sedation to day 30 • Duration of critical care unit stay • Depression at six months • Post traumatic Diagnostic Scale score of greater than 18 points at six months • Health-related quality of life at six months
Target accrual:	2,904 critical care patients
Inclusion criteria:	• Age 18 years or greater • Greater than 48 hours in critical care unit • Receipt of some Level 3 critical care during first 48 hours • Between +1 and -1 on the Richmond Agitation Sedation Scale • Glasgow Coma Score of 15 • English-speaking • Ability to communicate orally
Exclusion criteria:	• Pre-existing chronic cognitive impairment, such as dementia • Pre-existing psychotic illness, such as schizophrenia • Pre-existing chronic post-traumatic stress disorder • Receiving end-of-life care • Previously recruited to POPPI
Planned number of units:	Twenty-four NHS adult, general critical care units
Anticipated duration of recruitment:	Fifteen months
Duration of follow-up:	Six months
Definition of end of Trial:	Last patient last followed-up

2 Introduction

2.1 Background & rationale

Over 100,000 patients are admitted to adult, general critical care units in the National Health Service (NHS) each year and it has been estimated that around two thirds suffer serious emotional distress, and/or unusual experiences such as hallucinations and delusions, while in the unit.[1, 2] Emotional distress, including severe symptoms of anxiety, low mood and panic, may be caused by a range of stressful, cumulative experiences that are common in the critical care unit: fear of dying; invasive treatments such as mechanical ventilation; pain and discomfort; inability to communicate; and terrifying hallucinatory delusions.[1, 3-5] The aetiology of the characteristic hallucinations and delusions of critical care unit patients is unknown, but they have been linked to delirium, the provision and withdrawal of sedative and other psychoactive drugs, effects of illness (such as sepsis), immobility, and sensory and sleep deprivation.[2, 4, 6] Hallucinations and delusions are known, from the psychosis literature, to be exacerbated by, and co-morbid with, emotional stress. Critical care unit hallucinations frequently have horrifying themes such as conspiracy to kill by staff, torture, poisoning, demons, extortion or organ theft[7]; thus a vicious cycle of stress, confusion, and terror is common for critical care unit patients.

Experiencing acute psychological stress in the critical care unit, or having frequent memories of hallucinations and delusions, are also among the identified risk factors for longer-term post-critical care posttraumatic stress disorder (PTSD), depression, anxiety or cognitive impairment.[4, 8-12] Recently published systematic reviews of survivors of critical care identified rates of PTSD up to 27%, months or years after leaving critical care, and a mean PTSD prevalence of 20%.[3, 13] High rates of depression following critical care have also been reported, with a median prevalence of 28%.[14] A study that followed patients up to two years, found 40% with depression[15]. Patients who develop serious psychological morbidities are at much higher risk of further physical morbidities and mortality[16-18] representing a serious burden to patients, to their carers and to the NHS.[19, 20]

It is more than 15 years since the Department of Health explicitly recognised this serious problem, stating in the year 2000 that the critical care unit was extremely distressing for patients and that there was considerable need for psychological support for traumatised patients.[21] In 2009, the National Institute for Health and Care Excellence (NICE) recommended that all critically ill patients should be assessed for risk of non-physical morbidity, and that those at high risk of adverse outcomes such as PTSD, should receive structured psychological support, both during and after their unit stay.[22] NICE guidance on the diagnosis, prevention and management of delirium recommends that patients identified as being at high risk of delirium (including all critically ill patients), should be monitored closely, and strategies for intervention implemented as soon as possible.[23] Even more recently, in 2012, NICE has highlighted the importance of patients being regularly assessed for psychological needs, so that these can be rapidly addressed.[24]

Rigorous and relevant evidence is now urgently needed to reduce the burden of serious psychological morbidity on critical care patients and their carers, and cost effective strategies are needed to reduce the burden on the NHS.

The modification of clinical risk factors for PTSD such as duration of mechanical ventilation and sedation have been discussed in the literature[25, 26], but less invasive medical interventions or better drugs are not currently available. Yet little high-quality research has been conducted to evaluate psychological interventions that could alleviate the emotional distress experienced by patients in critical care, with a view to preventing longer-term psychological morbidity.[27] An unpublished systematic review of 18 studies found mostly weak and some moderate evidence that psychosocial interventions including music therapy, complementary therapy, psychotherapy or patient diaries could reduce short-term or medium-term distress for critical care unit patients. Only the patient diary intervention[28] and a psychotherapeutic intervention[29] were shown to have an effect on longer-term psychological outcomes in a sufficiently large sample. However, the diary

intervention targets critical care unit patients' memory gaps rather than stress, and has been critiqued for its lack of a solid psychological theoretical underpinning.[30]

Recent advances in the study of critical care psychology have made the evaluation of psychological interventions for the critically ill more feasible. Valid psychological assessment tools now exist for use with critical care patients (e.g. Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)[31]), including a tool measuring critical care-related distress (the Intensive care Psychological Assessment Tool (IPAT, Appendix B) that was developed and validated by our research team.[32] With respect to the best timing to provide psychological interventions for critical illness survivors, research suggests that post-discharge (e.g. at six weeks[33] or at outpatient follow-up clinics[20]) may be too late, and earlier intervention could be more beneficial. For example, a study with critically ill trauma patients indicated that considerably fewer individuals experienced PTSD, depression or anxiety a year after critical care unit stay, having received interventions by practitioner psychologists while in the critical care unit.[29] In today's NHS, practitioner psychologists are a scarce resource, and a more pragmatic approach would be to standardise brief evidence-based psychological interventions to be carried out by existing critical care unit staff, who would be given the necessary training.

Aiming to develop a nurse-led psychological intervention for critical care unit patients that would commence before they leave the unit, our research team has identified the most relevant, up-to-date evidence concerning psychological techniques that are effective in: a) reducing acute emotional distress; b) reducing the impact of unusual experiences such as hallucinations and delusions; and c) preventing PTSD after a trauma (psychological problems commonly associated with admission to the critical care unit). The evidence is summarised below:

Interventions comprising Cognitive Behavioural Therapy (CBT) techniques have been found to be effective in reducing many types of emotional distress in both physical and mental health settings. Studies have evaluated CBT as effective even when delivered in brief form, or by non-expert staff (including nurses) who receive specific training. For example, a randomised controlled trial (RCT) showed that twice as many patients with excessive health anxiety (HA) who received brief CBT from newly-trained, non-expert clinical staff in medical clinics, achieved normal HA levels, compared to a control group.[34]

A specific CBT model has also proved effective in reducing the impact of symptoms such as hallucinations and delusions in patients with psychosis.[35-40] CBT for psychosis (CBTp) interventions have proved to be particularly effective in cases of early, first episode or acute psychosis, which equate most closely to the critical care unit experience.[41, 42] Recent CBTp research has demonstrated the efficacy of brief interventions, targeting specific symptoms such as delusions.[43] CBTp has also been successfully delivered by nurses and other non-expert therapists to patients with psychosis in mental health settings.[44-46]

Finally RCTs have shown CBT to be the most effective psychological intervention in reducing PTSD symptoms following different types of trauma, including episodes of psychosis.[47, 48] There is also increasing evidence that *early* interventions soon after a trauma may help to *prevent* PTSD symptoms from developing in the longer-term. A recent update to the NICE PTSD guidelines[49] states specifically that a brief trauma-focused psychological intervention of three sessions, delivered in the period immediately after a trauma, may reduce the development of subsequent PTSD symptoms.

Given that these existing evidence-based psychological interventions could be modified to reduce the stress and trauma experienced by critical care unit patients, and be delivered by specially trained, well-motivated critical care unit nurses, there is an urgent need to evaluate their effectiveness in the critical care unit setting. Increasing psychological support may also provide a further benefit to patients and the NHS by permitting a reduction in use and duration of pharmacological sedation.

The POPPI cluster-RCT was preceded by a Feasibility Study (ISRCTN61088114) looking at feasibility of both the intervention and the RCT processes. These feasibility studies informed this protocol for the POPPI cluster-RCT.

2.2 Aim

The aim of POPPI is to evaluate the clinical and cost-effectiveness of a complex nurse-led preventative psychological intervention in reducing patient-reported post-traumatic stress disorder (PTSD) symptom severity and other reported psychological morbidities at six months.

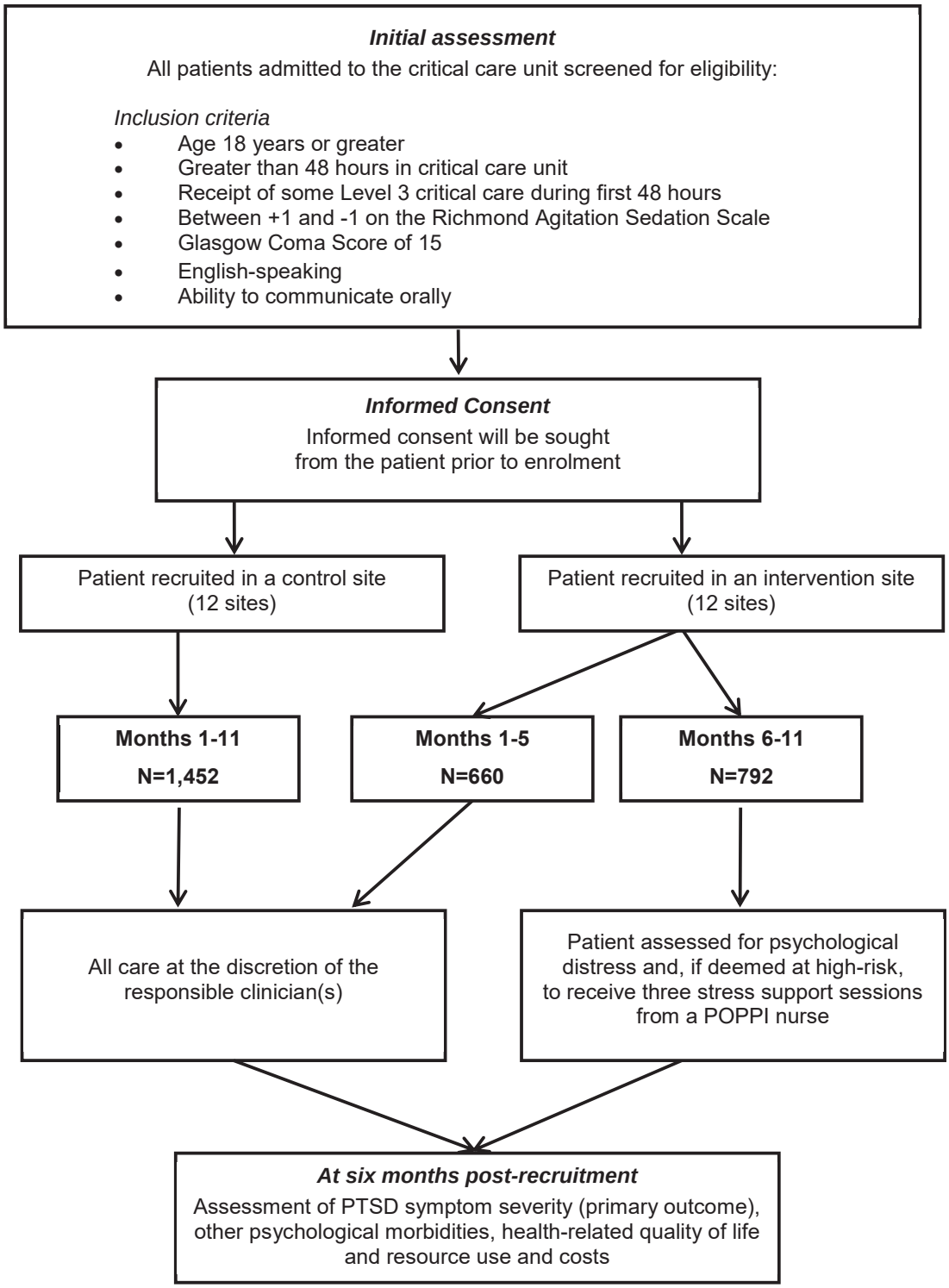
2.3 Objectives

- To evaluate the effect of the complex intervention on patient-reported PTSD symptom severity and other psychological morbidities and quality of life at six months; and
- To estimate, in an integrated economic analysis, the cost-effectiveness of the intervention.

An integrated process evaluation will be conducted to assess the fidelity and quality of the implementation of the intervention, and identify important contextual factors to better understand how the intervention works.

2.4 Trial schema

Figure 1. Overview of patient journey



3 Trial design

Parallel group cluster-RCT.

3.1 Setting

Twenty-four NHS adult, general, critical care units in the UK ('sites').

3.1.1 Site selection

The following criteria must be met for a site to participate in POPPI – a site must:

- show that recruitment to target, timely data collection, and delivery of the complex intervention are feasible - via completion of a site feasibility questionnaire;
- commit to dedicate adequate resources to carry out the complex intervention;
- agree to adhere to randomisation into either the control arm or the intervention arm;
- have an appropriate Principal Investigator (PI) identified to lead POPPI at the site;
- agree, where possible, to recruit all eligible patients to POPPI and to maintain a POPPI Screening Log to include reasons why eligible patients were not recruited
- agree to use the CAM-ICU for assessing delirium and RASS for assessing sedation status for the duration of the study; and
- be actively participating in the Case Mix Programme (CMP) – the national clinical audit for critical care units coordinated by ICNARC.

Sites who have taken part as an intervention site in the POPPI Feasibility Study (ISRCTN61088114) will not be eligible for selection.

3.2 Trial timeline

Sites will be open to recruitment in three groups of eight sites at two month intervals (see Figure 2). At the start of month two the group of eight sites will be randomised to be either intervention or control sites (four intervention; four control). Each site will recruit patients for a total of eleven months (see Figure 2) following the below schedule.

Control arm sites

Months 1-11: Usual care period (See section 5)

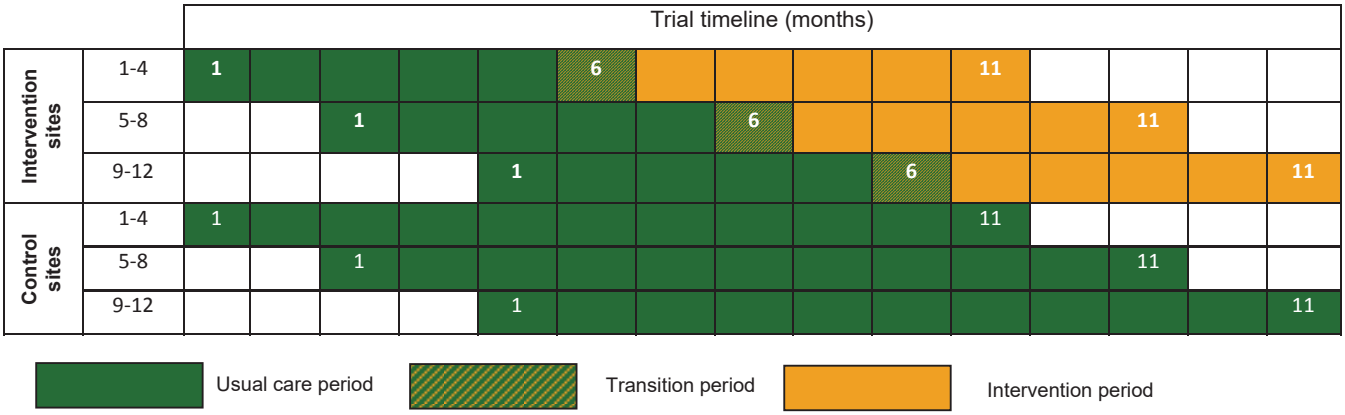
Intervention arm sites

Months 1-5: Usual care period (See section 5)

Month 6: Transition period (See section 7), during which intervention sites will undergo training and transition to delivering the intervention.

Month 7-11: Intervention period (See sections 7-8), in which the sites will deliver the full complex intervention.

Figure 2. Cluster–RCT schedule



3.3 Site activation

Once the ICNARC CTU have confirmed that all necessary documentation is in place (including signed Clinical Trial Site Agreement (CTSA) and local NHS permissions), a site activation e-mail will be issued to the PI outlining a date at which the site is to start screening and recruitment. Sites will undergo a site initiation meeting prior to commencing recruitment. All sites responsibilities are outlined in the CTSA.

3.4 Randomisation of sites

The 24 sites will be randomly assigned to either the intervention arm (N=12) or the control arm (N=12) using a restricted randomisation approach to ensure balance across the arms in geographical location, teaching status and size of unit. This will be completed at the start of month two.

It is necessary to randomise on a cluster, rather than individual, level to avoid contamination of usual care as it would not be possible to restrict parts of the intervention to individual patients.

3.5 Selection of POPPI nurses – intervention sites only

All intervention sites will be responsible for selecting the POPPI nurses following a personal specification provided to the site. This will include the following criteria:

- Be an expert practitioner in critical care
- Have excellent inter-personal skills
- Excellent communicator
- Able to take a flexible approach to their work
- Have an interest in improving critical care unit patients' psychological outcomes
- Able to attend the POPPI nurse Training course
- Committed to deliver the intervention for duration of intervention period
- Committed to support the rest of the critical care unit team in delivering the intervention

4 Patient recruitment

4.1 Patient eligibility

Patients admitted to participating NHS adult, general, critical care units and meeting the following criteria are eligible for recruitment into POPPI. Patients must meet the eligibility criteria prior to discharge from the critical care unit.

4.1.1 Inclusion criteria

Patients must meet all of the following criteria:

- Age 18 years or greater
- Greater than 48 hours in critical care
- Receipt of Level 3 critical care (for any period of time) during first 48 hours
- Between +1 and -1 on the Richmond Agitation Sedation Scale[50]
- Glasgow Coma Score of 15
- English-speaking and ability to communicate orally

4.1.2 Exclusion criteria

Patients must not meet any of the following criteria:

- Pre-existing chronic cognitive impairment, such as dementia
- Pre-existing psychotic illness, such as schizophrenia
- Pre-existing chronic posttraumatic stress disorder
- Receiving end-of-life care
- Previously recruited to POPPI

4.2 Informed Consent

All patients will be routinely screened for eligibility by unit staff. Patients who meet the eligibility criteria will be invited to take part in the trial.

The patient will be provided with written information about the trial which will be supplemented with information provided orally. Patients will be given a copy of the relevant Patient Information Sheet (different versions will be used for the Usual care period, and Transition/Intervention periods) and, if preferred, a shorter Patient Information Leaflet alongside the Patient Information Sheet.

This decision to also offer a shorter Patient Information Leaflet was made considering the severity of critical patients' illness. In particular, it is likely that many patients may find it easier to read or have read to them the Patient Information Leaflet initially, which is a shorter version of the written information. This leaflet will refer the patient to the Patient Information Sheet for full details. All patients will receive the Patient Information Sheet prior to providing Informed Consent.

The information provided to patients will include: details about the purpose of the trial; how the trial is being funded; the consequences of taking part or not; and data security. The contact details for the local Principal Investigator (PI) will be included on both the Patient Information Sheet and Patient Information Leaflet. Patients will be given the opportunity to ask questions and to discuss the study with family or friends before making their decision.

After the authorised staff member is satisfied that the Patient Information Sheet has been read and understood, and any questions have been adequately answered, patients will be invited to sign the Consent

Form. Once the patient has signed the Consent Form, the person taking informed consent will add their own name and countersign in the presence of the patient.

A copy of the signed Consent Form will be given to the patient, a copy placed in the Investigator Site File (ISF) with the original placed in the medical notes.

Standard Operating Procedures (SOPs) for screening and the informed consent process will be provided in the ISF.

5 Usual care period - patients

5.1 Overview

- Control sites will deliver usual care during months 1 to 11.
- Intervention sites will deliver usual care during months 1 to 5.

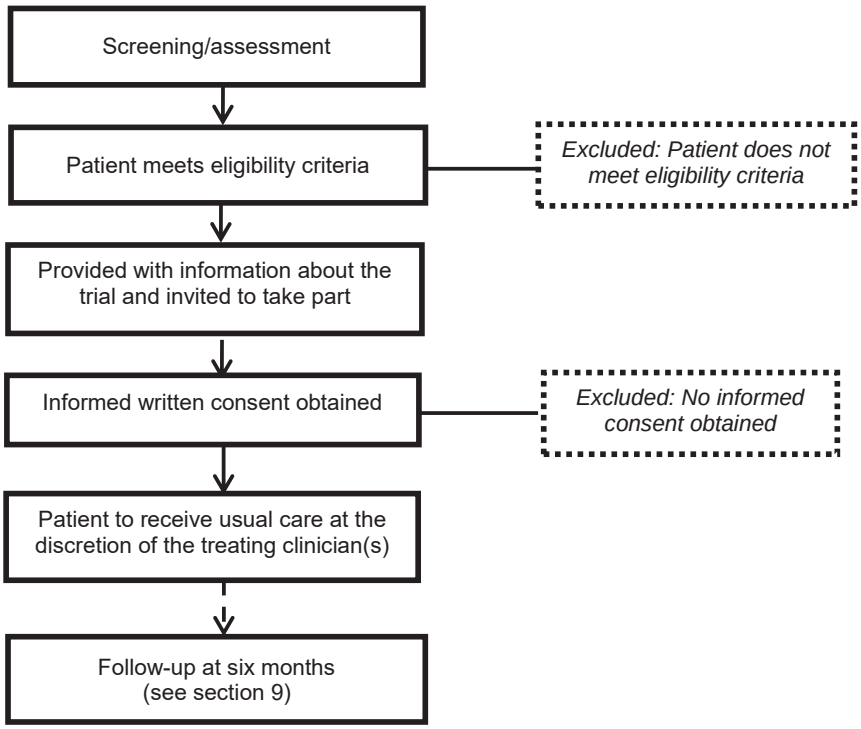
5.2 Definition of usual care

Patients should receive psychological support or treatment at the discretion of the treating clinician(s) following standard practice at their site.

5.3 Patient timeline

During the usual care period, eligible, consenting patients will receive usual care at the discretion of the treating clinician(s). Patients will be sent questionnaires six months after providing informed consent (see section 9 for further details).

Figure 3. Patient timeline during usual care



6 Intervention

The POPPI study involves a complex intervention comprising four related elements:

1) An education package (two training courses and associated materials) to train critical care unit staff to carry out elements 2-4 below;
2) Creating a therapeutic environment to promote calm and minimise stress in the critical care unit (all critical care unit staff);
3) Assessing for acute psychological stress and unusual experiences in critical care unit patients using the IPAT (all critical care unit staff);
4) Carrying out three, one-to-one CBT-inspired stress support sessions, for patients assessed as acutely stressed and at high-risk of psychological morbidity (delivered by specially trained POPPI nurses).

7 Transition period – site staff

All the procedures described in this section are relevant only to the intervention sites between months 6 to 11.

7.1 Overview

After the first five months of recruitment, intervention sites will undergo a transition period, during which they will transition from delivering usual care to delivering the complex intervention. Following the transition period, the full complex intervention will be delivered for a further five months.

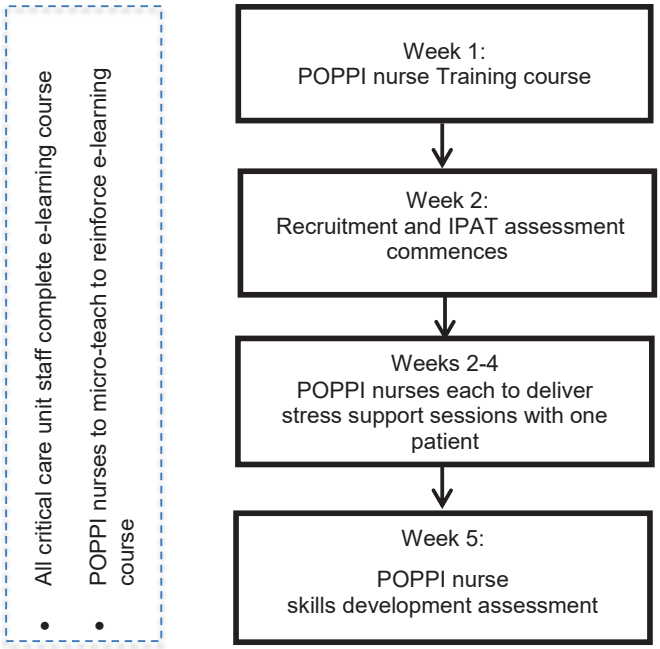
The transition period occurs during month 6 at each Intervention site and has the following aims:

- The POPPI nurses to attend a three day central training course (see section 7.3).
- Development of a therapeutic environment, with critical care unit staff completing the e-learning course (see section 7.4)
- Assess all consented patients using the IPAT (section 8.3)
- Each POPPI nurse to deliver stress support sessions with at least one patient (see section 7.5).
- Confirmation of POPPI nurses skills development (section 7.5)

7.2 Site timeline during transition period

At the beginning of the transition period all POPPI nurses at a site will attend the three-day central POPPI nurse Training course. After completing the course, the POPPI nurses will return to their critical care units and screening and consenting patients will commence (as per the flow in section 8.2). Each nurse should deliver stress support sessions (see: Section 8.4) to at least one consented patient, identified (using the IPAT) as being stressed and at high risk of psychological morbidity. In parallel, the POPPI nurses will also encourage culture change in their unit to create a therapeutic environment (see section 7.4) by ensuring all critical care staff complete the e-learning course and through micro-teaching at the bedside. At the end of this transition period, the POPPI nurses will undergo a skills development assessment.

Figure 4. Site timeline during transition period



7.3 POPPI nurse Training course

This is a three-day training course to train the POPPI nurses in their new role. The course was designed by the research team in consultation with experts in medical education and CBT training, and is delivered by two senior nurses and a psychologist. The main focus of the training course is on learning and practising new skills required to deliver the stress support sessions with patients. The POPPI nurse role also includes encouraging all staff in their units to complete the e-learning course; promoting the screening of patients with the IPAT; and micro-teaching good communication skills (reinforcing key messages from the e-learning course) at the bedside and training on these aspects of the role will also be provided.

Associated materials include a training folder; a POPPI nurse Training manual on the three stress support sessions; a tablet computer with a "relax and recover" programme for nurses to use with patients; a self-help booklet and DVD for nurses to give to patients; and a USB stick containing all training materials (including videos) for nurses to keep.

The course will cover:

- Psychological challenges of patients in critical care unit (including patient representative talks and videos)
- Screening for acute psychological stress using the IPAT
- CBT-based psychological support techniques required to deliver stress support sessions
- Content of stress support sessions
- Observe (in person and expert videos) example stress support sessions
- Practice stress support sessions

7.4 Creating a therapeutic environment

The POPPI nurses will create a therapeutic environment by encouraging culture change in their unit. This will be facilitated by ensuring all critical care unit staff complete the POPPI e-learning course and by micro-teaching good communication skills and psychological care at the bedside. In addition, they will ensure that POPPI materials are clearly displayed (e.g. posters) and distributed (e.g. pocket cards) throughout the unit.

7.4.1 POPPI e-learning course

POPPI nurses or research staff will register all critical care unit staff for the e-learning course. The learning is designed to aid the creation of a calm, less stressful environment by using good communication in the unit and delivering enhanced psychological care to patients.

The e-learning course takes approximately 30 minutes to complete and comprises five sections:

1. Understanding critical care unit patients' stress (including using the IPAT)
2. Reducing stress and fear in the critical care unit
3. Communicating with distressed or fearful critical care unit patients
4. Inspiring critical care unit patients with confidence and hope
5. Knowledge test

7.5 Supervision for POPPI nurses

All POPPI nurses will be allocated a supervisor from the POPPI training team to ensure they are supported by experts during the transition and intervention periods.

Supervision will focus on specific cases, and be aimed at improving POPPI nurses' skills in delivering the stress support sessions. Initial supervision will be carried out once a POPPI nurse has delivered stress support sessions to their first patient. Once all POPPI nurses at the site have delivered stress support sessions to one patient the POPPI training team will visit POPPI nurses in their units to offer further support and the POPPI nurses will undergo skills development assessment to ensure they meet the required levels of delivering the stress support sessions. If necessary, further support and training will be offered prior to the delivery of further sessions with patients.

POPPI nurses will continue to receive supervision either via telephone call or site visit. If necessary, extra supervision will be provided.

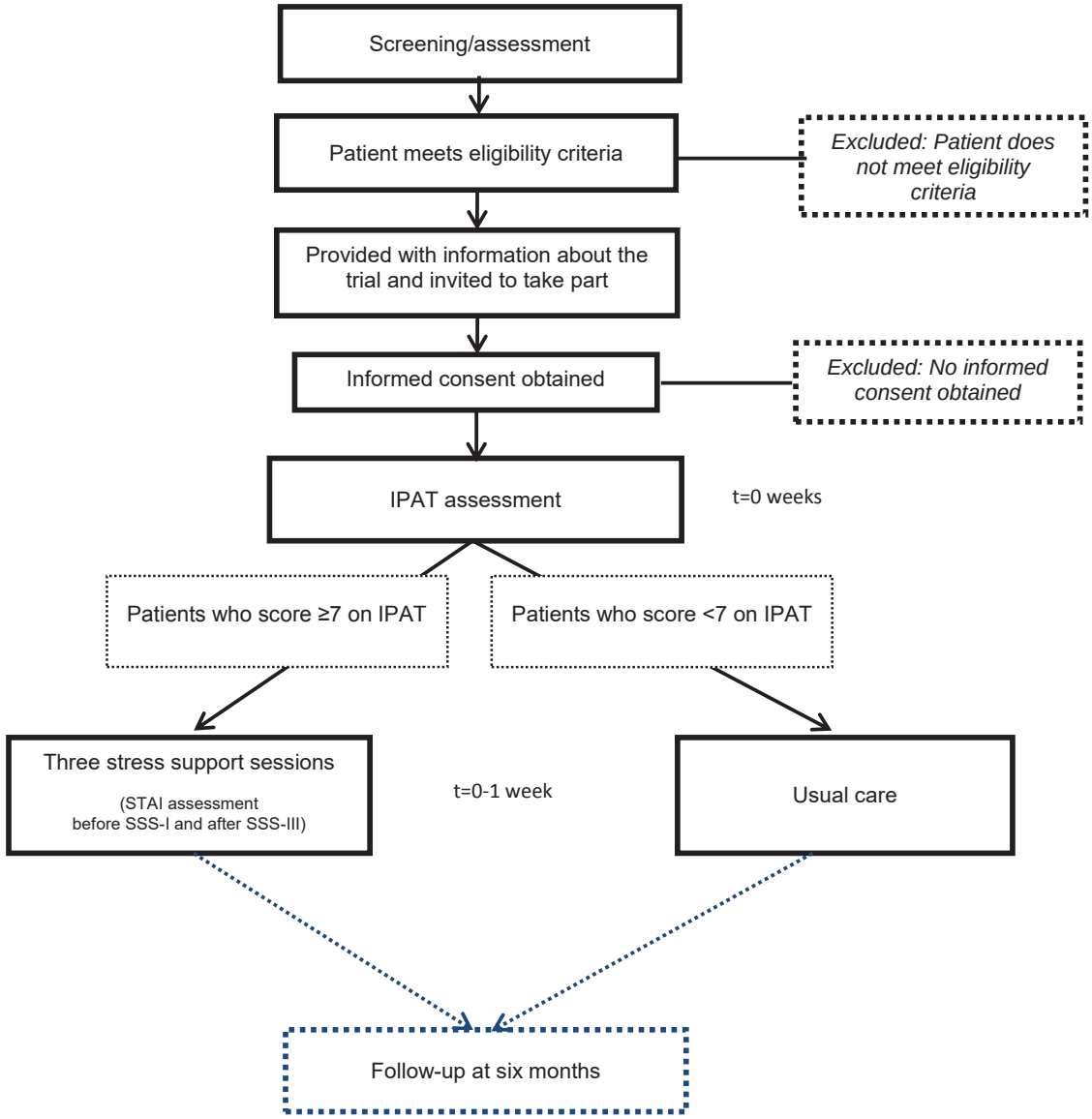
8 Transition and intervention periods – patients

8.1 Overview

Intervention sites will deliver the intervention (see section 6) to patients between months 6 to 11.

8.2 Patient timeline

Figure 5. Patient timeline during intervention period



8.3 IPAT assessment

The IPAT is a validated screening tool used to detect acute psychological stress and unusual experiences such as hallucinations in critically ill patients[51] (see Appendix B). Consented, eligible patients will be assessed using the IPAT by a trained authorised staff member (as per the Delegation Log) as soon as possible, but within 48 hours of consent being provided. A patient is deemed high-risk if they score seven or more on the IPAT and should be referred, as soon as possible, to a POPPI nurse to receive the three stress support sessions (see section 8.4). Patients who score less than seven on the IPAT will continue to receive usual care as determined by the treating clinician(s).

8.4 Stress support sessions

The aims of the stress support sessions are:

- to reduce acute stress, fear and intrusive memories of critical care before the patient leaves hospital; and
- to help patients find a path to psychological recovery and well-being after their stay in the critical care unit.

8.4.1 Delivery of stress support sessions

The three stress support sessions are to be delivered by the same POPPI nurse ideally within one week, with the first stress support session starting as soon as possible, but within 48 hours following IPAT assessment. Each session lasts approximately 30 minutes. If a patient shows signs of distress or fatigue, the session can be stopped and a new visit can be arranged at a more appropriate time.

The State Trait Anxiety Inventory (STAI, see Appendix C) will be used to assess the patients anxiety immediately prior to session one and at the end of stress support session three. If a patient is showing serious signs of distress at the end of their three sessions, their medical team will be informed.

8.4.2 Objectives of stress support sessions

The POPPI nurses' objectives during the stress support sessions are to:

- develop a trusting relationship with the patient;
- help a patient understand the links between the experience of being in the critical care unit and a range of common psychological reactions which are often disturbing;
- increase patients' sense of control by creating opportunities to talk about psychological reactions in the critical care unit and to take an active part in managing these;
- describe and demonstrate strategies for coping with stress (e.g. listening to music and using relaxation and mindfulness techniques on the supplied tablet computer);
- re-evaluate stressful thoughts;
- reduce patients' hopelessness through watching other patients' recovery stories; and
- build on evidence of progress and getting better.

8.4.3 Components of stress support sessions

Each stress support session includes five components and is structured as follows:

Stress support session one
The 'five Es'

- Establishing rapport with the patient
- Educating and normalising common psychological reactions and their causes in the critical care unit
- Eliciting worries and fears (patient encouraged to express any initial worries they feel safe disclosing)
- Encouraging information-seeking (speaking to staff about worries and fears and getting useful information, to increase control)
- Explaining coping strategies (using a relaxation and recovery package delivered via a tablet computer)

Stress support session two
The 'HINTS'

- Homework and review (key messages and coping strategies)
- Individual psychological reactions – encouraging patient to open up about fears
- Normalising individual reactions
- Thinking about thinking (identifying stressful thoughts; fears that may be driving distress)
- Seeking information (teaching patient the "test your fears" technique: gathering and exploring evidence for and against their worst fears, to reduce distress)

Stress support session three
The 'five elements' *(promotes five elements, known to reduce distress in people who have been through trauma:*[52]

- Confidence (review key messages and techniques)
- Connectedness (encourage patient to communicate experience to staff and family)
- Safety (contain and summarise their experiences; review "safe place" visualisation)
- Calm (provide self-help booklet and help create a personal stay well plan with the patient
- Hope (instil optimism; discuss return to normal life; provide recovery stories on DVD)

8.5 Audio-recording sessions

After the transition period, consented patients who have been assessed as being at high risk of psychological morbidity will be asked to consent to their stress support sessions being audio-recorded. If a patient agrees to their stress support sessions being audio-taped they will be asked to sign the Audio-recording Consent Form. This is optional and will not preclude the patient taking part in the trial or delivery of the stress support sessions. Audio recordings will be reviewed by the training team, in order to monitor treatment fidelity of the stress support sessions delivered, and will be destroyed at the end of the trial. If a patient withdraws consent for use of their session to be audio-recorded, then the audio file will be deleted and no longer used.

9 Patient follow-up

Six months after recruitment, consented patients will be asked to complete questionnaires on psychological distress, mood, health-related quality of life and use of health services. In particular, the questionnaires will include measures of PTSD symptom severity (using the Posttraumatic Stress Diagnostic Scale (PDS)[53] - see Appendix D), depression (using the Centre for Epidemiologic Studies Depression Scale (short form) (CES-D-10)[54] – see Appendix E), health-related quality of life (using the EuroQoL EQ-5D-5L – see Appendix F) and health services resource use (using Health Services Questionnaire – see Appendix G). Patients will be sent the questionnaires by post (including a stamp addressed envelope and a pen) sent by ICNARC CTU. Non-responders will be telephoned three weeks later, and asked to check whether they have received the questionnaire. If preferable for the patient, they will be given the option to complete the questionnaire over the telephone. If completed follow-up questionnaires, received by ICNARC CTU, indicate the presence of signs of serious stress or low mood, a referral letter from Dr Wade, Lead Clinical Investigator, will be sent to the patient's General Practitioner (GP).

10 Outcomes

10.1 Primary outcomes

10.1.1 Clinical evaluation

The primary outcome for the clinical evaluation will be patient-reported PTSD symptom severity at six months, measured using the PDS, which conforms to all DSM-IV diagnostic criteria for PTSD and which has been validated for use in critical care unit survivors.

10.1.2 Economic evaluation

The primary outcomes for the economic evaluation will be incremental costs (cost-effectiveness analysis (CEA)), quality-adjusted life years (QALYs) and net monetary benefit at six months.

10.2 Secondary outcomes

Secondary outcomes will be:

- days alive and free from sedation to day 30;
- duration of critical care unit stay;
- PDS greater than 18 points at six months;[55]
- depression at six months, measured using the short-form of the Center for Epidemiologic Studies Depression (CESD) Scale,; and
- health-related quality of life (HRQoL) at six months, measured by the EuroQol (EQ-5D-5L) questionnaire.

11 Sample size

The total required sample size for the RCT is 2,904 patients recruited from twenty-four sites, which will be randomly assigned to either intervention or control. The required sample size was calculated using the approach of Hussey & Hughes (2007)[56] to achieve 90% power to detect a reduction from 14 points to 10 points ($p<0.05$) in the mean PDS at six months, based on the following assumptions:

- Mean (14) and standard deviation (12) of the PDS were taken from control patients in a previous single centre study.[1]
- Between-site coefficient of variation 0.5 corresponding to between-site standard deviation 7 (conservative estimate as no multicentre data available).[57] Note: the inclusion of a baseline recruitment period means that the sample size calculation is less sensitive to the degree of clustering.[56]
- Treatment effect of a reduction of four points on the PDS based on: reliable change index for the PDS of eight points;[58] 50% of eligible patients in the intervention periods assessed as being at high risk of psychological morbidity;[32] to achieve an eight-point reduction among high risk patients after receiving brief CBT, an average four-point reduction in PDS across the whole population is required.
- Harmonic mean of the number of patients completing follow-up (76 per site per annum – corresponding to 32 in a five-month period) based on data from the CMP.

Of the 2,904 patients recruited to the POPPI trial, it is anticipated that 792 will be assessed using the IPAT, of which 396 (50%) will be assessed as being at high risk of psychological morbidity and receive the stress support sessions, equivalent to 5.5 patients receiving stress support sessions per site per month during intervention periods.

12 Data collection and management

12.1 Data collection – patients

The following data is to be collected by site staff whilst the patient is in-hospital. These data must be transcribed onto the paper Case Report Forms (CRF) (provided to sites) prior to entering onto the secure electronic CRF (eCRF). The original paper CRFs must be kept at site. All entries must be clear and legible. The use of abbreviations and acronyms must be avoided. The PI is responsible for the accuracy of all data reported in the paper CRF. All paper CRFs must be completed and signed by staff listed on the Delegation Log and authorised by the PI to perform this duty.

Any corrections made to a paper CRF at site must be made by drawing a single line through the incorrect item ensuring that the previous entry is not obscured. Each correction must be dated and initialled. Correction fluid must not be used. The amended paper CRF must be retained securely at site. These changes must also be made on the eCRF.

Security of the eCRF is maintained through user names and individual permissions approved centrally by ICNARC CTU. Central back-up procedures are in place. Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act.

Data collected for all patients:

Patient details

- Identifiers
- Sociodemographics

Baseline data

- Date and time of critical care unit admission
- Eligibility criteria
- Date and time of consent
- Illness severity score
- Prior delirium (assessed by CAM-ICU), anxiety or depression

Critical care unit stay data

- Drugs received
    - Sedatives, anxiolytics, anaesthetics, sleep medications, antipsychotics, analgesics, anti-depressants and vasoactive agents
- Mechanical ventilation received

Hospital discharge data

- Discharge status
- Discharge date/date and time of death

Data collected for patients recruited during the intervention period:

POPPI Intervention data

- IPAT score
- STAI scores before stress support session one and after stress support session three
- Delivery of the stress support sessions

The following data is to be collected by questionnaires sent directly to all patients. The detailed process for collection is outlined in section 7.

Follow-up data

- PDS
- CESD-10
- EQ-5D-5L
- Health Services Questionnaire

In addition, data will be linked to the CMP, the national clinical audit of adult critical care coordinated by ICNARC, which is ongoing in over all adult, general critical care units in England, Wales and Northern Ireland. Linked data will include demographics, surgical status, acute severity of illness and duration of organ support and duration of critical care unit stay. Support for the collection and use of patient identifiable data has been approved for the CMP by the Patient Information Advisory Group (PIAG) under Section 251 of the NHS Act 2006 (originally enacted under Section 60 of the Health and Social Care Act 2001) – Approval Number: PIAG 2-10(f)/2005. Section 251 support is reviewed annually by PIAG and covers all aspects of data management including data security.

Table 1 Patient data collection schedule

	Baseline (at point of recruitment)	End of critical care unit stay	Intervention sites only			Six months post-recruitment
			Before SSS-I	During sessions	After SSS-III	
Collected in-hospital						
Patient details	✓					
Clinical data	✓					
Critical care unit stay data		✓				
IPAT/STAI			✓			
Delivery of stress support sessions				✓		
STAI					✓	
Follow-up questionnaires sent to patients						
PDS						✓
CESD-10						✓
EQ-5D-5L						✓
Health Services Questionnaire						✓

12.1.2 Data management

The ICNARC CTU will work closely with staff at participating sites to ensure accurate (complete, valid and reliable) data. Extensive completeness, range and consistency checks will further enhance the quality of the data. Two levels of data validation will be incorporated into the eCRF. The first prevents obviously erroneous data from being entered, e.g. entering a date of birth that occurred after the date of consent. The second level checks for data completeness and any unusual data entered, e.g. a physiological variable, such as blood pressure, that was outside of the pre-defined range. Site staff will be able to generate data validation reports, listing all outstanding data queries, at any time via the eCRF. The site PI is responsible for ensuring that all data queries are resolved. Ongoing data entry, validation at adherence to the trial protocol at sites will be closely monitored by ICNARC CTU and any concerns will be raised with the site PI.

12.2 Data collection – sites

Prior to the start of recruitment the following data will be collected for each participating site:

- Provision of other psychological support
- Layout of critical care unit

12.3 Data collection – site staff

The following data will be collected on the site staff's participation in POPPI – only applicable to the intervention sites:

POPPI nurses

- Basic demographic data
- Self-efficacy questionnaire – completed by POPPI nurses prior to and after POPPI nurse Training course
- Skills development assessment scale – completed by assessors

All staff data

- End of e-learning course: number (%) and demographics of critical care staff completing course; knowledge test; number of attempts to pass knowledge test and number (%) of those who passed the test.

12.4 Process evaluation

The process evaluation for intervention sites will consider both quantitative and qualitative data.

Quantitative data will include assessments of nurse competence following the training course, and treatment fidelity of the stress support sessions. In particular, treatment fidelity will be assessed with a purpose-built measure of adherence to therapy assessed by independent reviewers based on a random sample of sessions digitally recorded by the POPPI nurses and sent centrally for evaluation.

The process evaluation will also incorporate site visits to intervention sites to observe and discuss the delivery of the intervention with the POPPI nurses and wider critical care unit staff. Each intervention site will receive a visit from the POPPI training team during the intervention period. The site visit will assess the delivery of three elements of the intervention:

- the therapeutic approach to interaction with critical care unit patients
- routine assessment of acute psychological distress using the IPAT
- stress support sessions

Qualitative data will be collected in the form of researcher observations, interviews with staff and structured field notes.

12.5 Monitoring

Sites must agree to allow trial-related monitoring and audits by providing direct access to source data/documents, as required. Patients' informed consent for this will also be obtained. Frequency of monitoring visits will be outlined in the POPPI Monitoring Plan and will consist of all sites visited at least once to monitor recruitment and adherence with the trial protocol. Additional on-site monitoring visits may be scheduled where there is evidence or suspicion of non-adherence by a site to important aspect(s) of the trial requirements.

Following the monitoring visit, the ICNARC CTU will provide the site with a monitoring report, which will summarise the documents reviewed, along with any findings. The PI at each site will be responsible for ensuring that the findings from the monitoring visit are addressed.

13 Statistical methods

13.1 Statistical methods – clinical effectiveness

The primary analysis for the clinical evaluation will determine if there is a significant difference in the mean PDS at six months between patients recruited during the intervention period in intervention sites compared with control sites of the cluster-RCT using a generalised linear mixed model (GLMM) at the individual patient level (patients nested within sites and time periods) including a random effect of site and a fixed effect of period (baseline or intervention), and adjusted for site-level factors included within the restricted randomisation algorithm.

For the primary outcome, the link function will be the identity link (i.e. linear regression) and standard errors will be estimated using a jackknife variance estimate, which has been demonstrated in simulation studies to maintain the size of the test.[56]

A secondary analysis will adjust for pre-specified baseline factors associated with poor psychological outcome (e.g. sedation) and ability to resource and deliver the intervention (e.g. size of critical care unit, teaching status) at both patient and site level. Results of the GLMMs will be reported as differences in means, 95% confidence intervals and p-values.

Analyses of secondary outcomes will be conducted using GLMMs, with the identity link (i.e. linear regression) for continuous secondary outcomes, reported as differences in means, and the logit link (i.e. logistic regression) for binary secondary outcomes, reported as odds ratios.

The above analyses will evaluate the effectiveness of the intervention among all patients meeting the inclusion criteria and consenting to follow-up, based on the intention to treat principle. A further secondary analysis will use structural mean models with an instrumental variable of allocated treatment to estimate the efficacy (adherence adjusted causal effect) of the stress support sessions among those patients consenting to psychological assessment and stress support sessions, assessed as being at high risk of psychological morbidity and receiving stress support sessions.[59]

13.2 Statistical methods – process evaluation

Analysis of the process evaluation will use a combination of qualitative and quantitative methods to assess and describe the variation in the delivery of the intervention across sites.[60] Analysis of the process evaluation will be conducted before the outcome evaluation to avoid any bias in the interpretation of the process data and to generate hypotheses that may be subsequently tested in statistical analyses of integrated process and outcome data. The structural mean models described above will be extended to incorporate additional potential mediator variables on the causal pathway between treatment allocation and treatment effect, e.g. nurse competence following training, adherence to the therapeutic approach and adherence to therapy.[61]

13.3 Statistical methods – cost-effectiveness

A full CEA will be undertaken to assess the relative cost-effectiveness of psychological assessment followed by stress support sessions for those assessed as being at high risk of psychological morbidity, versus usual care. Resource use and outcome data collected as part of the cluster-RCT will be used to report cost-effectiveness at six months and to project the lifetime cost-effectiveness of each strategy.

The cost analysis will take a health and personal health services perspective. Resource use data from the site visits, cluster-RCT dataset and six-month questionnaires will be combined with unit costs from the NHS

Payment by Results database and from local Trust Finance Departments, to report the total costs per patient at six months for intervention versus usual care.[62, 63]

HRQoL data from the EQ-5D-5L questionnaires at six months will be combined with survival data using linear interpolation to report QALYs at six months. The CEA will report the mean (95% confidence interval) incremental costs, QALYs and net monetary benefit at six months.

The CEA will use multilevel linear regression models that allow for clustering[64] including a random effect of site and a fixed effect of period. The analysis will adjust for pre-specified baseline covariates at both patient and site level.

Lifetime cost-effectiveness will be projected using a decision model informed by the best evidence on long-term survival and HRQoL after critical care unit stay.[65, 66] The long-term modelling will extrapolate from the cluster-RCT data by fitting alternative parametric survival curves (e.g. Weibull, exponential, lognormal, log logistic and Gompertz) to the observed survival data. The chosen method of extrapolation for the base case will be the one judged most plausible.[67] In the base case, quality of life calculated at six months will be assumed to apply to each subsequent year of life, after allowing for decrements in quality of life according to advancing age. Predicted survival and HRQoL will be combined to report lifetime QALYs, and to project lifetime incremental costs, incremental QALYs, and incremental net benefits for the alternative strategies of care. Sensitivity analyses will test whether the results are robust to methodological assumptions (e.g. specification of the statistical model, extrapolation approach, alternative HRQoL assumptions, and learning curve effects).

14 Monitoring and oversight

14.1 Trial Management Group (TMG)

All day to day management of POPPI will be the responsibility of Professor Kathryn Rowan (Chief Investigator) and Paul Mouncey (Senior Trial Manager). Staff who work on POPPI (including the Trial Statistician, Sarah Power, and Research Assistant, Alvin Richards-Belle) will meet regularly to discuss, the progress of the trial and findings from other related research.

14.2 Trial Steering Committee (TSC)

The progress of the trial will be monitored and supervised by the TSC. At least 75% of the members will be independent (including the Chair). It will also consist of at least two service user representatives, the Chief Investigator and the Lead Clinical Investigator.

14.3 Data Monitoring and Ethics Committee (DMEC)

The DMEC will include experienced critical care clinicians and an experienced statistician. All members of the DMEC will be independent of both the trial and the TSC. The DMEC will operate under the DAMOCLES Charter[68],and will report to the TSC, making recommendations on the continuation, or not, of the trial.

14.4 Role of the ICNARC CTU

The ICNARC CTU will be responsible for the day to day management and coordination of the trial and will act as custodian of the data. The ICNARC CTU will ensure that all SAEs are appropriately reported to the REC.

15 Trial closure

15.1 End of trial

The end of the trial will be when the final patient has completed their six months follow-up. At which point the Declaration of End of Trial Form will be submitted to the participating ethical committee, as required.

15.2 Archiving of trial documentation

At the end of the trial, the ICNARC CTU will archive securely all centrally held trial related documentation for a minimum of 10 years. Arrangements for its confidential destruction will then be made. It is the responsibility of PIs at each site to keep data and all essential documents relating to the trial held at site for a minimum of 10 years after the end of the trial and in accordance with national legislation and for the maximum period of time permitted by the site, as per local policy.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of Good Clinical Practice (GCP) and all applicable regulatory requirements.

If a patient withdraws consent for any data to be used it will be confidentially destroyed.
The ICNARC CTU will notify sites when documentation held at sites may be archived. All archived documents must still be available for inspection and monitoring by appropriate authorities and the ICNARC CTU upon request.

15.3 Early discontinuation of trial

The trial may be stopped before completion by the TSC. This can be upon recommendation of the DMEC. Sites will be informed in writing by the ICNARC CTU of reasons for early closure and the actions to be taken with regard to treatment of patients. Patients should continue to be followed up as per protocol.

15.4 Withdrawal from trial participation by a site

Should a site choose to close to recruitment the PI must inform the ICNARC CTU in writing. Follow-up as per the protocol must continue for all patients recruited into POPPI at that site. Sites that contravene the POPPI Trial Protocol and the Clinical Trial Site Agreement will be subject to review by the TMG and Sponsor and may be suspended or closed down by the ICNARC CTU.

16 Ethical and regulatory compliance

16.1 Research ethics approval

This Protocol, Patient Information Sheets, Informed Consent Forms and other trial-related documents will be reviewed and approved by the Sponsor and Research Ethics Committee (REC) with respect to scientific content and compliance with applicable research regulations involving human subjects. Details of the informed consent procedure are reported in section 4.2.

16.2 Protocol amendments

Any modification to the protocol and/or trial-related documents which may impact on the conduct of the trial, potential benefit to patients or patient safety will require a formal amendment to the protocol. Such amendments will be agreed by the Sponsor, TMG and approved by the REC. Administrative changes of the protocol, which have no impact on the conduct of the trial or patient safety, will be agreed by the Sponsor and TMG. The REC will be notified but formal approval will not be required.

16.3 Confidentiality

The POPPI trial will be managed according to the Medical Research Council's (MRC) Guidelines for Good Clinical Practice in Clinical Trials and Good Research Practice: Principles and Guidelines, which are based on the principles of the International Conference on Harmonisation (ICH) GCP. The ICNARC CTU has developed its own policies and procedures, based on these MRC guidelines, for the conduct of all its research activities. In addition, ICNARC has contractual confidentiality agreements with all members of staff. Policies regarding alleged scientific misconduct and breach of confidentiality are reinforced by disciplinary procedures.

The ICNARC CTU will act to preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Any patient identifiable data leaving the hospital will be encrypted to ensure anonymity. All procedures for handling, processing, storing and destroying data are compliant with the Data Protection Act 1998.

16.4 Withdrawal of patients consent

In consenting to the trial, patients are consenting to assessments, intervention (where applicable), follow-up and data collection.

If a patient explicitly states their wish not to contribute further data to the trial their decision must be respected and the ICNARC CTU notified in writing. Details should be recorded in the patient's hospital records and no further trial data will be requested.

17 Dissemination policy

The progress and results of POPPI will be widely and actively disseminated. The results will be submitted to relevant peer-review journals for publication. They will also be presented at: national and international critical care and clinical and health psychology conferences/meetings; the Annual Meeting of the ICNARC Case Mix Programme; and the Annual Meeting of the UK Critical Care Research Forum.

A Study Report to the NIHR HS&DR programme will present a detailed description of the trial and the results along with recommendations for future policy, practice and research.

18 Sponsorship and Indemnity

ICNARC is the Sponsor for the POPPI cluster-RCT and holds professional indemnity insurance (Markel International Insurance Co Ltd) to meet the potential legal liability of the Sponsor and employees for harm to participants arising from the design and management of the research.

Indemnity to meet the potential legal liability of investigators/collaborators for harm to participants arising from the conduct of the research is provided by the NHS indemnity scheme or through professional indemnity.

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Appendix A: Protocol version history

Protocol:		Amendments:		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version.**
v1.0	20 April 2015	N/A	N/A	N/A

Appendix B: Intensive care Psychological Assessment Tool (IPAT)

I would like to ask you some questions about your stay in intensive care, and how you've been feeling in yourself. These feelings can be an important part of your recovery. To answer, please circle the answer that is closest to how you feel, or answer in any way you are able to, e.g. by speaking or pointing.

	Since you've been in the intensive care unit:	**A**	**B**	**C**
1	Has it been hard to communicate?	No	Yes, a bit	Yes, a lot
2	Has it been difficult to sleep?	No	Yes, a bit	Yes, a lot
3	Have you been feeling tense?	No	Yes, a bit	Yes, a lot
4	Have you been feeling sad?	No	Yes, a bit	Yes, a lot
5	Have you been feeling panicky?	No	Yes, a bit	Yes, a lot
6	Have you been feeling hopeless?	No	Yes, a bit	Yes, a lot
7	Have you felt disorientated (not quite sure where you are)?	No	Yes, a bit	Yes, a lot
8	Have you had hallucinations (seen or heard things you suspect were not really there)?	No	Yes, a bit	Yes, a lot
9	Have you felt that people were *deliberately* trying to harm or hurt you?	No	Yes, a bit	Yes, a lot
10	Do upsetting memories of intensive care keep coming into your mind?	No	Yes, a bit	Yes, a lot

Do you have any comments to add in relation to any of the answers?

_____

_____

SCORING

Any answer in column A = 0 points

Any answer in column B = 1 point

Any answer in column C = 2 points

Sum up the scores of each item for a total I-PAT score out of 20

Cut-off point ≥7 - indicates patient at risk

Appendix C: State-Trait Anxiety Inventory (STAI)

Please read the words below and after each one, circle the answer that is closest to how you have been feeling in the past few days.

During the past few days I have been feeling…					
1	**Calm**	Not at all	Somewhat	Moderately	Very much
2	**Tense**	Not at all	Somewhat	Moderately	Very much
3	**Upset**	Not at all	Somewhat	Moderately	Very much
4	**Relaxed**	Not at all	Somewhat	Moderately	Very much
5	**Content**	Not at all	Somewhat	Moderately	Very much
6	**Worried**	Not at all	Somewhat	Moderately	Very much

Appendix D: Patient Emotional Reactions Questionnaire (PDS)

These questions are about reactions people may have after intensive care.

Please circle how often a problem has bothered you **in the past month**.

1. Have you had upsetting thoughts or images about intensive care that came into your head when you didn't want them to?

Not at all	**Once per week or less**	**2 – 4 times per week**	**5 or more times per week**

2. Have you had bad dreams or nightmares about intensive care?

Not at all	**Once per week or less**	**2 – 4 times per week**	**5 or more times per week**

3. Have you relived your time in intensive care, acting or feeling as if it were happening again?

Not at all	**Once per week or less**	**2 – 4 times per week**	**5 or more times per week**

4. Have you felt emotionally upset when you were reminded of your time in intensive care (e.g. feeling scared, angry, sad, guilty)?

Not at all	**Once per week or less**	**2 – 4 times per week**	**5 or more times per week**

5. Have you had physical reactions when you remember your time in intensive care (e.g. breaking into a sweat, heart beating fast?)

Not at all	**Once per week or less**	**2 – 4 times per week**	**5 or more times per week**

6. Have you tried not to think about, talk about, or have feelings about your time in intensive care?

Not at all	**Once per week or less**	**2 – 4 times per week**	**5 or more times per week**

7. Have you tried to avoid activities, people or places that remind you of your time in intensive care?

Not at all	**Once per week or less**	**2 – 4 times per week**	**5 or more times per week**

8. Have you found that you were not able to remember an important part of your time in intensive care?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

9. Have you had much less interest in important activities?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

10. Have you felt distant or cut off from people around you?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

11. Have you felt emotionally numb (unable to cry or have loving feelings?)

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

12. Have you felt as if your future plans or hopes would not come true?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

13. Have you had trouble falling or staying asleep?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

14. Have you felt irritable or had fits of anger?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

15. Have you had trouble concentrating (e.g. forgetting what you read, losing track of a story on television)?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

16. Have you been too alert (for example, checking to see who is around you, not being comfortable with your back to a door)?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

17. Have you been jumpy or easily startled (for example, when someone walks up behind you)?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

If you reported any problems in your answers to questions 1-17, then please answer the following questions:

The next two questions are about the timing of emotional reactions people may have after intensive care.

Please circle the answer that is closest to your experience.

18. How long have you experienced these problems?

Not at all	Less than 1 month	1 to 3 months	More than 3 months

19. If you reported any problems in your answers to questions 1-17, how long after leaving Intensive care did these problems begin?

I have not had these type of problems	Less than 1 month	1 to 3 months	More than 3 months

In the past month have the above problems:

20. Affected your relationships or social life?

Not at all	A little Bit	Moderately	Quite a bit	Extremely

21. Affected your work or ability to work?

Not at all	A little Bit	Moderately	Quite a bit	Extremely

22. Affected any other important part of your life such as parenting, or school or college work, or other important activities?

Not at all	A little Bit	Moderately	Quite a bit	Extremely

Appendix E: Patient Mood Questionnaire (CES-D-10)

How often you have felt any of the following during **the past week**?
Please circle one answer for each item.

1. I was bothered by things that usually don't bother me

Less than 1 day	1- 2 days	3-4 days	5-7 days

2. I had trouble keeping my mind on what I was doing

Less than 1 day	1- 2 days	3-4 days	5-7 days

3. I felt depressed

Less than 1 day	1- 2 days	3-4 days	5-7 days

4. I felt that everything I did was an effort

Less than 1 day	1- 2 days	3-4 days	5-7 days

5. I felt hopeful about the future

Less than 1 day	1- 2 days	3-4 days	5-7 days

6. I felt fearful

Less than 1 day	1- 2 days	3-4 days	5-7 days

7. My sleep was restless

Less than 1 day	1- 2 days	3-4 days	5-7 days

8. I was happy

Less than 1 day	1- 2 days	3-4 days	5-7 days

9. I felt lonely

Less than 1 day	1- 2 days	3-4 days	5-7 days

10. I could not "get going"

Less than 1 day	1- 2 days	3-4 days	5-7 days

Appendix F: Patient Health Questionnaire (EuroQoL - EQ-5D-5L)

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

MOBILITY

I have no problems in walking about ❑

I have slight problems in walking about ❑

I have moderate problems in walking about ❑

I have severe problems in walking about ❑

I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑

I have slight problems washing or dressing myself ❑

I have moderate problems washing or dressing myself ❑

I have severe problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

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

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑

I am slightly anxious or depressed ❑

I am moderately anxious or depressed ❑

I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

We would like to know how good or bad your health is **TODAY**.

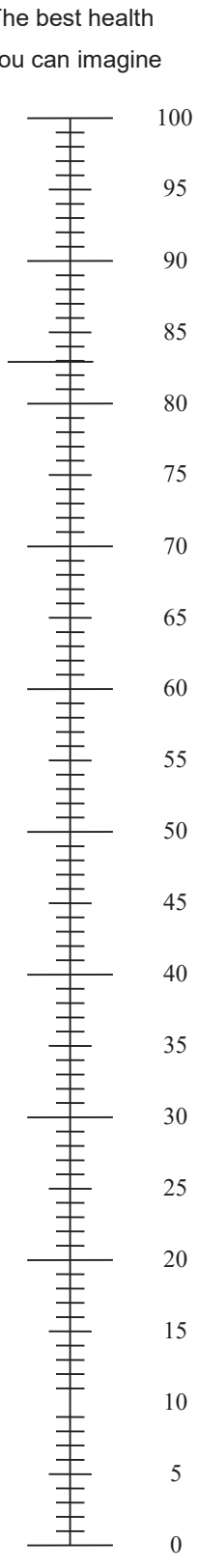
This scale is numbered from 0 to 100.

100 means the **best** health you can imagine.
0 means the **worst** health you can imagine.

Mark an **X** on the scale to indicate how your health is **TODAY**.

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix G: Health Services Questionnaire

Health services

These questions will help us understand the care you needed after leaving the hospital.

Please answer the multiple choice questions by putting a ✓ in **ONE** box for each question.

Q1 Where are you now?

- ◯ At home (your own home, or a relative's home)
- ◯ In residential care (e.g. nursing home, hospice)
- ◯ In short-term rehabilitation
- ◯ In long-term rehabilitation
- ◯ In hospital
- ◯ Other (please specify): _____

Q2 Hospital stays

Since you left hospital on
have you stayed overnight in hospital for any reason?

- ◯ **No** – *Please go to Q3*
- ◯ **Yes** – *Please give details about the number of stays below*

For EACH TIME you stayed in hospital please answer the following:

	Number of nights		1 – 3 nights	4 – 10 nights	11 or more nights	Did you spend any part of your stay in intensive care?
1st stay		*Or tick...*	◯	◯	◯	◯
2nd stay		*Or tick...*	◯	◯	◯	◯
3rd stay		*Or tick...*	◯	◯	◯	◯
4th stay*		*Or tick...*	◯	◯	◯	◯

**If you have stayed in hospital more than 4 times, please could you provide information on these further hospital stays in Q7 of the questionnaire.*

Q3 Visits to hospital outpatients

Outpatient visits are when a patient comes to the hospital to see a specialist (e.g. consultant) but does not stay overnight.

Since you left hospital on
have you visited hospital outpatients about ANY ASPECT of your health?

- ○ **No** – *Please go to Q4*
- ○ **Yes** – *Please give details about the number of outpatients visit(s) below*

Number of visits		1 – 3 visits	4 – 10 visits	11 or more visits
☐	*Or tick...*	○	○	○

Q4 Visits to health care providers

Since you left the hospital on
have you visited any of the health care providers listed below about ANY ASPECT of your health?

- ○ **No** – *Please go to Q5*
- ○ **Yes** – *Please give details about the number of visits below*

For EACH PROVIDER please answer the following:

Did you visit this provider?	(please tick)	Number of visits		1 – 3 visits	4 – 10 visits	11 or more visits
GP	○	☐	*Or tick...*	○	○	○
Nurse at your GP clinic	○	☐	*Or tick...*	○	○	○
Nurse at hospital or elsewhere	○	☐	*Or tick...*	○	○	○
Health visitor	○	☐	*Or tick...*	○	○	○
Critical care follow-up clinic	○	☐	*Or tick...*	○	○	○

POPPI

Health services

Q5 Visits to your home by health care providers

Since you left hospital on
have you had home visits from any of the following health care providers about ANY ASPECT of your health?

○ **No** – *Please go to Q6*

○ **Yes** – *Please give details about the number of visits below*

For EACH PROVIDER please answer the following:

Were you visited at home by this provider?	(please tick)	Number of visits		1 – 3 visits	4 – 10 visits	11 or more visits
GP	○	☐	*Or tick...*	○	○	○
Nurse from your GP clinic	○	☐	*Or tick...*	○	○	○
Health visitor or district nurse	○	☐	*Or tick...*	○	○	○

Q6 Visits to other service providers

Since you left hospital on
have had contact (either visits to the provider or home visits) with any of the following service providers about ANY ASPECT of your health?

○ **No** – *Please go to Q7*

○ **Yes** – *Please give details about the number of visits below*

For EACH PROVIDER please answer the following:

Have you had contact with any of these providers?	(please tick)	Number of visits		1 – 3 visits	4 – 10 visits	11 or more visits
Occupational therapist	○	☐	*Or tick...*	○	○	○
Speech and Language therapist	○	☐	*Or tick...*	○	○	○
Physiotherapist	○	☐	*Or tick...*	○	○	○
Psychiatrist	○	☐	*Or tick...*	○	○	○
Psychiatric nurse	○	☐	*Or tick...*	○	○	○
Psychologist	○	☐	*Or tick...*	○	○	○
Counsellor	○	☐	*Or tick...*	○	○	○

POPPI

Health services

Q7 **Other services not listed so far**

Since you left hospital on
have you had further hospital stays or used any any other health care services for ANY ASPECT of your health that you haven't included previously?

○ **No** – *Please go to Q8*

○ **Yes** – *Please give details about the number of visits below*

For EACH PROVIDER please answer the following:

Type of service provider	Number of visits	Reason

Q8 Your views are important to us. Please feel free to provide any other comments you have in the box below.

Thank you for your time

Provision Of Psychological support to People in Intensive care

Psychological Outcomes following a nurse-led Preventative Psychological Intervention for critically ill patients (POPPI) trial

NHS REC Committee no:	**15/SC/0287**
IRAS no:	**173772**
Trial Sponsor:	**ICNARC**
Trial Sponsor reference:	**01/03/14**
Trial funder(s):	**NIHR HS&DR Programme**
Funder(s) reference:	**12/64/124**
ISRCTN Registry no:	**ISRCTN53448131**
NIHR CRN Portfolio no:	**18940**
Protocol version:	**2.2**
Protocol version date:	**6 March 2017**

Role:	**Name and Position:**	**Date:**
Chief Investigator:	Professor Kathryn Rowan Director of Scientific & Strategic Development/CTU Director, ICNARC	6 March 2017
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NHS National Institute for Health Research

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Funding

National Institute for Health Research (NIHR) – Health Services & Delivery Research Programme (HS&DR) (Project: 12/64/124)

Contents

Abbreviations

CAM-ICU	Confusion Assessment Method for the Intensive Care Unit
CBT	Cognitive Behavioural Therapy
CBTp	Cognitive Behavioural Therapy for psychosis
CEA	Cost-effectiveness Analysis
CI	Confidence interval
CMP	Case Mix Programme
CRF	Case Report Form
CTSA	Clinical Trial Site Agreement
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
eCRF	Electronic Case Report Form
EQ-5D	European Quality of Life Scale
GCP	Good Clinical Practice
GLMM	Generalised linear mixed model
GP	General Practitioner
HA	Health Anxiety
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health Related Quality of Life
HS&DR	Health Services & Delivery Research
ICH	International Conference on Harmonisation
ICNARC	Intensive Care National Audit & Research Centre
ICU	Intensive Care Unit
IPAT	Intensive care Psychological Assessment Tool
ISF	Investigator Site File
LSHTM	London School of Hygiene & Tropical Medicine
MRC	Medical Research Council
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PI	Principal Investigator
PIAG	Patient Information Advisory Group
POPPI	Psychological Outcomes following a nurse-led Preventative Psychological Intervention for critically ill patients
PSS-SR	PTSD Symptom Scale – Self-Report version
PTSD	Post-traumatic Stress Disorder
QALY	Quality-adjusted life year
R&D	Research & Development
RASS	Richmond Agitation Sedation Scale
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SOP	Standard Operating Procedure

SSS	Stress Support Session
STAI	State Trait Anxiety Inventory
TMG	Trial Management Group
TSC	Trial Steering Committee
UCLH	University College London Hospitals NHS Foundation Trust

Protocol summary

1.1 Summary of trial design

Title (acronym):	Psychological Outcomes following a nurse-led Preventative Psychological Intervention for critically ill patients (POPPI)
Public Title	Provision Of Psychological support to People in Intensive care
Short Title:	POPPI
Sponsor name:	Intensive Care National Audit & Research Centre (ICNARC)
Funder name & reference:	NIHR Health Services & Delivery Research Programme, 12/64/124
Design:	Cluster-randomised controlled trial (cluster-RCT)
Aim:	To evaluate the clinical and cost-effectiveness of a complex nurse-led preventative psychological intervention in reducing patient-reported post-traumatic stress disorder (PTSD) symptom severity, and other reported psychological morbidities, at six months versus usual care.
Primary outcomes:	To evaluate: • Patient-reported PTSD symptom severity at six months • Incremental costs, quality adjusted life years and net monetary benefit
Secondary outcomes:	To compare: • Days alive and free from sedation to day 30 • Duration of critical care unit stay • Depression at six months • Anxiety at six months • Post traumatic Diagnostic Scale score of greater than 18 points at six months • Health-related quality of life at six months
Anticipated accrual:	1,378 critical care patients
Inclusion criteria:	• Age 18 years or greater • Greater than 48 hours in critical care unit • Receipt of some Level 3 critical care during first 48 hours • Between +1 and -1 on the Richmond Agitation Sedation Scale • Glasgow Coma Score of 15 • English-speaking • Ability to communicate orally
Exclusion criteria:	• Pre-existing chronic cognitive impairment, such as dementia • Pre-existing psychotic illness, such as schizophrenia • Pre-existing chronic post-traumatic stress disorder • Receiving end-of-life care • Previously recruited to POPPI
Planned number of units:	Twenty-four NHS adult, general critical care units
Anticipated duration of recruitment:	Seventeen months
Duration of follow-up:	Six months
Definition of end of Trial:	Last patient, last follow-up

2 Introduction

2.1 Background & rationale

Over 100,000 patients are admitted to adult, general critical care units in the National Health Service (NHS) each year and it has been estimated that around two thirds suffer serious emotional distress, and/or unusual experiences such as hallucinations and delusions, while in the unit.[1, 2] Emotional distress, including severe symptoms of anxiety, low mood and panic, may be caused by a range of stressful, cumulative experiences that are common in the critical care unit: fear of dying; invasive treatments such as mechanical ventilation; pain and discomfort; inability to communicate; and terrifying hallucinatory delusions.[1, 3-5] The aetiology of the characteristic hallucinations and delusions of critical care unit patients is unknown, but they have been linked to delirium, the provision and withdrawal of sedative and other psychoactive drugs, effects of illness (such as sepsis), immobility, and sensory and sleep deprivation.[2, 4, 6] Hallucinations and delusions are known, from the psychosis literature, to be exacerbated by, and co-morbid with, emotional stress. Critical care unit hallucinations frequently have horrifying themes such as conspiracy to kill by staff, torture, poisoning, demons, extortion or organ theft[7]; thus a vicious cycle of stress, confusion, and terror is common for critical care unit patients.

Experiencing acute psychological stress in the critical care unit, or having frequent memories of hallucinations and delusions, are also among the identified risk factors for longer-term post-critical care posttraumatic stress disorder (PTSD), depression, anxiety or cognitive impairment.[4, 8-12] Recently published systematic reviews of survivors of critical care identified rates of PTSD up to 27%, months or years after leaving critical care, and a mean PTSD prevalence of 20%.[3, 13] High rates of depression following critical care have also been reported, with a median prevalence of 28%.[14] A study that followed patients up to two years, found 40% with depression[15]. Patients who develop serious psychological morbidities are at much higher risk of further physical morbidities and mortality[16-18] representing a serious burden to patients, to their carers and to the NHS.[19, 20]

It is more than 15 years since the Department of Health explicitly recognised this serious problem, stating in the year 2000 that the critical care unit was extremely distressing for patients and that there was considerable need for psychological support for traumatised patients.[21] In 2009, the National Institute for Health and Care Excellence (NICE) recommended that all critically ill patients should be assessed for risk of non-physical morbidity, and that those at high risk of adverse outcomes such as PTSD, should receive structured psychological support, both during and after their unit stay.[22] NICE guidance on the diagnosis, prevention and management of delirium recommends that patients identified as being at high risk of delirium (including all critically ill patients), should be monitored closely, and strategies for intervention implemented as soon as possible.[23] Even more recently, in 2012, NICE has highlighted the importance of patients being regularly assessed for psychological needs, so that these can be rapidly addressed.[24]

Rigorous and relevant evidence is now urgently needed to reduce the burden of serious psychological morbidity on critical care patients and their carers, and cost effective strategies are needed to reduce the burden on the NHS.

The modification of clinical risk factors for PTSD such as duration of mechanical ventilation and sedation have been discussed in the literature[25, 26], but less invasive medical interventions or better drugs are not currently available. Yet little high-quality research has been conducted to evaluate psychological interventions that could alleviate the emotional distress experienced by patients in critical care, with a view to preventing longer-term psychological morbidity.[27] An unpublished systematic review of 18 studies found mostly weak and some moderate evidence that psychosocial interventions including music therapy, complementary therapy, psychotherapy or patient diaries could reduce short-term or medium-term distress for critical care unit patients. Only the patient diary intervention[28] and a psychotherapeutic intervention[29] were shown to have an effect on longer-term psychological outcomes in a sufficiently large sample. However, the diary

intervention targets critical care unit patients' memory gaps rather than stress, and has been critiqued for its lack of a solid psychological theoretical underpinning.[30]

Recent advances in the study of critical care psychology have made the evaluation of psychological interventions for the critically ill more feasible. Valid psychological assessment tools now exist for use with critical care patients (e.g. Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)[31]), including a tool measuring critical care-related distress (the Intensive care Psychological Assessment Tool (IPAT, Appendix B) that was developed and validated by our research team.[32] With respect to the best timing to provide psychological interventions for critical illness survivors, research suggests that post-discharge (e.g. at six weeks[33] or at outpatient follow-up clinics[20]) may be too late, and earlier intervention could be more beneficial. For example, a study with critically ill trauma patients indicated that considerably fewer individuals experienced PTSD, depression or anxiety a year after critical care unit stay, having received interventions by practitioner psychologists while in the critical care unit.[29] In today's NHS, practitioner psychologists are a scarce resource, and a more pragmatic approach would be to standardise brief evidence-based psychological interventions to be carried out by existing critical care unit staff, who would be given the necessary training.

Aiming to develop a nurse-led psychological intervention for critical care unit patients that would commence before they leave the unit, our research team has identified the most relevant, up-to-date evidence concerning psychological techniques that are effective in: a) reducing acute emotional distress; b) reducing the impact of unusual experiences such as hallucinations and delusions; and c) preventing PTSD after a trauma (psychological problems commonly associated with admission to the critical care unit). The evidence is summarised below:

Interventions comprising Cognitive Behavioural Therapy (CBT) techniques have been found to be effective in reducing many types of emotional distress in both physical and mental health settings. Studies have evaluated CBT as effective even when delivered in brief form, or by non-expert staff (including nurses) who receive specific training. For example, a randomised controlled trial (RCT) showed that twice as many patients with excessive health anxiety (HA) who received brief CBT from newly-trained, non-expert clinical staff in medical clinics, achieved normal HA levels, compared to a control group.[34]

A specific CBT model has also proved effective in reducing the impact of symptoms such as hallucinations and delusions in patients with psychosis.[35-40] CBT for psychosis (CBTp) interventions have proved to be particularly effective in cases of early, first episode or acute psychosis, which equate most closely to the critical care unit experience.[41, 42] Recent CBTp research has demonstrated the efficacy of brief interventions, targeting specific symptoms such as delusions.[43] CBTp has also been successfully delivered by nurses and other non-expert therapists to patients with psychosis in mental health settings.[44-46]

Finally RCTs have shown CBT to be the most effective psychological intervention in reducing PTSD symptoms following different types of trauma, including episodes of psychosis.[47, 48] There is also increasing evidence that *early* interventions soon after a trauma may help to *prevent* PTSD symptoms from developing in the longer-term. A recent update to the NICE PTSD guidelines[49] states specifically that a brief trauma-focused psychological intervention of three sessions, delivered in the period immediately after a trauma, may reduce the development of subsequent PTSD symptoms.

Given that these existing evidence-based psychological interventions could be modified to reduce the stress and trauma experienced by critical care unit patients, and be delivered by specially trained, well-motivated critical care unit nurses, there is an urgent need to evaluate their effectiveness in the critical care unit setting. Increasing psychological support may also provide a further benefit to patients and the NHS by permitting a reduction in use and duration of pharmacological sedation.

The POPPI cluster-RCT was preceded by a Feasibility Study (ISRCTN61088114) looking at feasibility of both the intervention and the RCT processes. These feasibility studies informed this protocol for the POPPI cluster-RCT.

2.2 Aim

The aim of POPPI is to evaluate the clinical and cost-effectiveness of a complex nurse-led preventative psychological intervention in reducing patient-reported post-traumatic stress disorder (PTSD) symptom severity, and other reported psychological morbidities, at six months.

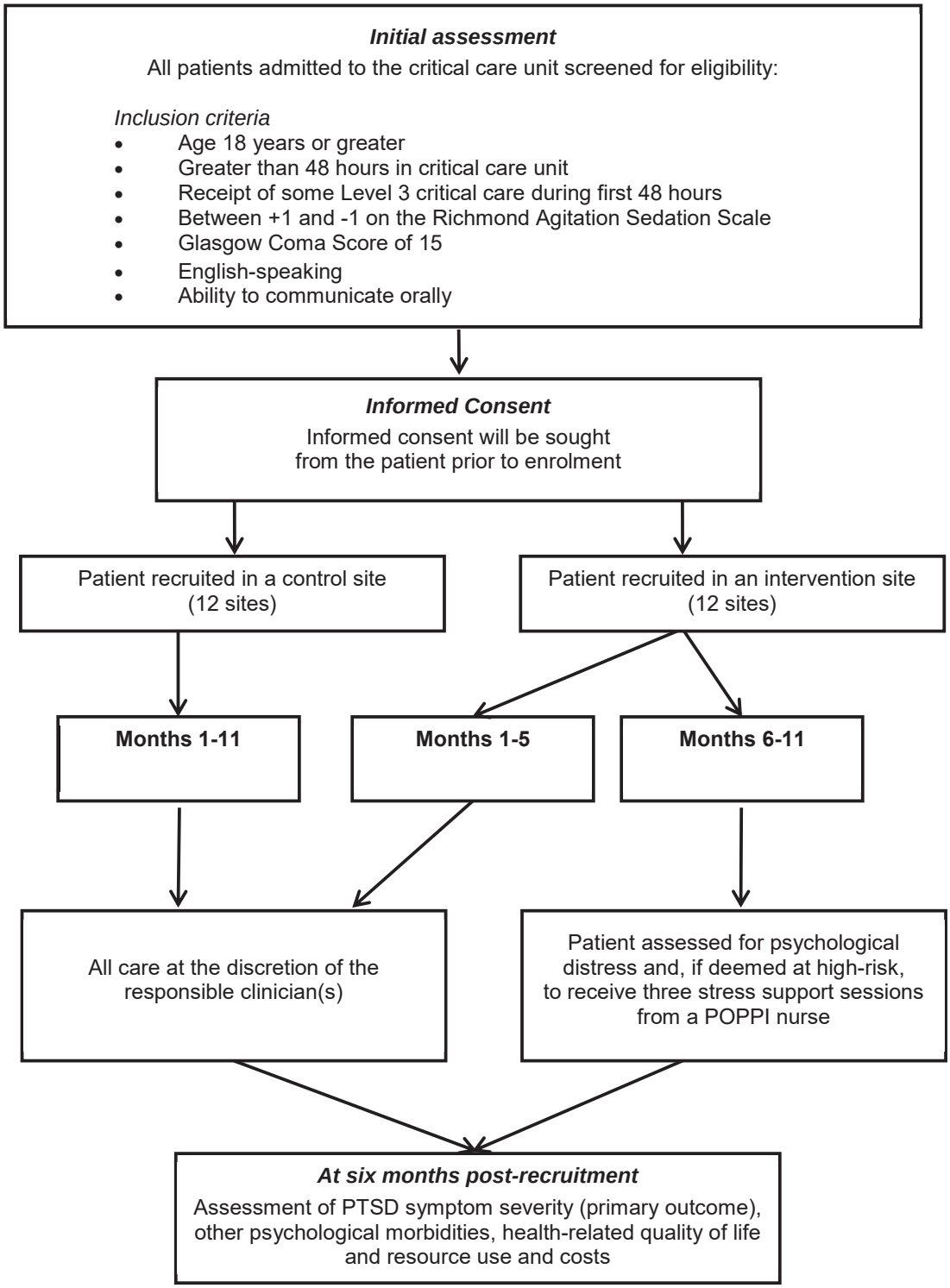
2.3 Objectives

- To evaluate the effect of the complex intervention on patient-reported PTSD symptom severity and other psychological morbidities and quality of life at six months; and
- To estimate, in an integrated economic analysis, the cost-effectiveness of the intervention.

An integrated process evaluation will be conducted to assess the fidelity and quality of the implementation of the intervention, and identify important contextual factors to better understand how the intervention works.

2.4 Trial schema

Figure 1. Overview of patient journey



3 Trial design

Parallel group cluster-RCT.

3.1 Setting

Twenty-four NHS adult, general, critical care units in the UK ('sites').

3.1.1 Site selection

The following criteria must be met for a site to participate in POPPI – a site must:

- show that recruitment to target, timely data collection, and delivery of the complex intervention are feasible - via completion of a site feasibility questionnaire;
- commit to dedicate adequate resources to carry out the complex intervention;
- agree to adhere to randomisation into either the control group or the intervention group;
- have two Joint Principal Investigators (PIs) identified to lead POPPI at the site (a lead nurse and a lead clinician);
- agree, where possible, to recruit all eligible patients to POPPI and to maintain a POPPI Screening Log to include reasons why eligible patients were not recruited
- agree to use the CAM-ICU for assessing delirium and RASS for assessing sedation status for the duration of the trial; and
- be actively participating in the Case Mix Programme (CMP) – the national clinical audit for critical care units coordinated by ICNARC.

Sites who have taken part as an intervention site in the POPPI Feasibility Study (ISRCTN61088114) will not be eligible for selection.

3.2 Trial timeline

Sites will be open to recruitment in three groups of eight sites at two month intervals (see Figure 2). At the start of month two the group of eight sites will be randomised to be either intervention or control sites (four intervention; four control). Each site will recruit patients for a total of between 13 to 17 months (see Figure 2) following the below schedule.

Control group sites

Months 1-17: Usual care period (See section 5)

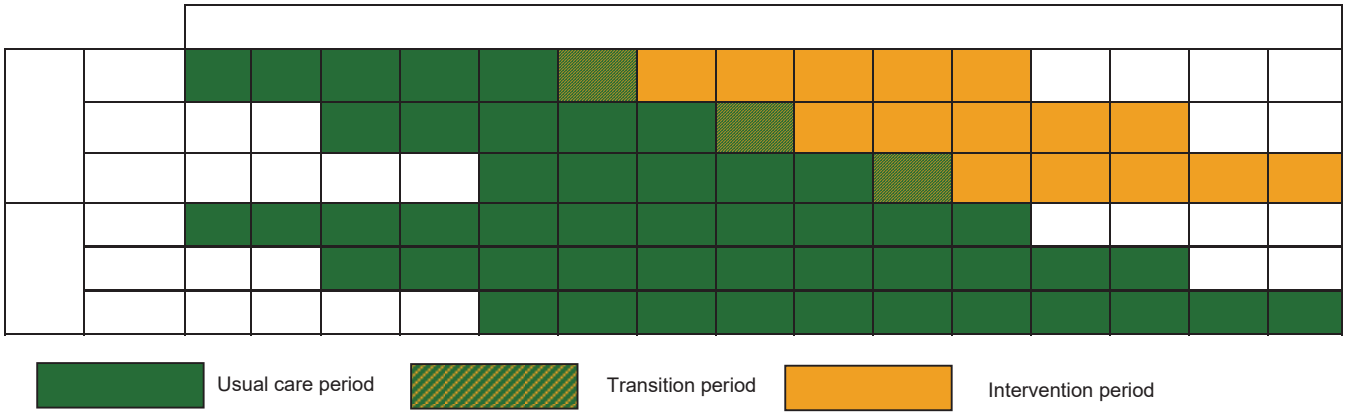
Intervention group sites

Months 1-5: Usual care period (See section 5)

Month 6: Transition period (See section 7), during which intervention sites will undergo training and transition to delivering the intervention.

Month 7-17: Intervention period (See sections 7-8), in which the sites will deliver the full complex intervention.

Figure 2. Cluster–RCT schedule



		Trial timeline (months)																
Intervention group sites	1-4	1					6											17
	5-8			1					6									15
	9-12					1					6							13
Control group sites	1-4	1																17
	5-8			1														15
	9-12					1												13

3.3 Site activation

Once the ICNARC CTU have confirmed that all necessary documentation is in place (including signed Clinical Trial Site Agreement (CTSA) and local NHS permissions), a site activation e-mail will be issued to the PI outlining a date at which the site is to start screening and recruitment. Sites will undergo a site initiation meeting prior to commencing recruitment. All sites responsibilities are outlined in the CTSA.

3.4 Randomisation of sites

The 24 sites will be randomly assigned to either the intervention group (N=12) or the control group (N=12) using a restricted randomisation approach to ensure balance across the groups in geographical location, teaching status and size of unit. This will be completed at the start of month two.

It is necessary to randomise on a cluster, rather than individual, level to avoid contamination of usual care as it would not be possible to restrict parts of the intervention to individual patients.

3.5 Selection of POPPI nurses – intervention sites only

All intervention group sites will be responsible for selecting the POPPI nurses following a personal specification provided to the site. All POPPI nurses will be required to sign a commitment form. This will include the following criteria:

- Be an expert practitioner in critical care
- Have excellent inter-personal skills
- Excellent communicator
- Able to take a flexible approach to their work
- Have an interest in improving critical care unit patients' psychological outcomes
- Able to attend the POPPI nurse training course
- Committed to deliver the intervention for duration of intervention period
- Committed to support the rest of the critical care unit team in delivering the intervention

4 Patient recruitment

4.1 Patient eligibility

Patients admitted to participating NHS adult, general, critical care units and meeting the following criteria are eligible for recruitment into POPPI. Patients must meet the eligibility criteria prior to discharge from the critical care unit.

4.1.1 Inclusion criteria

Patients must meet all of the following criteria:

- Age 18 years or greater
- Greater than 48 hours in the critical care unit
- Receipt of Level 3 critical care (for any period of time) during first 48 hours in the critical care unit
- Between +1 and -1 on the Richmond Agitation Sedation Scale[50]
- Glasgow Coma Scale score of 15
- English-speaking
- Ability to communicate orally

4.1.2 Exclusion criteria

Patients must not meet any of the following criteria:

- Pre-existing chronic cognitive impairment, such as dementia
- Pre-existing psychotic illness, such as schizophrenia
- Pre-existing chronic posttraumatic stress disorder
- Receiving end-of-life care
- Previously recruited to POPPI

4.2 Informed Consent

All patients will be routinely screened for eligibility by unit staff. Patients who meet the eligibility criteria will be invited to take part in the trial.

The patient will be provided with written information about the trial which will be supplemented with information provided orally. Patients will be given a copy of the relevant Patient Information Sheet (different versions will be used for the Usual care period, and Transition/Intervention periods) and, if preferred, a shorter Patient Information Leaflet alongside the Patient Information Sheet.

This decision to also offer a shorter Patient Information Leaflet was made considering the severity of critical care unit patients' illness. In particular, it is likely that many patients may find it easier to read or have read to them the Patient Information Leaflet initially, which is a shorter version of the written information. This leaflet will refer the patient to the Patient Information Sheet for full details of the trial. All patients will receive the Patient Information Sheet prior to providing Informed Consent.

The information provided to patients will include: details about the purpose of the trial; how the trial is being funded; the consequences of taking part or not; and data security. The contact details for the local Principal Investigators (PI) will be included on both the Patient Information Sheet and Patient Information Leaflet. Patients will be given the opportunity to ask questions and to discuss the trial with family or friends before making their decision.

After the authorised staff member is satisfied that the Patient Information Sheet has been read and understood, and any questions have been adequately answered, patients will be invited to sign the Consent Form. Once the patient has signed the Consent Form, the person taking informed consent will add their own name and countersign the Consent Form in the presence of the patient.

A copy of the signed Consent Form will be given to the patient, a copy placed in the Investigator Site File (ISF) with the original placed in the patient's medical notes.

Standard Operating Procedures (SOPs) for screening and the informed consent process will be provided in the ISF.

5 Usual care period - patients

5.1 Overview

- Control sites will deliver usual care during months 1 to 17.
- Intervention sites will deliver usual care during months 1 to 5.

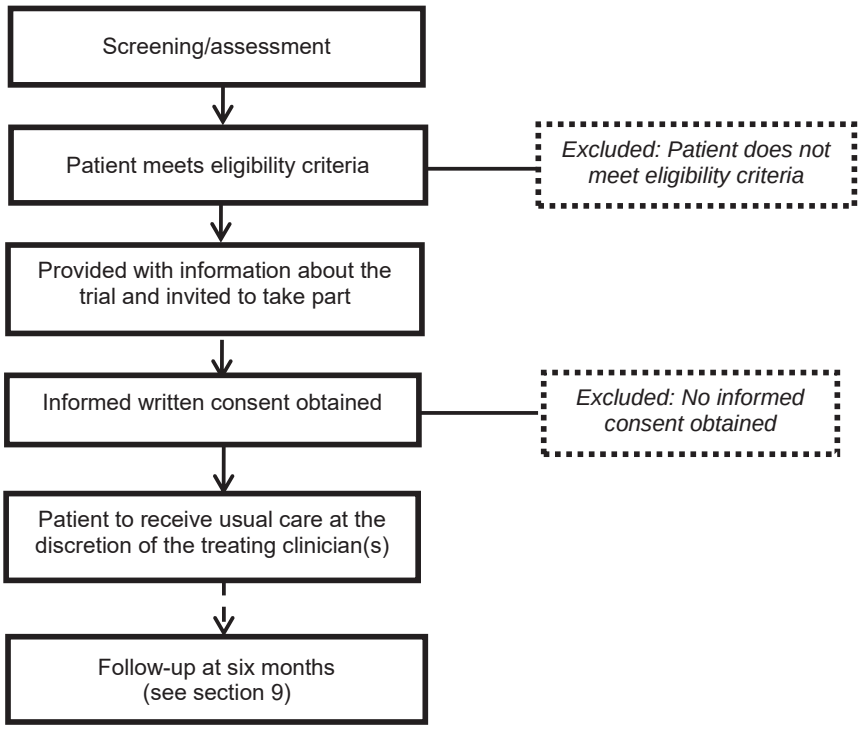
5.2 Definition of usual care

Patients should receive psychological support or treatment at the discretion of the treating clinician(s) following standard practice at their site.

5.3 Patient timeline

During the usual care period, eligible, consenting patients will receive usual care at the discretion of the treating clinician(s). Patients will be sent questionnaires six months after providing informed consent (see section 9 for further details).

Figure 3. Patient timeline during usual care



6 Intervention

The POPPI trial involves a complex intervention comprising four related elements:

1) An education package (two training courses and associated materials) to train critical care unit staff to carry out elements 2-4 below;
2) Creating a therapeutic environment to promote calm and minimise stress in the critical care unit (all critical care unit staff);
3) Assessing for acute psychological stress and unusual experiences in critical care unit patients using the IPAT (research staff);
4) Carrying out three, one-to-one CBT-inspired stress support sessions, for patients assessed as acutely stressed and at high-risk of psychological morbidity (delivered by specially trained POPPI nurses).

7 Transition period – site staff

All the procedures described in this section are relevant only to the intervention sites between months 6 to 17.

7.1 Overview

After the first five months of recruitment, intervention sites will undergo a transition period, during which they will transition from delivering usual care to delivering the complex intervention. Following the transition period, the full complex intervention will be delivered until the end of the recruitment period.

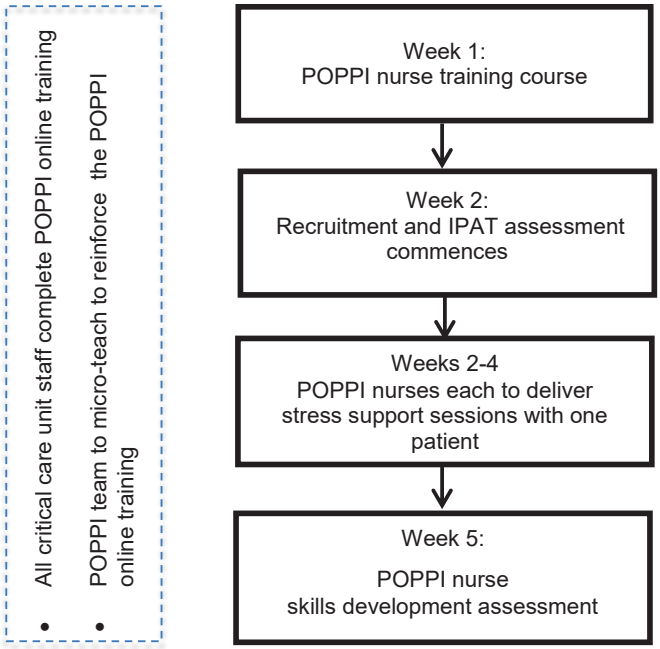
The transition period occurs during month 6 at each Intervention site and has the following aims:

- The POPPI nurses to attend a three day central training course (see section 7.3).
- Development of a therapeutic environment, with critical care unit staff completing the POPPI online training (see section 7.4)
- Assess all consented patients using the IPAT (section 8.3)
- Each POPPI nurse to deliver stress support sessions with at least one patient (see section 7.5)
- Confirmation of POPPI nurses skills development (section 7.5).

7.2 Site timeline during transition period

At the beginning of the transition period all POPPI nurses at a site will attend the three-day central POPPI nurse training course. After completing the course, the POPPI nurses will return to their critical care units where screening and consenting eligible patients will commence (as per the flow in section 8.2). Each nurse should deliver stress support sessions (see: Section 8.4) to at least one consented patient, identified (using the IPAT) as being stressed and at high risk of psychological morbidity. In parallel, the POPPI nurses and research teams will also encourage culture change in their unit to create a therapeutic environment (see section 7.4) by ensuring all critical care staff complete the POPPI online training and through teaching at the bedside. At the end of this transition period, the POPPI nurses will undergo a skills development assessment.

Figure 4. Site timeline during transition period



7.3 POPPI nurse training course

This is a three-day training course to train the POPPI nurses in their new role. The course was designed by the trial team in consultation with experts in medical education and CBT training, and is delivered by two senior nurses and a psychologist. The main focus of the training course is on learning and practising new skills required to deliver the stress support sessions with patients.

The POPPI nurse role also includes encouraging all staff in their units to complete the POPPI online training; promoting the screening of patients with the IPAT; and teaching good communication skills and psychological care (reinforcing key messages from the POPPI online training) at the bedside and training on these aspects of the role will also be provided. These tasks will be completed in conjunction with the research team at each intervention site as a team approach.

Associated materials include a training folder; a POPPI nurse training manual on the three stress support sessions; a tablet computer with a "relax and recover" programme for nurses to use with patients; a self-help booklet and DVD for nurses to give to patients; and electronic materials will also be provided on a dedicated web page which only POPPI nurses will be able to access.

The course will cover:

- Psychological challenges of patients in the critical care unit (including patient representative talks and videos)
- CBT-based psychological support techniques required to deliver stress support sessions
- Content of stress support sessions
- Observe (in person and expert videos) example stress support sessions
- Practice stress support sessions

7.4 Creating a therapeutic environment

The POPPI team will create a therapeutic environment by encouraging culture change in their unit. This will be facilitated by ensuring all critical care unit staff complete the POPPI online training and by teaching good communication skills and psychological care at the bedside. In addition, they will ensure that POPPI materials are clearly displayed (e.g. posters) and distributed (e.g. pocket cards) throughout the unit.

7.4.1 POPPI online training

The POPPI team will register all critical care unit staff for the POPPI online training. The learning is designed to aid the creation of a calm, less stressful environment by using good communication in the unit and delivering enhanced psychological care to patients.

The POPPI online training takes approximately 30 minutes to complete and comprises five sections:

1. Understanding the stresses of intensive care patients
2. Reducing stress and fear in patients
3. Communicating with distressed patients
4. Inspiring patients with confidence and hope
5. Summary and assessment.

7.5 Supervision for POPPI nurses

All POPPI nurses will be allocated a supervisor from the POPPI training team to ensure they are supported by experts during the transition and intervention periods.

Supervision will focus on specific cases, and be aimed at improving POPPI nurses' skills in delivering the stress support sessions. Initial supervision will be carried out once a POPPI nurse has delivered stress support sessions to their first patient. Once all POPPI nurses at the site have delivered stress support sessions to one patient the POPPI training team will visit POPPI nurses in their units to offer further support and the POPPI nurses will undergo a skills development assessment to ensure they meet the required levels of delivering the stress support sessions. If necessary, further support and training will be offered prior to the delivery of further sessions with patients.

POPPI nurses will continue to receive supervision either via telephone call or site visit. If necessary, extra supervision will be provided.

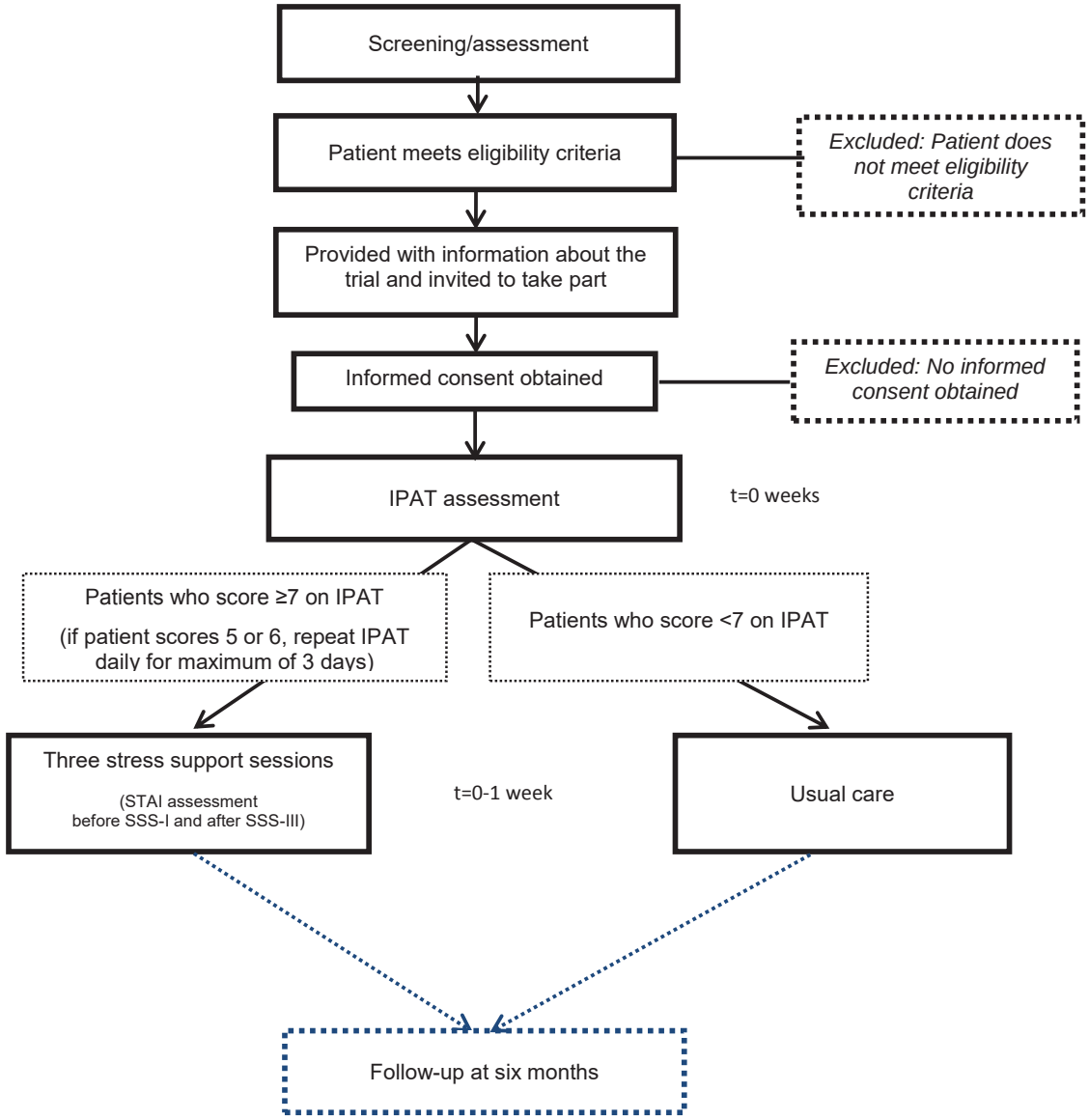
8 Transition and intervention periods – patients

8.1 Overview

Intervention sites will deliver the intervention (see section 6) to patients between months 6 to 17.

8.2 Patient timeline

Figure 5. Patient timeline during intervention period



8.3 IPAT assessment

The IPAT is a validated screening tool used to detect acute psychological stress and unusual experiences such as hallucinations in critically ill patients[51] (see Appendix B). Consented, eligible patients will be assessed using the IPAT by a trained authorised staff member (as per the Delegation Log) as soon as possible, but within 48 hours of consent being provided. A patient is deemed high-risk if they score seven or more on the IPAT and should be referred, as soon as possible, to a POPPI nurse to receive the three stress support sessions (see section 8.4). Patients who score less than seven on the IPAT will continue to receive usual care as determined by the treating clinician(s). If the patient scores five or six on the IPAT they should be reassessed daily, for a maximum of three days, until they either leave the critical care unit or the score drops below five.

8.4 Stress support sessions

The aims of the stress support sessions are:

- to reduce acute stress, fear and intrusive memories of the critical care unit before the patient leaves hospital; and
- to help patients find a path to psychological recovery and well-being after their stay in the critical care unit.

8.4.1 Delivery of stress support sessions

The three stress support sessions are to be delivered by the same POPPI nurse ideally within one week, with the first stress support session starting as soon as possible, but within 48 hours following IPAT assessment. Each session lasts approximately 30 minutes. If a patient shows signs of distress or fatigue, the session can be stopped and a new visit can be arranged at a more appropriate time.

The State Trait Anxiety Inventory (STAI, see Appendix C) will be used to assess the patients anxiety prior to session one and at the end of stress support session three. If a patient is showing serious signs of distress at the end of their three sessions, their medical team will be informed.

8.4.2 Objectives of stress support sessions

The POPPI nurses' objectives during the stress support sessions are to:

- develop a trusting relationship with the patient;
- help a patient understand the links between the experience of being in the critical care unit and a range of common psychological reactions which are often disturbing;
- increase patients' sense of control by creating opportunities to talk about psychological reactions in the critical care unit and to take an active part in managing these;
- describe and demonstrate strategies for coping with stress (e.g. listening to music and using relaxation and mindfulness techniques on the supplied tablet computer);
- re-evaluate stressful thoughts;
- reduce patients' hopelessness through watching other patients' recovery stories; and
- build on evidence of progress and getting better.

8.4.3 Components of stress support sessions

There are three common components to each stress support session: Start; Building Rapport; and Finish. In addition, each stress support session includes three additional components and is structured as follows:

Stress support session one – helping patients understand and cope with stress

- Normalise psychological reactions
- Encourage communication
- Teach coping strategies

Stress support session two – managing frightening thoughts from critical care

- Stress reactions
- Explain stressful thinking
- Teaching “check out my fear” technique

Stress support session three – creating confidence and hope for a good recovery

- Summarise key messages and review
- Action plan
- Future expectations

8.5 Audio-recording sessions

After the transition period, a sample of consented patients who have been assessed as being at high risk of psychological morbidity will be asked to consent to their stress support sessions being audio-recorded. If a patient agrees to their stress support sessions being audio-taped they will be asked to sign the Audio-recording Consent Form. This is optional and will not preclude the patient taking part in the trial or delivery of the stress support sessions. Audio recordings will be reviewed by the training team, in order to monitor treatment fidelity of the stress support sessions delivered, and will be destroyed at the end of the trial. If a patient withdraws consent for use of their session to be audio-recorded, then the audio file will be deleted and no longer used.

9 Patient follow-up

Six months after recruitment, consented patients will be asked to complete questionnaires on psychological distress, mood, health-related quality of life and use of health services. In particular, the questionnaires will include measures of PTSD symptom severity (using the PTSD Symptom Scale – Self-Report version (PSS-SR)[52] - see Appendix D), depression and anxiety (using the Hospital Anxiety and Depression Scale (HADS)[53] – see Appendix E), health-related quality of life (using the EuroQoL EQ-5D-5L – see Appendix F) and health services resource use (using Health Services Questionnaire – see Appendix G). Patients will be sent the questionnaires by post (including a stamp addressed envelope and a pen) by ICNARC CTU. A gift voucher [54] will also be included for patients followed-up in the last four months of the trial. Non-responders will be telephoned three weeks later, and asked to check whether they have received the questionnaire. If preferable for the patient, they will be given the option to complete the questionnaire over the telephone. If completed follow-up questionnaires, received by ICNARC CTU, indicate the presence of signs of serious stress or low mood, a referral letter from Dr Wade, Lead Clinical Investigator, will be sent to the patient's General Practitioner (GP) and the recruiting site (if requested).

10 Outcomes

10.1 Primary outcomes

10.1.1 Clinical evaluation

The primary outcome for the clinical evaluation will be patient-reported PTSD symptom severity at six months, measured using the PSS-SR, which conforms to all DSM-IV diagnostic criteria for PTSD and which has been validated for use in critical care unit survivors.

10.1.2 Economic evaluation

The primary outcomes for the economic evaluation will be incremental costs (cost-effectiveness analysis (CEA)), quality-adjusted life years (QALYs) and net monetary benefit at six months.

10.2 Secondary outcomes

Secondary outcomes will be:

- days alive and free from sedation to day 30;
- duration of critical care unit stay;
- PSS-SR greater than 18 points at six months;[55]
- depression at six months, measured using the Hospital Anxiety and Depression Scale (HADS);
- anxiety at six months, measured using the HADS; and
- health-related quality of life (HRQoL) at six months, measured by the EuroQol (EQ-5D-5L) questionnaire.

11 Power calculation

11.1 Pre-trial power calculation

The power calculation was completed using the approach of Hussey & Hughes (2007)[56] to achieve 90% power to detect a reduction from 6 points to 3.1 points ($p<0.05$) in the mean PSS-SR at six months, and was based on the following assumptions:

- Mean (6) and standard deviation (7.5) of the PSS-SR were taken from patients in the feasibility study.
- Estimated intra-cluster correlation (ICC) of 0.138 – between-site coefficient of variation 0.5 corresponding to between-site standard deviation 3 (conservative estimate as no multicentre data available).[57] Note: the inclusion of a baseline recruitment period means that the sample size calculation is less sensitive to the degree of clustering.[56]
- Treatment effect of a reduction of 2.9 points on the PSS-SR based on: reliable change index for the PSS-SR of 8.6 points[58] being observed in 40% of eligible patients in the intervention periods assessed as being at high risk of psychological morbidity using the IPAT, with 16% of recruiting patients declining the intervention.[32].
- Harmonic mean of the number of patients completing follow-up (52 per site per annum – corresponding to 22 in a five-month period) based on data from the CMP.

With the design and the above assumptions, the estimated total number of patients recruited (based on CMP data) for the RCT would be 1,914 patients from the twenty-four sites. It is anticipated that 438 will be assessed using the IPAT, of which 175 (40%) will be assessed as being at high risk of psychological morbidity and receive the stress support sessions.

11.2 Final review of assumptions in pre-trial power calculation

During recruitment, in consultation with the TSC and DMEC, a review of assumptions underlying the pre-trial power calculation once outcome data were available for patients recruited during the five-month baseline period in both intervention and control sites. This review, undertaken using data available on 9 August 2016, identified the following re-estimation of the assumptions:

- Mean (10.3) and standard deviation (10.8) of the PSS-SR.
- ICC of 0.087 (95% confidence interval 0 to 0.192) [with mean, standard deviation and ICC estimated using all available data from the previous observational study, the feasibility study and the baseline period of the cluster-RCT]
- Treatment effect of a reduction of 4.2 points on the PSS-SR – estimated by retaining the same effect size as a multiple of the within-site standard deviation.
- Harmonic mean of the number of patients completing follow-up (30.7 per site per annum – corresponding to 12.8 in a five-month period) estimated using observed data from the baseline period.

This review of assumptions established that the planned design had an anticipated 78% power under the observed parameter estimates (allowing for uncertainty in the between-site variation, between 73% and 85% power).

Consequently, the decision was taken to extend recruitment in all sites to the end of planned recruitment in stagger 3 sites (corresponding to an harmonic mean of 16.5 patients completing follow-up per site during the intervention period, allowing for the variation from five months to nine months duration across staggers). With this extension to recruitment, the planned design had an anticipated 85% power (allowing for uncertainty in the between-site variation, between 79% and 91% power). It was anticipated that, with this extension to recruitment, the estimated total number of patients recruited would be 1,378. Recruitment continued to be

monitored to ensure 1,378 or more patients were recruited. A final decision to extend recruitment by an additional two months in all sites was taken to ensure this minimum number was achieved.

12 Data collection and management

12.1 Data collection – patients

The following data is to be collected by site staff whilst the patient is in-hospital. These data must be transcribed onto the paper Case Report Forms (CRF) (provided to sites) prior to entering onto the secure electronic CRF (eCRF). The original paper CRFs must be kept at site. All entries must be clear and legible. The use of abbreviations and acronyms must be avoided. The PI is responsible for the accuracy of all data reported in the paper CRF. All paper CRFs must be completed and signed by staff listed on the Delegation Log and authorised by the PI to perform this duty.

Any corrections made to a paper CRF at site must be made by drawing a single line through the incorrect item ensuring that the previous entry is not obscured. Each correction must be dated and initialled. Correction fluid must not be used. The amended paper CRF must be retained securely at site. These changes must also be made on the eCRF.

Security of the eCRF is maintained through user names and individual permissions approved centrally by ICNARC CTU. Central back-up procedures are in place. Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act.

Data collected for all patients:

Patient details

- Identifiers
- Sociodemographics

Baseline data

- Date and time of critical care unit admission
- Eligibility criteria
- Date and time of consent
- Illness severity scores (including quality of life)
- Prior delirium (assessed by CAM-ICU), anxiety or depression

Critical care unit stay data

- Delirium
- Drugs received
    - Sedatives, anxiolytics, anaesthetics, sleep medications, antipsychotics, analgesics, anti-depressants and vasoactive agents
- Mechanical ventilation received

Hospital discharge data

- Discharge status
- Discharge date/date and time of death

Data collected for patients recruited during the intervention period:

POPPI Intervention data

- IPAT score
- STAI scores before stress support session one and after stress support session three
- Delivery of the stress support sessions

The following data is to be collected by questionnaires sent directly to all patients. The detailed process for collection is outlined in section 7. Patients will also be given the opportunity to feed back their experiences of the stress support sessions via email or an online form.

Follow-up data

- PSS-SR
- HADS
- EQ-5D-5L
- Health Services Questionnaire

In addition, data will be linked to the CMP, the national clinical audit of adult critical care coordinated by ICNARC, which is ongoing in all adult, general critical care units in England, Wales and Northern Ireland. Linked data will include demographics, surgical status, acute severity of illness and duration of organ support and duration of critical care unit stay. Support for the collection and use of patient identifiable data has been approved for the CMP by the Patient Information Advisory Group (PIAG) under Section 251 of the NHS Act 2006 (originally enacted under Section 60 of the Health and Social Care Act 2001) – Approval Number: PIAG 2-10(f)/2005. Section 251 support is reviewed annually by PIAG and covers all aspects of data management including data security.

On entry into the study, the patient's GP will be sent a letter confirming recruitment. This will also include a form that can be completed to the returned to the ICNARC CTU if the GP is aware of any new mental health difficulty that has arisen since recruitment onto the study.

Table 1 Patient data collection schedule

	Baseline (at point of recruitment)	End of critical care unit stay	Intervention sites only			Six months post-recruitment
			Before SSS-I	During sessions	After SSS-III	
Collected in-hospital						
Patient details	✓					
Clinical data	✓					
Critical care unit stay data		✓				
IPAT			✓			
Delivery of stress support sessions				✓		
STAI					✓	
Follow-up questionnaires sent to patients						
PSS-SR						✓
HADS						✓
EQ-5D-5L						✓
Health Services Questionnaire						✓

12.1.2 Data management

The ICNARC CTU will work closely with staff at participating sites to ensure accurate (complete, valid and reliable) data. Extensive completeness, range and consistency checks will further enhance the quality of the data. Two levels of data validation will be incorporated into the eCRF. The first prevents obviously erroneous data from being entered, e.g. entering a date of birth that occurred after the date of consent. The second level checks for data completeness and any unusual data entered, e.g. a physiological variable, such as blood pressure, that was outside of the pre-defined range. Site staff will be able to generate data validation reports, listing all outstanding data queries, at any time via the eCRF. The site PI is responsible for ensuring that all data queries are resolved. Ongoing data entry, validation at adherence to the trial protocol at sites will be closely monitored by ICNARC CTU and any concerns will be raised with the site PI.

12.2 Data collection – sites

Prior to randomisation the following data will be collected, via the process evaluation, for each participating site:

- Provision of current psychological support
- Layout of critical care unit

12.3 Data collection – site staff

The following data will be collected on the site staff's participation in POPPI – only applicable to the intervention sites:

POPPI nurses

- Basic demographic data
- Self-efficacy questionnaire – completed by POPPI nurses prior to and after POPPI nurse Training course
- Skills development assessment scale – completed by assessors

All staff data

- End of POPPI online training: number (%) and demographics of critical care staff completing course; knowledge test; number of attempts to pass knowledge test and number (%) of those who passed the test.

12.4 Process evaluation

The process evaluation for intervention sites will consider both quantitative and qualitative data.

Quantitative data will include assessments of nurse competence following the training course, and treatment fidelity of the stress support sessions. In particular, treatment fidelity will be assessed with a purpose-built measure of adherence to therapy assessed by independent reviewers based on a random sample of sessions digitally recorded by the POPPI nurses and sent centrally for evaluation.

The process evaluation will also incorporate site visits to intervention sites to observe and discuss the delivery of the intervention with the POPPI nurses and wider critical care unit staff. Each intervention site will receive a visit from the POPPI training team during the intervention period. The site visit will assess the delivery of three elements of the intervention:

- the therapeutic approach to interaction with critical care unit patients
- routine assessment of acute psychological distress using the IPAT
- stress support sessions

Qualitative data will be collected in the form of researcher observations, interviews with staff and structured field notes.

12.5 Monitoring

Sites must agree to allow trial-related monitoring and audits by providing direct access to source data/documents, as required. Patients' informed consent for this will also be obtained. Frequency of monitoring visits will be outlined in the POPPI Monitoring Plan and will consist of all sites visited at least once to monitor recruitment and adherence with the trial protocol. Additional on-site monitoring visits may be scheduled where there is evidence or suspicion of non-adherence by a site to important aspect(s) of the trial requirements.

Following the monitoring visit, the ICNARC CTU will provide the site with a monitoring report, which will summarise the documents reviewed, along with any findings. The PI at each site will be responsible for ensuring that the findings from the monitoring visit are addressed.

13 Statistical methods

13.1 Statistical methods – clinical effectiveness

The primary analysis for the clinical evaluation will determine if there is a significant difference in the mean PSS-SR at six months between patients recruited during the intervention period in intervention sites compared with control sites of the cluster-RCT using a generalised linear mixed model (GLMM) at the individual patient level (patients nested within sites and time periods) including a random effect of site and a fixed effect of period (baseline or intervention), and adjusted for site-level factors included within the restricted randomisation algorithm.

For the primary outcome, the link function will be the identity link (i.e. linear regression) and standard errors will be estimated using robust variance method, to ensure that deviations from the model's assumption such as non-linear relationship between exposure and outcome as well as over/under dispersion of data are adjusted for to provide meaningful precision estimates.[56]

A secondary analysis will adjust for pre-specified baseline factors associated with poor psychological outcome (e.g. sedation) and ability to resource and deliver the intervention (e.g. size of critical care unit, teaching status) at both patient and site level. Results of the GLMMs will be reported as differences in means, 95% confidence intervals (CIs) and p-values.

Analyses of secondary outcomes will be conducted using GLMMs, with the identity link (i.e. linear regression) for continuous secondary outcomes, reported as differences in means with 95% CI and the logit link (i.e. logistic regression) for binary secondary outcomes, reported as odds ratios with 95% CI.

The above analyses will evaluate the effectiveness of the intervention among all patients meeting the inclusion criteria and consenting to follow-up, based on the intention to treat principle. A further secondary analysis will use structural mean models with an instrumental variable of allocated treatment to estimate the efficacy (adherence adjusted causal effect) of the stress support sessions among those patients consenting to psychological assessment and stress support sessions, assessed as being at high risk of psychological morbidity and receiving stress support sessions.[59]

13.2 Statistical methods – process evaluation

Analysis of the process evaluation will use a combination of qualitative and quantitative methods to assess and describe the variation in the delivery of the intervention across sites.[60] Analysis of the process evaluation will be conducted before the outcome evaluation to avoid any bias in the interpretation of the process data and to generate hypotheses that may be subsequently tested in statistical analyses of integrated process and outcome data. The structural mean models described above will be extended to incorporate additional potential mediator variables on the causal pathway between treatment allocation and treatment effect, e.g. nurse competence following training, adherence to the therapeutic approach and adherence to therapy.[61]

13.3 Statistical methods – cost-effectiveness

A full CEA will be undertaken to assess the relative cost-effectiveness of psychological assessment followed by stress support sessions for those assessed as being at high risk of psychological morbidity, versus usual care. Resource use and outcome data collected as part of the cluster-RCT will be used to report cost-effectiveness at six months and to project the lifetime cost-effectiveness of each strategy.

The cost analysis will take a health and personal health services perspective. Resource use data from the site visits, cluster-RCT dataset and six-month questionnaires will be combined with unit costs from the NHS

Payment by Results database and from local Trust Finance Departments, to report the total costs per patient at six months for intervention versus usual care.[62, 63]

HRQoL data from the EQ-5D-5L questionnaires at six months will be combined with survival data using linear interpolation to report QALYs at six months. The CEA will report the mean (95% confidence interval) incremental costs, QALYs and net monetary benefit at six months.

The CEA will use multilevel linear regression models that allow for clustering[64] including a random effect of site and a fixed effect of period. The analysis will adjust for pre-specified baseline covariates at both patient and site level.

Lifetime cost-effectiveness will be projected using a decision model informed by the best evidence on long-term survival and HRQoL after critical care unit stay.[65, 66] The long-term modelling will extrapolate from the cluster-RCT data by fitting alternative parametric survival curves (e.g. Weibull, exponential, lognormal, log logistic and Gompertz) to the observed survival data. The chosen method of extrapolation for the base case will be the one judged most plausible.[67] In the base case, quality of life calculated at six months will be assumed to apply to each subsequent year of life, after allowing for decrements in quality of life according to advancing age. Predicted survival and HRQoL will be combined to report lifetime QALYs, and to project lifetime incremental costs, incremental QALYs, and incremental net benefits for the alternative strategies of care. Sensitivity analyses will test whether the results are robust to methodological assumptions (e.g. specification of the statistical model, extrapolation approach, alternative HRQoL assumptions, and learning curve effects).

14 Monitoring and oversight

14.1 Trial Management Group (TMG)

All day to day management of POPPI will be the responsibility of Professor Kathryn Rowan (Chief Investigator) and Paul Mouncey (Senior Trial Manager). Staff who work on POPPI (including the Trial Statistician, Jerome Wulff, and Assistant Trial Manager, Alvin Richards-Belle) will meet regularly to discuss, the progress of the trial and findings from other related research.

14.2 Trial Steering Committee (TSC)

The progress of the trial will be monitored and supervised by the TSC. At least 75% of the members will be independent (including the Chair). It will also consist of at least two service user representatives, the Chief Investigator and the Lead Clinical Investigator.

14.3 Data Monitoring and Ethics Committee (DMEC)

The DMEC will include experienced critical care clinicians and an experienced statistician. All members of the DMEC will be independent of both the trial and the TSC. The DMEC will operate under the DAMOCLES Charter[68],and will report to the TSC, making recommendations on the continuation, or not, of the trial.

14.4 Role of the ICNARC CTU

The ICNARC CTU will be responsible for the day to day management and coordination of the trial and will act as custodian of the data. The ICNARC CTU will ensure that all SAEs are appropriately reported to the REC.

15 Trial closure

15.1 End of trial

The end of the trial will be when the final patient has completed their six months follow-up. At which point the Declaration of End of Trial Form will be submitted to the participating ethical committee, as required.

15.2 Archiving of trial documentation

At the end of the trial, the ICNARC CTU will archive securely all centrally held trial related documentation for a minimum of 10 years. Arrangements for its confidential destruction will then be made. It is the responsibility of PIs at each site to keep data and all essential documents relating to the trial held at site for a minimum of 10 years after the end of the trial and in accordance with national legislation and for the maximum period of time permitted by the site, as per local policy.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of Good Clinical Practice (GCP) and all applicable regulatory requirements.

If a patient withdraws consent for any data to be used it will be confidentially destroyed.
The ICNARC CTU will notify sites when documentation held at sites may be archived. All archived documents must still be available for inspection and monitoring by appropriate authorities and the ICNARC CTU upon request.

15.3 Early discontinuation of trial

The trial may be stopped before completion by the TSC. This can be upon recommendation of the DMEC. Sites will be informed in writing by the ICNARC CTU of reasons for early closure and the actions to be taken with regard to treatment of patients. Patients should continue to be followed up as per protocol.

15.4 Withdrawal from trial participation by a site

Should a site choose to close to recruitment the PI must inform the ICNARC CTU in writing. Follow-up as per the protocol must continue for all patients recruited into POPPI at that site. Sites that contravene the POPPI Trial Protocol and the Clinical Trial Site Agreement will be subject to review by the TMG and Sponsor and may be suspended or closed down by the ICNARC CTU.

16 Ethical and regulatory compliance

16.1 Research ethics approval

This Protocol, Patient Information Sheets, Informed Consent Forms and other trial-related documents will be reviewed and approved by the Sponsor and Research Ethics Committee (REC) with respect to scientific content and compliance with applicable research regulations involving human subjects. Details of the informed consent procedure are reported in section 4.2.

16.2 Protocol amendments

Any modification to the protocol and/or trial-related documents which may impact on the conduct of the trial, potential benefit to patients or patient safety will require a formal amendment to the protocol. Such amendments will be agreed by the Sponsor, TMG and approved by the REC. Administrative changes of the protocol, which have no impact on the conduct of the trial or patient safety, will be agreed by the Sponsor and TMG. The REC will be notified but formal approval will not be required.

16.3 Confidentiality

The POPPI trial will be managed according to the Medical Research Council's (MRC) Guidelines for Good Clinical Practice in Clinical Trials and Good Research Practice: Principles and Guidelines, which are based on the principles of the International Conference on Harmonisation (ICH) GCP. The ICNARC CTU has developed its own policies and procedures, based on these MRC guidelines, for the conduct of all its research activities. In addition, ICNARC has contractual confidentiality agreements with all members of staff. Policies regarding alleged scientific misconduct and breach of confidentiality are reinforced by disciplinary procedures.

The ICNARC CTU will act to preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Any patient identifiable data leaving the hospital will be encrypted to ensure anonymity. All procedures for handling, processing, storing and destroying data are compliant with the Data Protection Act 1998.

16.4 Withdrawal of patients consent

In consenting to the trial, patients are consenting to assessments, intervention (where applicable), follow-up and data collection.

If a patient explicitly states their wish not to contribute further data to the trial their decision must be respected and the ICNARC CTU notified in writing. Details should be recorded in the patient's hospital records and no further trial data will be requested.

17 Dissemination policy

The progress and results of POPPI will be widely and actively disseminated. The results will be submitted to relevant peer-review journals for publication. They will also be presented at: national and international critical care and clinical and health psychology conferences/meetings; the Annual Meeting of the ICNARC Case Mix Programme; and the Annual Meeting of the UK Critical Care Research Forum.

A Study Report to the NIHR HS&DR programme will present a detailed description of the trial and the results along with recommendations for future policy, practice and research.

18 Sponsorship and Indemnity

ICNARC is the Sponsor for the POPPI cluster-RCT and holds professional indemnity insurance (Markel International Insurance Co Ltd) to meet the potential legal liability of the Sponsor and employees for harm to participants arising from the design and management of the research.

Indemnity to meet the potential legal liability of investigators/collaborators for harm to participants arising from the conduct of the research is provided by the NHS indemnity scheme or through professional indemnity.

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Appendix A: Protocol version history

Protocol:		**Amendments:**		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version.**
v1.0	20 April 2015	N/A	N/A	N/A
v2.0	25 January 2016	Substantial amendment 1	9 11 12	Revision of patient follow-up questionnaires Revision of the sample size Addition of a GP reporting form
N/A	24 November 2016	Non-substantial amendment 2	1.1 3.2 5.1 7 7.1 8.1	Increased recruitment period from 15 months to 17 months
v2.1	2 January 2017	Substantial amendment 2	11	Inclusion of final review of assumptions in pre-trial power calculation

Appendix B: Intensive care Psychological Assessment Tool (IPAT)

I would like to ask you some questions about your stay in intensive care, and how you've been feeling in yourself. These feelings can be an important part of your recovery. To answer, please circle the answer that is closest to how you feel, or answer in any way you are able to, e.g. by speaking or pointing.

	Since you've been in the intensive care unit:	**A**	**B**	**C**
1	Has it been hard to communicate?	No	Yes, a bit	Yes, a lot
2	Has it been difficult to sleep?	No	Yes, a bit	Yes, a lot
3	Have you been feeling tense?	No	Yes, a bit	Yes, a lot
4	Have you been feeling sad?	No	Yes, a bit	Yes, a lot
5	Have you been feeling panicky?	No	Yes, a bit	Yes, a lot
6	Have you been feeling hopeless?	No	Yes, a bit	Yes, a lot
7	Have you felt disorientated (not quite sure where you are)?	No	Yes, a bit	Yes, a lot
8	Have you had hallucinations (seen or heard things you suspect were not really there)?	No	Yes, a bit	Yes, a lot
9	Have you felt that people were *deliberately* trying to harm or hurt you?	No	Yes, a bit	Yes, a lot
10	Do upsetting memories of intensive care keep coming into your mind?	No	Yes, a bit	Yes, a lot

Do you have any comments to add in relation to any of the answers?

_____

_____

SCORING

Any answer in column A = 0 points

Any answer in column B = 1 point

Any answer in column C = 2 points

Sum up the scores of each item for a total IPAT score out of 20

Cut-off point ≥7 - indicates patient at risk

Appendix C: State-Trait Anxiety Inventory (STAI)

Please read the words below and after each one, circle the answer that is closest to how you have been feeling in the past few days.

During the past few days I have been feeling…					
1	**Calm**	Not at all	Somewhat	Moderately	Very much
2	**Tense**	Not at all	Somewhat	Moderately	Very much
3	**Upset**	Not at all	Somewhat	Moderately	Very much
4	**Relaxed**	Not at all	Somewhat	Moderately	Very much
5	**Content**	Not at all	Somewhat	Moderately	Very much
6	**Worried**	Not at all	Somewhat	Moderately	Very much

Appendix D: Patient Emotional Reactions Questionnaire (PSS-SR)

These questions are about reactions people may have after intensive care.

Please circle how often a problem has bothered you **in the past month**.

1. Have you had upsetting thoughts or images about intensive care that came into your head when you didn't want them to?

Not at all	**Once per week or less**	**2 – 4 times per week**	**5 or more times per week**

2. Have you had bad dreams or nightmares about intensive care?

Not at all	**Once per week or less**	**2 – 4 times per week**	**5 or more times per week**

3. Have you relived your time in intensive care, acting or feeling as if it were happening again?

Not at all	**Once per week or less**	**2 – 4 times per week**	**5 or more times per week**

4. Have you felt emotionally upset when you were reminded of your time in intensive care (e.g. feeling scared, angry, sad, guilty)?

Not at all	**Once per week or less**	**2 – 4 times per week**	**5 or more times per week**

5. Have you had physical reactions when you remember your time in intensive care (e.g. breaking into a sweat, heart beating fast?)

Not at all	**Once per week or less**	**2 – 4 times per week**	**5 or more times per week**

6. Have you tried not to think about, talk about, or have feelings about your time in intensive care?

Not at all	**Once per week or less**	**2 – 4 times per week**	**5 or more times per week**

7. Have you tried to avoid activities, people or places that remind you of your time in intensive care?

Not at all	**Once per week or less**	**2 – 4 times per week**	**5 or more times per week**

8. Have you found that you were not able to remember an important part of your time in intensive care?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

9. Have you had much less interest in important activities?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

10. Have you felt distant or cut off from people around you?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

11. Have you felt emotionally numb (unable to cry or have loving feelings?)

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

12. Have you felt as if your future plans or hopes would not come true?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

13. Have you had trouble falling or staying asleep?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

14. Have you felt irritable or had fits of anger?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

15. Have you had trouble concentrating (e.g. forgetting what you read, losing track of a story on television)?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

16. Have you been too alert (for example, checking to see who is around you, not being comfortable with your back to a door)?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

17. Have you been jumpy or easily startled (for example, when someone walks up behind you)?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

If you reported any problems in your answers to questions 1-17, then please answer the following questions:

The next two questions are about the timing of emotional reactions people may have after intensive care.

Please circle the answer that is closest to your experience.

18. How long have you experienced these problems?

Not at all	Less than 1 month	1 to 3 months	More than 3 months

19. If you reported any problems in your answers to questions 1-17, how long after leaving Intensive care did these problems begin?

I have not had these type of problems	Less than 1 month	1 to 3 months	More than 3 months

In the past month have the above problems:

20. Affected your relationships or social life?

Not at all	A little Bit	Moderately	Quite a bit	Extremely

21. Affected your work or ability to work?

Not at all	A little Bit	Moderately	Quite a bit	Extremely

22. Affected any other important part of your life such as parenting, or school or college work, or other important activities?

Not at all	A little Bit	Moderately	Quite a bit	Extremely

Appendix E: Patient Mood Questionnaire (HADS)

How are you **CURRENTLY** feeling?
Please circle one answer for each item.

1. I feel tense or wound up

Most of the time	A lot of the time	From time to time, occasionally	Not at all

2. I still enjoy the things I used to enjoy

Definitely as much	Not quite so much	Only a little	Hardly at all

3. I get a sort of frightened feeling as if something awful is about to happen

Very definitely and quite badly	Yes, but not too badly	A little, but it doesn't worry me	Not at all

4. I can laugh and see the funny side of things

As much as I always could	Not quite so much now	Definitely not so much now	Not at all

5. Worrying thoughts go through my mind

A great deal of time	A lot of the time	From time to time, but not often	Only occasionally

6. I feel cheerful

Not at all	Not often	Sometimes	Most of the time

7. I can sit at ease and feel relaxed

Definitely	Usually	Not often	Not at all

8. I feel if I am slowed down

Nearly all the time	Very often	Sometimes	Most of the time

9. I get a sort of frightened feeling like 'butterflies' in the stomach

Not at all	Occasionally	Quite often	Very often

10. I have lost interest in my appearance

Definitely	I don't take as much care as I should	I may not take quite as much care	I take just as much care as ever

11. I feel restless as I have to be on the move

Very much indeed	Quite a lot	Not very much	Not at all

12. I look forward with enjoyment to things

As much as I ever did	Rather less than I used to	Definitely less than I used to	Hardly at all

13. I get sudden feelings of panic

Very often indeed	Quite often	Not very often	Not at all

14. I can enjoy a good book or radio or tv program

Often	Sometimes	Not often	Very seldom

Appendix F: Patient Health Questionnaire (EuroQoL - EQ-5D-5L)

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

MOBILITY

I have no problems in walking about ❑

I have slight problems in walking about ❑

I have moderate problems in walking about ❑

I have severe problems in walking about ❑

I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑

I have slight problems washing or dressing myself ❑

I have moderate problems washing or dressing myself ❑

I have severe problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

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

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑

I am slightly anxious or depressed ❑

I am moderately anxious or depressed ❑

I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

We would like to know how good or bad your health is **TODAY**.

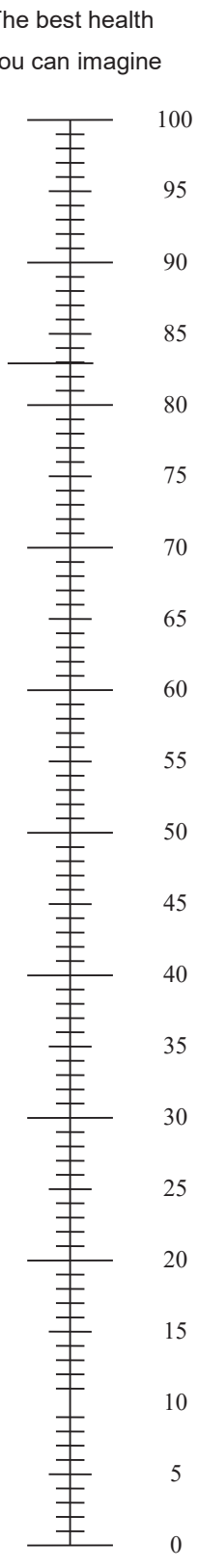
This scale is numbered from 0 to 100.

100 means the **best** health you can imagine.
0 means the **worst** health you can imagine.

Mark an **X** on the scale to indicate how your health is **TODAY**.

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix G: Health Services Questionnaire

Health services

These questions will help us understand the care you needed after leaving the hospital.

Please answer the multiple choice questions by putting a ✓ in **ONE** box for each question.

Q1 Where are you now?

- ◯ At home (your own home, or a relative's home)
- ◯ In residential care (e.g. nursing home, hospice)
- ◯ In short-term rehabilitation
- ◯ In long-term rehabilitation
- ◯ In hospital
- ◯ Other (please specify): _____

Q2 Hospital stays

Since you left hospital on
have you stayed overnight in hospital for any reason?

- ◯ **No** – *Please go to Q3*
- ◯ **Yes** – *Please give details about the number of stays below*

For EACH TIME you stayed in hospital please answer the following:

	Number of nights		1 – 3 nights	4 – 10 nights	11 or more nights	Did you spend any part of your stay in intensive care?
1st stay	☐	*Or tick...*	◯	◯	◯	◯
2nd stay	☐	*Or tick...*	◯	◯	◯	◯
3rd stay	☐	*Or tick...*	◯	◯	◯	◯
4th stay*	☐	*Or tick...*	◯	◯	◯	◯

**If you have stayed in hospital more than 4 times, please could you provide information on these further hospital stays in Q7 of the questionnaire.*

Q3 **Visits to hospital outpatients**

Outpatient visits are when a patient comes to the hospital to see a specialist (e.g. consultant) but does not stay overnight.

Since you left hospital on
have you visited hospital outpatients about ANY ASPECT of your health?

○ **No** – *Please go to Q4*

○ **Yes** – *Please give details about the number of outpatients visit(s) below*

Number of visits		1 – 3 visits	4 – 10 visits	11 or more visits
☐	*Or tick...*	○	○	○

Q4 **Visits to health care providers**

Since you left the hospital on
have you visited any of the health care providers listed below
about ANY ASPECT of your health?

○ **No** – *Please go to Q5*

○ **Yes** – *Please give details about the number of visits below*

For EACH PROVIDER please answer the following:

Did you visit this provider?	(please tick)	Number of visits		1 – 3 visits	4 – 10 visits	11 or more visits
GP	○	☐	*Or tick...*	○	○	○
Nurse at your GP clinic	○	☐	*Or tick...*	○	○	○
Nurse at hospital or elsewhere	○	☐	*Or tick...*	○	○	○
Health visitor	○	☐	*Or tick...*	○	○	○
Critical care follow-up clinic	○	☐	*Or tick...*	○	○	○

POPPI

Health services

Q5 Visits to your home by health care providers

Since you left hospital on
have you had home visits from any of the following health care providers about ANY ASPECT of your health?

○ **No** – *Please go to Q6*

○ **Yes** – *Please give details about the number of visits below*

For EACH PROVIDER please answer the following:

Were you visited at home by this provider?	(please tick)	Number of visits		1 – 3 visits	4 – 10 visits	11 or more visits
GP	○		*Or tick...*	○	○	○
Nurse from your GP clinic	○		*Or tick...*	○	○	○
Health visitor or district nurse	○		*Or tick...*	○	○	○

Q6 Visits to other service providers

Since you left hospital on
have had contact (either visits to the provider or home visits) with any of the following service providers about ANY ASPECT of your health?

○ **No** – *Please go to Q7*

○ **Yes** – *Please give details about the number of visits below*

For EACH PROVIDER please answer the following:

Have you had contact with any of these providers?	(please tick)	Number of visits		1 – 3 visits	4 – 10 visits	11 or more visits
Occupational therapist	○		*Or tick...*	○	○	○
Speech and Language therapist	○		*Or tick...*	○	○	○
Physiotherapist	○		*Or tick...*	○	○	○
Psychiatrist	○		*Or tick...*	○	○	○
Psychiatric nurse	○		*Or tick...*	○	○	○
Psychologist	○		*Or tick...*	○	○	○
Counsellor	○		*Or tick...*	○	○	○

POPPI

Health services

Q7 **Other services not listed so far**

Since you left hospital on
have you had further hospital stays or used any any other health care services for ANY ASPECT of your health that you haven't included previously?

○ **No** – *Please go to Q8*

○ **Yes** – *Please give details about the number of visits below*

For EACH PROVIDER please answer the following:

Type of service provider	Number of visits	Reason

Q8 Your views are important to us. Please feel free to provide any other comments you have in the box below.

Thank you for your time

Trial Protocol summary of changes

Protocol v1.0, 20 April 2015

Original protocol

Protocol v2.0, 25 January 2016

1) Replacement of the Centre for Epidemiological Studies Depression Scale patient follow-up questionnaire by the Hospital Anxiety and Depression Scale, as the Trial Management Group felt it would be important to understand the effect of the intervention on patients' depression and anxiety, rather than solely depression.

2) Update of power calculation. Following completion and analysis of the feasibility study and prior to the start of recruitment to the cluster-RCT, the assumptions underlying the initial pre-feasibility study power calculation were reviewed, and ratified by the Data Monitoring and Ethics Committee (DMEC), using results from the feasibility study.

3) Addition of a form to the GP letter for to enable them to inform the ICNARC CTU of any new patient significant psychological difficulties that they may be aware of.

4) Minor typographical and administrative changes.

Protocol v2.1, 2 January 2017

1) Update of power calculation. In consultation with the Independent Chairs and members of the Trial Steering Committee (TSC) and the DMEC a further review of the assumptions underlying the pre-cluster-RCT power calculation once outcome data were available for patients recruited during the five-month baseline period in both intervention and control sites.

2) Increased recruitment period from 15 months to 17 months.

3) Minor typographical and administrative changes.

Protocol v2.2, 6 March 2017

1) On the recommended by the TSC, a £5.00 gift voucher for participants receiving their follow-up questionnaire at six months post-randomisation was included to maximise response rates.

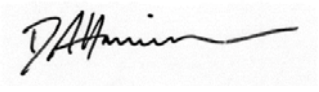
Provision Of Psychological support
to People in Intensive care

Psychological Outcomes following a nurse-led Preventative Psychological Intervention for critically ill patients (POPPI) trial

Statistical Analysis Plan

Version 1.0, 10/08/2017

REC number:	15/SC/0287
Trial sponsor:	ICNARC
Trial sponsor reference:	ICNARC/01/03/14
Trial funder:	NIHR HS&DR Programme
Funder reference:	12/64/124
ISRCTN number:	ISRCTN53448131
NIHR CRN Portfolio ID number:	18940
Author:	Dr Jerome Wulff

Role, Name and Position	Signature	Date
Chief investigator: Prof Kathryn Rowan (Director of Scientific & Strategic Development/CTU Director, ICNARC)		10/08/2017
Senior Statistician: Dr David Harrison (Head Statistician, ICNARC)		10/08/2017

Version history

Version number	Date	Summary of main changes from previous versions
1.0	10/08/2017	N/A

Abbreviations

AIC	Akaike Information Criteria
BIC	Bayesian Information Criteria
CEA	Cost Effectiveness Analysis
CES-D	Centre for Epidemiologic Studies Depression scale
CI	Confidence Intervals
Cluster-RCT	Cluster-Randomised Controlled Trial
CMP	Case Mix Programme
CSR	Clinical Study Report
EQ-5D	European Quality of Life Scale
GCS	Glasgow Coma Scale
GLMM	General/Generalised Linear Mixed Model
HRQoL	Health Related Quality of Life
ICNARC	Intensive Care National Audit and Research Centre
IMD	Index of Multiple Deprivation
IPAT	Intensive care Psychological Assessment Tool
ITT	Intent-to-treat population
NHS	National Health Service
NMB	Net Monetary Benefit
PDS	Post-traumatic Stress Diagnostic Scale
POPPI	Psychological Outcomes following a nurse-led Preventative Psychological Intervention for critically ill patients
PP	Per-Protocol Population
PTSD	Post-Traumatic Stress Disorder
QALYs	Quality Adjusted Life Years
RCT	Randomised Controlled Trial
RASS	Richmond Agitation Sedation Scale
SAP	Statistical Analysis Plan
STAI	State Trait Anxiety Inventory

Table of contents

1. Background and rationale

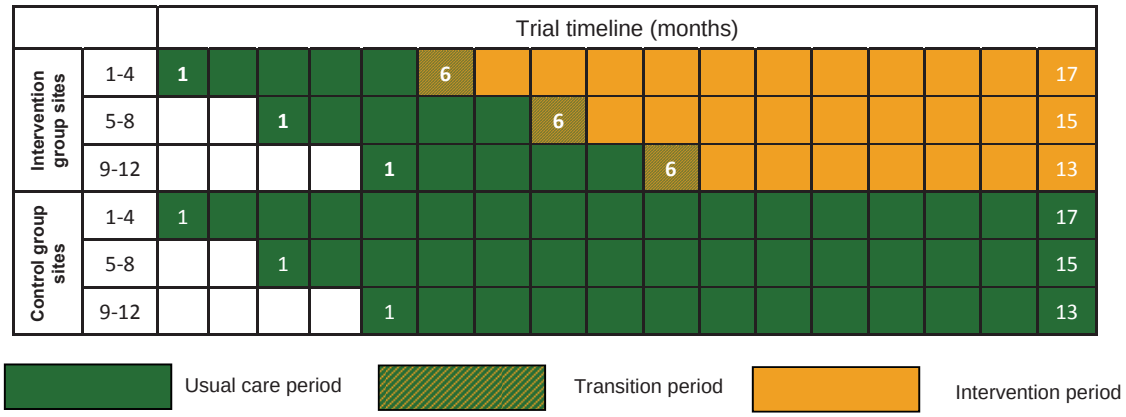
The POPPI (Psychological Outcomes following a nurse-led Preventative Psychological Intervention for critically ill patients) trial ("the Trial") is a cluster-randomised controlled trial (cluster-RCT) comparing a complex nurse-led preventative psychological intervention with usual care in reducing patient-reported post-traumatic stress disorder (PTSD) symptom severity, and other reported psychological morbidities at six months.

The study design (Figure 1) is of 24 sites, randomly assigned to either intervention or control (usual care) groups, each recruiting for between 13 and 17 months, with a staggered start to allow for roll-out of the intervention. The end of the Trial will be when the final patient has completed their six months follow-up.

The purpose of this Statistical Analysis Plan (SAP) is to document the planned analyses to be carried out to support the completion of the Final Report to the study funder and for inclusion in manuscripts for publication in the scientific literature. Additional exploratory analyses, not necessarily identified in this SAP, may also be performed. Any post-hoc or unplanned analyses not identified in this SAP will be clearly identified as such in the respective Report/manuscript.

This SAP has been agreed in advance of inspecting any outcome data from the intervention period of the Trial, so that data-derived decisions in the analyses are avoided.

Figure 1. Cluster-RCT schedule



2. Aim and objectives

2.1. Aim

The aim of the Trial is to evaluate the clinical and cost-effectiveness of a complex nurse-led preventative psychological intervention in reducing patient-reported PTSD[1] symptom severity, and other reported psychological morbidities at six months.

2.2. Objectives

The specific objectives are:

i. To evaluate the effect of the complex intervention on patient-reported PTSD symptom severity and other psychological morbidities and quality of life at six months; and
ii. To estimate, in an integrated economic analysis, the cost-effectiveness of the intervention.

An integrated process evaluation will be conducted to assess the fidelity and quality of the implementation of the intervention, and identify important contextual factors to better understand how the intervention works.

3. Methods

3.1. Trial design

Parallel group cluster-RCT, with staggered opening and a baseline (pre-intervention) period.

3.2. Setting

Twenty-four NHS adult, general critical care units in the UK ("sites").

3.3. Inclusion and exclusion criteria

The inclusion and exclusion criteria of this study are as described below.

3.3.1. Eligibility criteria for sites (clusters)

The following criteria must be met for a site to participate in the Trial. A site must:

i. show that recruitment to target, timely data collection, and delivery of the complex intervention are feasible - via completion of a site feasibility questionnaire;
ii. commit to dedicate adequate resources to carry out the complex intervention;
iii. agree to adhere to randomisation into either the control group or the intervention group;
iv. have two Joint Principal Investigators (PIs) identified to lead POPPI at the site (a lead nurse and a lead clinician);
v. agree, where possible, to recruit all eligible patients to POPPI and to maintain a POPPI Screening Log to include reasons why eligible patients were not recruited
vi. agree to use the CAM-ICU[2] for assessing delirium and RASS for assessing sedation status for the duration of the trial; and
vii. be actively participating in the Case Mix Programme (CMP) – the national clinical audit for critical care units coordinated by ICNARC.

Sites that have taken part as an intervention site in the POPPI Feasibility Study (ISRCTN61088114) were not be eligible for selection.

3.3.1. Inclusion criteria for patients

Patients must meet all of the following criteria:

viii. Age 18 years or greater
ix. Greater than 48 hours in the critical care unit
x. Receipt of Level 3 critical care (for any period of time) during first 48 hours in the critical care unit
xi. Between +1 and -1 on the Richmond Agitation Sedation Scale[3]

xii. Glasgow Coma Scale score of 15
xiii. English-speaking
xiv. Ability to communicate orally

3.3.2. Exclusion criteria for patients

Patients must not meet any of the following criteria:

i. Pre-existing chronic cognitive impairment, such as dementia
ii. Pre-existing psychotic illness, such as schizophrenia
iii. Pre-existing chronic posttraumatic stress disorder
iv. Receiving end-of-life care
v. Previously recruited to POPPI

3.4. Outcomes

All outcomes will be assessed and reported at the individual patient level.

3.4.1. Primary outcomes

The primary outcome for the clinical evaluation will be patient-reported PTSD symptom severity at six months, measured using the PTSD Symptom Scale – Self Report version (PSS-SR), which conforms to all DSM-IV diagnostic criteria for PTSD and which has been validated for use in critical care unit survivors.

The primary outcomes for the economic evaluation will be incremental costs, quality-adjusted life years (QALYs) and net monetary benefit at six months.

3.4.2. Secondary outcomes

The secondary outcomes will be:

i. days alive and free from sedation to day 30;
ii. duration of critical care unit stay;
iii. PSS-SR greater than 18 points at six months[4];
iv. depression at six months, measured using the Hospital Anxiety and Depression Scale (HADS)[5];
v. anxiety at six months, measured using the HADS[5]; and
vi. health-related quality of life (HRQoL) at six months, measured by the EuroQol (EQ-5D-5L) questionnaire.

3.5. Power calculation

The initial power calculation for the POPPI cluster-RCT was calculated for the original grant submission and prior to conducting the POPPI feasibility study. It was based on very limited data to inform it – available at that time – namely, routine non-specific (with respect to the proposed POPPI trial population) data from the ICNARC Case Mix Programme (the national clinical audit for adult critical care in the UK) and more specific outcome data but only from a single-centre study of 100 patients. Despite this, to ensure a smooth transition from the POPPI feasibility study to the POPPI cluster-RCT (in the eventuality that feasibility was demonstrated), the initial pre-feasibility study power calculation formed the basis for the original ethics application for the POPPI cluster-RCT.

Following completion of the POPPI feasibility study, the assumptions underlying the initial pre-feasibility study power calculation were reviewed using the results from the feasibility study to ensure the proposed design retained adequate power – to produce the pre-cluster-RCT power calculation. The amount of additional information on which to update the assumptions, however, remained small – with only two critical care units having participated in the RCT processes and procedures feasibility study (providing information on the outcome measure) and a further two critical care units having participated in the delivery of the intervention feasibility study (providing information on rates of consent and patients assessed as being at high risk).

Finally, during the early phase of recruitment to the POPPI cluster-RCT, the assumptions underlying the pre-cluster-RCT power calculation were reviewed again once outcome data became available from the baseline (pre-intervention) period for 20 (of the 24) sites.

Details of these three stages are set out below.

3.5.1. Initial pre-feasibility study power calculation

The original POPPI cluster-RCT design, prior to conducting the POPPI feasibility study, was for 24 sites each recruiting eligible admissions for eleven months. The eleven months consisted of a five-month baseline period during which both intervention and control sites delivered usual care, a one-month transition period (to be excluded from the primary analysis of the cluster-RCT) during which intervention sites were trained and began to deliver the intervention, and a five-month intervention period during which intervention sites delivered the intervention. Control sites continued to deliver usual care throughout the baseline, transition and intervention periods. This design was selected to provide at least 90% power,

based on the method of Hussey and Hughes for a general, multi-period, cluster-randomised controlled trial[3] with a type I error rate of 0.05 and based on the following assumptions:

- a mean of 14 points and standard deviation of 12 points for the PSS-SR (primary outcome measure) for control group patients and for intervention group patients during the baseline period – estimated from patients receiving usual care in a previous single-centre study[6];
- an estimated intra-cluster correlation (ICC) of 0.254 – estimated, as there was no multicentre data available for the PSS-SR, by making a conservative assumption of 0.5 for the between-site coefficient of variation[7] (corresponding to a between-site standard deviation of 7 points);
- a detectable treatment effect of a reduction of 4 points on the PSS-SR based on a difference between groups equivalent to the reliable change index for the PSS-SR[8] (of 8 points) being observed in 50% of eligible patients assessed as being at high risk of psychological morbidity using the IPAT[9] in intervention sites during the intervention period;
- an estimated harmonic mean of the number of patients completing follow-up of 76 per site per annum (corresponding to 32 in each five-month period) – estimated using data from the ICNARC Case Mix Programme for potentially eligible patients admitted to adult, general critical care units across England, Wales and Northern Ireland, assuming 10% mortality at six months following recruitment and 80% follow-up among survivors.

It was anticipated that, with the above design and assumptions, the estimated total number of patients recruited would be 2,904 (based on Case Mix Programme data). Staged roll-out in three staggers, each of eight sites (four intervention and four control) two months apart, was planned solely for practical delivery of the training for the intervention.

The above initial pre-feasibility study power calculation was included in the original trial protocol submitted for ethical approval (submitted during the feasibility study due to the need to transition rapidly from feasibility study to cluster-RCT) and was in place at the start of recruitment to the POPPI cluster-RCT.

3.5.2. Pre-cluster-RCT power calculation

Following completion of the feasibility study and prior to the start of recruitment to the cluster-RCT, the assumptions underlying the initial pre-feasibility study power calculation were reviewed using results from the feasibility study, resulting in the following assumptions:
a mean of 6 points and standard deviation of 7.5 points for the PSS-SR (primary outcome measure);

- an estimated ICC of 0.138 – estimated by retaining a conservative assumption of 0.5 for the between-site coefficient of variation (corresponding to a between-site standard deviation of 3 points);
- a detectable treatment effect of a reduction of 2.9 points on the PSS-SR based on a difference between groups equivalent to a re-estimated reliable change index for the PSS-SR (of 8.6 points) being observed in 40% of eligible patients assessed as being at high risk of psychological morbidity using the IPAT, with 16% of recruited patients declining the intervention;
- an estimated harmonic mean of the number of patients completing follow-up of 52 per site per annum (corresponding to 22 in each five-month period) – re-estimated using data from the ICNARC Case Mix Programme for potentially eligible patients admitted to the 24 critical care units participating in the POPPI cluster-RCT, and retaining the assumptions, supported by data from the feasibility study, of 10% mortality at six months following recruitment and 80% follow-up among survivors.

This power calculation review established that the planned design retained greater than 90% power under these revised assumptions. It was anticipated that, with the above design and assumptions, the estimated total number of patients recruited would be 1,914 (based on Case Mix Programme data) in the 24 sites.

3.5.3. Final review of assumptions in pre-cluster-RCT power calculation

During the early phase of recruitment to the cluster-RCT, the day-to-day Trial Management Group noted that the recruitment rate was below anticipated. A decision was taken, in consultation with the Independent Chairs and members of the Trial Steering Committee and the Data Monitoring and Ethics Committee, to undertake a further review of the assumptions underlying the pre-cluster-RCT power calculation once outcome data were available for patients recruited during the five-month baseline period in both intervention and control sites. This review, undertaken using data available on 9 August 2016 (in month 12 of study recruitment), identified:

- a mean of 10.3 points and standard deviation of 10.8 points for the PSS-SR (primary outcome measure);
- an ICC of 0.087 (95% confidence interval 0 to 0.192) for the PSS-SR;
  [with mean, standard deviation and ICC estimated using all available data from the previous observational study, the feasibility study and the baseline period of the cluster-RCT]
- a detectable treatment effect of a reduction of 4.2 points on the PSS-SR – estimated by retaining the same effect size as a multiple of the within-site standard deviation;

- an harmonic mean of the number of patients completing follow-up of 30.7 per site per annum (corresponding to 12.8 in each five-month period) – estimated using observed data from the baseline period.

This review of assumptions established that the planned design had an anticipated 78% power under the observed parameter estimates (and, allowing for uncertainty in the between-site variation, between 73% and 85% power).

Consequently, the decision was taken to extend recruitment in stagger 1 and 2 sites to the end of planned recruitment in stagger 3 sites (corresponding to an harmonic mean of 16.5 patients completing follow-up per site during the intervention period, allowing for the variation from five to nine months duration across staggers). With this extension to recruitment, the planned design had an anticipated 85% power (and, allowing for uncertainty in the between-site variation, between 79% and 91% power). It was anticipated that, with this extension to recruitment, the estimated total number of patients recruited would be 1,378.

Recruitment continued to be monitored closely to ensure 1,378 (or more) patients were recruited and, to ensure this, a further extension to recruitment for an additional two months in all sites was approved by the Independent Chairs and members of the Trial Steering Committee and the Data Monitoring and Ethics Committee.

3.6. Allocation of sites

Participating sites will be allocated to intervention or control groups' using a restricted randomisation approach. A full enumeration approach to minimising imbalance[10] will be selected to ensure balance across the arms in geographical location, teaching status and size of unit. Balance on geographical location will be ensured by grouping the sites within each stagger according to location. We will perform simulations of alternative ways to balance on size of unit comparing:

i. Balancing on teaching status and number of beds
ii. Balancing on teaching status and number of level 3 admissions
iii. Balancing on teaching status, number of beds and number of level 3 admissions

The best combination of balancing on the above three factors will be used to perform the final random allocation. Each stagger will be made up of 8 sites and allocated 4 each to the intervention and control groups. The site allocations will be done for staggers one to three on 3 November 2015, 16 December 2015 and 17 February 2016 respectively.

4. Statistical methods

4.1. General analysis issues

4.1.1. Analysis population

All analyses will be based on the intention to treat principle. The patients will be analysed according to the group they were randomised to, irrespective of whether the treatment allocated was received.

4.1.2. Sequence of planned analyses

All final, planned, analyses identified in the protocol and in this SAP will be performed only after the last patient has completed his/her treatment and the outcome measures have been recorded. A blinded data review meeting may be held prior to database lock and completion of the final analyses. In addition, the database will not be unlocked, random code unblinded or analyses completed until this SAP has been approved.

As the duration of follow-up for the primary outcome (6 months) is long relative to the duration of recruitment (intervention period between 7 and 11 months), no interim analysis of effectiveness was planned.

4.1.3. Analysis software

Analyses will be performed using Stata/SE Version 14.2 for Windows 64-bit x86-64 (StataCorp LP, College Station, Texas, USA). Multiple imputation will be performed using the 'jomo' package in R Version 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria)[11].

4.1.4. Methods for withdrawals and missing data

All the patients who provided informed consent will be accounted for in the report of the Trial. Mortality at six months is anticipated to be 10% and loss to follow-up for the primary outcome is anticipated to be 20% among survivors. Loss-to follow-up for mortality at six months is anticipated to be <1%. Patients that withdraw from the trial and do not give permission for data collected prior to withdrawal will be used in the final analysis, those that die before six months and those lost to follow-up for mortality will be excluded from the analysis of six month psychological outcomes. Patients recruited during the transition period will also be excluded from the analysis. All other recruited patients will be included in the primary analysis, with outcomes imputed.

Loss to follow-up will be reported by treatment group. Reasons for withdrawal and loss to follow-up will be reported, when known.

Multiple imputation will be used to complete non and partial responses for the PSS-SR, HADS and EQ-5D-5L, under the assumption that responses are missing at random (MAR) conditional on the observed data. Two-level imputation (patients nested in sites) will be implemented using the 'jomo' package in R[11,12]. The overall scores on each measure will be imputed, not individual item responses. The imputation model will include the following covariates:

- Site level covariates (* denotes covariates used to balance treatment allocation):
    - Teaching status of hospital (teaching, non-teaching)*
    - Number of beds in the critical care unit (linear)*
    - Number of critical care unit admissions receiving Level 3 care staying at least 48h during the pre-trial period,1 April 2014 to 31 March 2015 (linear)*
    - Allocated treatment group (intervention, control)
- Patient level covariates:
    - Time period (baseline, intervention) and interaction with treatment group
    - Age in years (linear)
    - Gender (female, male)
    - Ethnicity (white, non-white)
    - Quintile of Index of Multiple Deprivation (IMD) 2015 (categorical)[13]
    - Documented pre-existing anxiety and/or depression prior to hospital admission (anxiety, depression, both, none)
    - Planned admission to the critical care unit following elective/scheduled surgery (yes, no)
    - ICNARC Physiology Score[14] from the first 24h following admission to the critical care unit (linear)
    - Last National Early Warning Score (NEWS)[15] prior to consent (linear)
    - Health-related quality of life (HRQOL) at time of consent, assessed as health thermometer score from 0 to 100 (linear)
    - Short-form State-Trait Anxiety Inventory (STAI-6)[16] at time of consent, scored from 6 to 24 (linear)
    - Duration of stay in the critical care unit in days (linear)
    - Number of days of delirium, as assessed by the CAM-ICU[2], in the critical care unit (linear)
    - Number of days receiving sedatives/anxiolytics/anaesthetics in the critical care unit (linear)
    - Number of days receiving sleep medications in the critical care unit (linear)

- Receipt of benzodiazepines in the critical care unit (yes, no)
- Number of days receiving antipsychotics in the critical care unit (linear)
- Number of days receiving analgesics in the critical care unit (linear)
- Number of days receiving antidepressants in the critical care unit (linear)
- Number of days receiving vasoactive agents in the critical care unit (linear)
- Number of days receiving mechanical ventilation in the critical care unit (linear)
- Duration of stay in hospital following discharge from the critical care unit (linear)
- PSS-SR at six months (linear)
- HADS at six months (linear)
- EQ-5D-5L at six months (linear)

Twenty multiply imputed datasets will be generated using Markov Chain Monte Carlo (MCMC) drawing a sample every 1000 iterations, following an initial 1000 iteration burn-in. The random number seed will be set to 6627.

For the primary clinical and cost effectiveness outcomes two sensitivity analyses will be used to address alternative assumptions regarding the missing data mechanism: missing completely at random (MCAR) and missing not at random (MNAR).

To evaluate the results under the assumption of MCAR, the analyses will be repeated using complete case data (i.e. only those patients returning a completed questionnaire).

To evaluate the results under the assumption that responses are MNAR, i.e. the probability of missing data depends on the patient's outcome after conditioning on the observed data; a pattern-mixture model approach[17] will be used. Pattern-mixture models allow the outcome to be modelled differently according to whether it is observed or missing. To inform the assumptions about the parameters for the missing pattern that cannot be estimated from the data (sensitivity parameters), expert opinion about outcome differences between patients with missing versus complete data will be elicited from a representative sample of the clinical staff involved with the POPPI trial across the different trial centres and other interested experts[18].

4.1.5. Data transformation

If applicable, appropriate method of transformation (e.g. log, squared, cubic, square root, etc.) will be use to transform non-normally distributed continuous variables.

4.1.6. Multiple comparisons and multiplicity

No adjustment will be made to account for multiple endpoints or multiple subgroups; P<0.05 will be taken to represent a statistically significant result. The results of subgroup analyses will be interpreted taking into account the number of significant findings that would have been expected by chance alone.

4.2. Statistical analyses

4.2.1. Screening and recruitment

Screening, recruitment and follow-up will be presented in the form of a CONSORT diagram, based on the CONSORT extension for cluster-randomised trials.

Descriptive statistics will be performed using the screening logs completed by all the participating sites during patient recruitment period. Patients' data recorded which will be summarized are as follows:

1. Total patients admitted
2. Total patients who stayed >48 hrs (Yes/No) – n (% of total admitted)
3. Total patients completed screening (patients with a final status) – n
4. Total patients not completed screening (patients without final status) – n
5. Patients who met stable criteria (Yes/No) – n (% of total completed screening)
    a. Reason did not meet stable criteria:
        i. No level 3 care in 1st 48 hrs – n (% of those not meeting stable criteria)
        ii. Not aged ≥ 18 yrs – n (% of those not meeting stable criteria)
        iii. Not English speaking – n (% of those not meeting stable criteria)
        iv. Previous recruited to POPPI – n (% of those not meeting stable criteria)
        v. Pre-existing chronic cognitive impairment – n (% of those not meeting stable criteria)
        vi. Pre-existing chronic PTSD – n (% of those not meeting stable criteria)
        vii. Pre-existing psychotic illness – n (% of those not meeting stable criteria)
6. Met daily transient criteria (Yes/No) – n (% of those meeting stable criteria)
   (To work out Yes: Met stable criteria = Yes AND Final status = Not eligible)
7. Reason did not meet transient criteria:
    a. Able to communicate orally - n (% of those not meeting transient criteria
    b. Between +1 and -1 on the RASS - n (% of those not meeting transient criteria)

c. GCS of 15 - n (% of those not meeting transient criteria)
d. Not receiving end of life care - n (% of those not meeting transient criteria)
e. Able to consent - n (% of those not meeting transient criteria)

8. Potentially eligible patients (enrolled, refused, eligible not enrolled, other AND eligibility unknown)
   a. Missed – n (%)
   b. Eligibility unknown (%)
9. Approached (enrolled AND refused consent) (Yes/No) – n (% of potentially eligible)
   a. Enrolled – n (% of approached)
   b. Refused consent – n (% of approached)
10. Patient level indicators (to be produced overall and per month):
   a. How many times each patient underwent daily screening
      i. When screening ended for each patient (date of admission + day last screened)
   b. Percentage of days screening not occurring (e.g. weekends)

4.2.2. Demographic and baseline characteristics

Baseline demographic and clinical data will be summarised for the ITT population, for each of the two treatment groups in each of the two time periods. Continuous variables will be summarized as mean (standard deviation) and median (interquartile range) whilst categorical variables will be summarized as number (percent). There will be no statistical testing for any of the summary measures whilst comparing the baseline variables between the treatment groups. The following baseline variables will be compared between the two treatment groups.

i. Age in years
ii. Gender (female, male)
iii. Ethnicity (white, mixed, Asian, black, other, not stated)
iv. Quintile of IMD 2015 (1=least deprived to 5=most deprived)
i. Documented pre-existing anxiety/depression (anxiety, depression, both, none)
ii. Planned admission to the critical care unit following elective/scheduled surgery (yes, no)
iii. ICNARC Physiology Score from the first 24h following admission to the critical care unit
iv. APACHE II score from the first 24h following admission to the critical care unit
v. Duration of stay in the critical care unit prior to consent
vi. Number of days experiencing delirium in the critical care unit prior to consent
vii. Last NEWS prior to consent

viii. STAI-6 at time of consent
ix. HRQOL at time of consent (health thermometer score)

4.2.3. Treatments received in the critical care unit

Treatments received in the critical care unit will be summarised for the ITT population, for each of the two treatment groups in each of the two time periods. Treatments received will be summarised as number (percent) of patients receiving the treatment, the median (interquartile range) number of days on which the treatment was received (among those receiving the treatment) and the mean (SD) number of days on which the treatment was received (for all patients, including those that did not receive the treatment). There will be no statistical testing for any of the summary measures whilst comparing the treatment variables between the treatment groups. The following treatment variables will be compared between the two treatment groups:

i. Sedatives/anxiolytics/anaesthetics
ii. Sleep medications
iii. Benzodiazepines (note that benzodiazepines will also be included as either sedatives/anxiolytics/anaesthetics or sleep medications, as appropriate)
iv. Antipsychotics
v. Analgesics
vi. Antidepressants
vii. Vasoactive agents
viii. Mechanical ventilation

4.2.4. Delivery of the intervention

Uptake of the POPPI Online Training will be reported for intervention sites over time as the percentage of the enumerated critical care unit staff that had completed the training course by month against a target of >80% completion.

Delivery of the intervention at a patient level will be summarised for patients in the intervention group during the intervention period. The following will be reported for all patients:

i. Number (percent) of patients consenting to assessment using the Intensive care Psychological Assessment Tool (IPAT)
ii. Among those consenting, number (percent) of patients assessed using the IPAT
iii. Median (interquartile range) IPAT score
iv. Number (percent) of patients with IPAT score ≥ 7

The following will be reported for patients with IPAT score ≥ 7:

v. Number (percent) of patients by number of stress support sessions received (0, 1, 2, 3)
vi. Reasons for not receiving all three stress support sessions
vii. Number of patients receiving tablet computer (percent of those receiving stress support session one)
viii. Number of patients reporting using tablet computer (percent of those receiving tablet computer)
ix. Numbers of patients receiving Relax and Recover DVD and Getting well, staying well booklet (percent of patients receiving stress support session two)

4.2.5. Clinical effectiveness analysis – primary outcome

The primary analysis for the clinical evaluation will examine if there is a significant difference in the mean PSS-SR at six months between patients recruited to the intervention group compared to the control group using a generalised linear mixed model (GLMM) at the individual patient level (patients nested within sites and within treatment group/time period).

The model will include the following terms:

- Fixed effects at the site level (* denotes covariates used to balance treatment allocation):
    - Teaching status of hospital (teaching, non-teaching)*
    - Number of beds in the critical care unit (linear)*
    - Number of critical care unit admissions receiving Level 3 care staying at least 48h during the pre-trial period,1 April 2014 to 31 March 2015 (linear)*
    - Allocated treatment group (intervention, control)
- Fixed effects at the patient level:
    - Time period (baseline, intervention) and interaction with treatment group
    - Age in years (restricted cubic splines, 4 knots)
    - Gender (female, male)
    - Ethnicity (white, non-white)
    - Quintile of IMD 2015 (categorical)
    - Documented pre-existing anxiety and/or depression prior to hospital admission (anxiety, depression, both, none)
    - Planned admission to the critical care unit following elective/scheduled surgery (yes, no)
    - ICNARC Physiology Score from the first 24h following admission to the critical care unit (restricted cubic splines, 4 knots)
- Random effects (intercepts) at the following levels:
    - Site

The identity link (i.e. linear regression) will be used as the link function for the model and robust variance estimation[19,20] will be used to estimate the standard errors of the covariates as it adjusts for possible deviations from the model's assumptions. Rubin's rules will be used to combine estimates from the multiply imputed datasets. The coefficients with their 95% confidence intervals (CI) and p-values will be presented for the fixed effect covariates whilst only the coefficients with their 95% CI will be reported for the random effect variables. The primary effect estimate will be the interaction (difference in difference) between treatment group and time period. Similar models will be developed for the secondary outcomes.

A secondary analysis will use structural mean models with an instrumental variable of randomised allocated treatment to estimate the efficacy (adherence adjusted causal effect) of the stress support sessions among those patients consenting to psychological assessment and stress support sessions, assessed as being at high risk of psychological morbidity (IPAT score ≥ 7) and receiving at least two stress support sessions[21].

A sensitivity analysis allowing the missing PSS-SR to be MNAR will use Bayesian pattern-mixture models, consistent with the specification for the primary analysis. All priors will be 'minimally informative', except those governing the differences between the observed and missing outcomes which will be informed by expert opinion. The sensitivity of the results to a full range of diversity of opinion will be examined through a comparison of pooled and individual priors. Posterior probabilities and 95% credible intervals will be reported.

4.2.6. Clinical effectiveness analysis – secondary outcomes

Analyses of the secondary outcomes will also be performed using GLMMs (like the primary outcome analysis), with identity link (i.e. linear regression) for continuous secondary outcomes (reported as difference in means with 95% CI and p-value) and logit link (i.e. logistic regression) for binary secondary outcomes (reported as odds ratio with 95% CI and p-value). Robust variance estimation method[19,20] will be used to estimate the standard errors of the covariates in both the mixed linear and logistic regression models.

4.2.7. Sub-group analyses

There are planned subgroups and interaction analyses proposed for this study. The a priori identified subgroups that will be used for the subgroup analyses are as follows:

i. Age
    - Quartiles

ii. Gender
    - Male versus Female

iii. Socio-economic status - Quintile of IMD 2015
    - 1 - Least deprived vs 2 vs 3 vs 4 vs 5 - Most deprived
iv. Duration of delirium
    - No delirium vs Delirium < median duration vs Delirium ≥ median duration
v. State trait anxiety inventory score (STAI)
    - Quartiles
vi. Surgical status
    - Emergency/urgent surgery vs Elective/scheduled surgery vs Non-surgical
vii. Overall site engagement (from process evaluation work)
    - Low vs Medium vs High
viii. Heterogeneity of treatment effect
    - Derivation of a risk prediction model for the primary outcome using the usual care patients' data adjusting for a priori important covariates (age, gender, socioeconomic status, duration of delirium, STAI, surgical status) and then grouping patients based on quintiles of predicted risk of outcome

The evaluation of the treatment effect on the primary outcome of this study will be carried out using a formal test of interaction which will be obtained from the linear mixed effect regression models[22]. The linear mixed effect model will contain a main effect term denoting the specific subgroup of interest, a main effect term for treatment group and a subgroup x treatment interaction term.

4.2.8. Process evaluation

Analysis of the process evaluation will use a combination of qualitative and quantitative methods to assess and describe the variation in the delivery of the intervention across sites.[(10)] Analysis of the process evaluation will be conducted independent of the Trial team before the outcome evaluation to avoid any bias in the interpretation of the process data and to generate hypotheses that may be subsequently tested in statistical analyses of integrated process and outcome data. The structural mean models described above will be extended to incorporate additional potential mediator variables on the causal pathway between treatment allocation and treatment effect identified by the independent process evaluation team, e.g. nurse competence following training, adherence to the therapeutic approach, adherence to therapy and overall site engagement[23].

4.2.9. Economic evaluation

A full CEA will be undertaken to assess the relative cost-effectiveness of psychological assessment followed by stress support sessions for those assessed as being at high risk of psychological morbidity versus usual care. Resource use and outcome data collected as part

of the cluster-RCT will be used to report cost-effectiveness at six months and to project the lifetime cost-effectiveness of each strategy.

The cost analysis will take a health and personal health services perspective[24]. Cost will be calculated from patient level resource use data on length of stay in critical care and hospital, for the index admission and any readmission before six months (recorded in the trial dataset), use of personal health services after hospital discharge and within six months post-randomisation (collected through patient questionnaire), and additional staff time required to deliver the interventions (collected from site visits). Resource use data from the site visits, cluster-RCT dataset and six-month questionnaires will be combined with unit costs from the NHS Payment by Results database and from local Trust Finance Departments, to report the total costs per patient at six months for intervention versus usual care[25,26].

HRQoL data from the EQ-5D-5L questionnaires at six months will be combined with survival data to report QALYs at six months. QALY will be calculated by valuing each patient's survival time by their health-related QOL at six months according to the 'area under the curve' approach[27]. For six months survivors, QALYs will be calculated using the EQ-5D scores at six months, assuming an EQ-5D score of zero at randomisation, and a linear interpolation between randomisation and six months. For decedents between randomisation and six months, we will assume zero QALYs.

The CEA will follow the intention-to-treat principle and report the mean (95% confidence interval) incremental costs, QALYs and net monetary benefit (NMB) at six months. Missing data in resource use and HRQoL will be handled with Multiple Imputation methods as described in the clinical analysis section. As a sensitivity analysis, Bayesian pattern-mixture models will be used to allow departures from MAR for the missing HRQoL, using a similar approach to that for the clinical effectiveness primary outcome.

The CEA will use general linear mixed regression models that allow for clustering[28] of patients including site as a random effect variable and period as a fixed effect variable. The analysis will adjust for pre-specified baseline covariates at both patient and site level. The primary effect estimate will be the interaction (difference in difference) between treatment groups and time period. The cost-effectiveness analysis will use this model to estimate the effect of the intervention on mean cost and mean QALY (allowing for the correlation between the costs and QALY at the individual and cluster level).

Lifetime cost-effectiveness will be projected by summarising the relative effects of alternative strategies on long-term survival and HRQoL, informed by extrapolations of patient survival

data[29,30]. The long-term modelling will extrapolate from the cluster-RCT data by fitting alternative parametric survival curves (e.g. Weibull, exponential, lognormal, log logistic and Gompertz) to the maximum available survival data recorded in the trial dataset. The chosen method of survival extrapolation for the base case analysis will be the one judged most plausible[31] according to model fit (Akaike information criteria (AIC) or Bayesian information criteria (BIC)), and in comparison with age-gender matched all-cause mortality[32]. Quality of life generally deteriorates after critical care discharge for up to 6 months and then slowly improves overtime but remains lower than that in the general population over long-term[33], In the base case analysis, quality of life decrement of the study population compared with age-gender matched population[34] at six months will be applied allowing for improvement in quality of life over the years of excess mortality. After period of excess mortality, quality of life from age-gender matched general population will be applied. Lifetime costs attributable to initial episode of critical illness will be estimated by utilising longer term readmission costs data to patients who were randomised early. The longer term costs will be applied over the period of excess mortality. Predicted survival and HRQoL will be combined to report lifetime QALYs, and to project lifetime incremental costs, incremental QALYs, and incremental net benefits for the alternative strategies of care. Sensitivity analyses will test whether the results are robust to methodological assumptions (e.g. specification of the statistical model, extrapolation approach, alternative HRQoL assumptions, and learning curve effects).

Adherence adjusted analysis and subgroup analysis will be undertaken for the pre-specified subgroups as per the analysis of clinical effectiveness.

5. Reporting conventions

The following reporting conventions will be adopted for the SAP. These conventions will enhance the review of the study report and help to standardize presentation with common notations.

i. Sample sizes will be presented for each treatment group as totals in the column header as “(N = xxx)”, where appropriate.

ii. Sample sizes shown with summary statistics are the samples sizes (n) of patients with non-missing values.

iii. All summaries for categorical variables will include all categories that were available and will not be restricted to those with at least one response.

iv. Summaries for continuous variables that are approximately normally distributed will be reported as n, mean and standard deviation (SD).

v. Summaries for continuous variables that are not normally distributed will be reported as n, median and quartiles.

vi. All percentages will be rounded and reported to a single decimal place (xx.x%). A percentage of 0% will be reported as “0%”; a percentage of 100% will be reported as “100%”.

vii. Summaries that include P-values will report the P-value to three decimal places with a leading zero (0.xxx). P-values of less than 0.0005 will be reported as “<0.001” not “0.000”.

viii. Missing values for both numeric and string variables will be presented as dashes (“---”) or as “Not available” / “Not applicable” / “Not reported” (as appropriate) in tables or data listings.

6. Proposed tables and figures

6.1. Clinical evaluation tables

Table 1: Baseline demographic and clinical variables by treatment groups

Variables	Baseline period		Intervention period	
	Intervention	Usual Care	Intervention	Usual Care
	N = XXX	N = XXX	N = XXX	N = XXX
Demography				
Age (years):				
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)
Gender:				
Female, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Male, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Ethnicity:				
White, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Mixed, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Asian/Asian British, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Black/Black British, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Not stated, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Quintile of IMD 2015:				
1 - Least deprived, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
2, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
3, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
4, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
5 - Most deprived, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Documented pre-existing anxiety/depression:				
Anxiety, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Depression, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Both, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
None, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Planned admission to the critical care unit following elective/schedule surgery				
Yes, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
No, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
ICNARC Physiology Score:				
mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)
APACHE II score:				
mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)

n: Number of patients; %: Percentage of patients; N: Total number of patients
SD: Standard deviation; IQR: Inter-quartile range; BMI: Body mass index.

Table 1: Con't

Variables	Baseline period		Intervention period	
	Intervention	Usual Care	Intervention	Usual Care
	N = XXX	N = XXX	N = XXX	N = XXX
Duration of critical care unit stay prior to consent:				
mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)
Number of days experiencing delirium in the critical care unit prior to consent				
mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)
Last NEWS prior to consent				
mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)
STAI-6 at time of consent				
mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)
HRQOL (health thermometer score) at time of consent:				
mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)

Table 2: Concomitant medications used by treatment groups

Variables	Baseline period		Intervention period	
	Intervention	Usual Care	Intervention	Usual Care
	N = XXX	N = XXX	N = XXX	N = XXX
Sedatives/anxiolytics/anaesthetics received:				
Chlordiazepoxide, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Clobazam, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Clonidine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Desflurane, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Dexmedetomidine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Diazepam, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Etomidate, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Halothane, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Isoflurane, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Ketamine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Lorazepam, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Midazolam, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Propofol, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Sevoflurane, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Thiopentone, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Sleep medication received:				
Flurazepam, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Lormetazepam, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Nitrazepam, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Temazepam, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Zolpidem, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Zopiclone, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Benzodiazepines	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Antipsychotic medication received:				
Chlorpromazine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Clozapine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Flupentixol, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Haloperidol, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Olanzapine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Quetiapine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Risperidone, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)

Table 2: Con't

Variables	Baseline period		Intervention period	
	Intervention	Usual Care	Intervention	Usual Care
	N = XXX	N = XXX	N = XXX	N = XXX
Analgesics received:				
Alfentanil, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Co-codamol, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Codeine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Co-dydramol, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Diamorphine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Dihydrocodeine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Fentanyl, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Morphine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Oxycodone, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Remifentanil, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Tramadol, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Antidepressants received:				
Amitriptyline, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Citalopram, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Fluoxetine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Mirtazapine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Paroxetine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Reboxetine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Sertraline, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Venlafaxine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Actual vasoactive agent received:				
Adrenaline, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Dobutamine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Dopamine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Dopexamine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Metaraminol, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Noradrenaline, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Phenylephrine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Vasopressin, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)

n: number of patients; %: percentage of patients; N: total number of patients

Table 3: Linear mixed effect model for PSS-SR at six months – primary analysis

Variables	Coefficient	95% CI	P-value
Fixed effects at the site level*:			
Teaching status of hospital*:			
Teaching	0		
Non-Teaching	XX.X	XX.X , XX.X	0.XXX
Number of beds in the critical care unit (per additional bed)*	XX.X	XX.X , XX.X	0.XXX
Number of CCU admissions receiving Level 3 care staying at least 48hr during the pre-trial period,1 April 2014 to 31 March 2015 (per additional 100 admissions)*	XX.X	XX.X , XX.X	0.XXX
Allocated treatment group:			
Usual care	0		
Intervention	XX.X	XX.X , XX.X	0.XXX
Fixed effects at the patient level:			
Time period:			
Baseline period	0		
Intervention period	XX.X	XX.X , XX.X	0.XXX
Interaction between time period and treatment group:			
Intervention period * Intervention group	XX.X	XX.X , XX.X	0.XXX
Age in years (restricted cubic splines, 4 knots)			
Age spline 1	XX.X	XX.X , XX.X	0.XXX
Age spline 2	XX.X	XX.X , XX.X	
Age spline 3	XX.X	XX.X , XX.X	
Gender:			
Male	0		
Females	XX.X	XX.X , XX.X	0.XXX
Ethnicity:			0.XXX
White, n (%)	0		
Mixed, n (%)	XX.X	XX.X , XX.X	
Asian/Asian British, n (%)	XX.X	XX.X , XX.X	
Black/Black British, n (%)	XX.X	XX.X , XX.X	
Others, n (%)	XX.X	XX.X , XX.X	
Quintile of IMD 2015:			0.XXX
1 - Least deprived, n (%)	0		
2, n (%)	XX.X	XX.X , XX.X	
3, n (%)	XX.X	XX.X , XX.X	
4, n (%)	XX.X	XX.X , XX.X	
5 - Most deprived, n (%)	XX.X	XX.X , XX.X	
Pre-existing anxiety/depression:			0.XXX
Anxiety, n(%)	0		
Depression, n(%)	XX.X	XX.X , XX.X	
Both, n(%)	XX.X	XX.X , XX.X	
None, n(%)	XX.X	XX.X , XX.X	
Planned admission to the CCU following elective/schedule surgery			
Yes, n(%)	0		

No, n(%)	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score from the first 24h following admission to the critical care unit (restricted cubic splines, 4 knots)			
ICNARC Physiology Score spline 1	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score spline 2	XX.X	XX.X , XX.X	
ICNARC Physiology Score spline 3	XX.X	XX.X , XX.X	
Random Effects			
Site	XX.X	XX.X , XX.X	-

CI: Confidence interval.

* - Covariates used to balance treatment allocation

Table 4a: Linear mixed effect model for days alive and free from sedation to day 30

Variables	Coefficient	95% CI	P-value
Fixed effects at the site level*:			
Teaching status of hospital*:			
Teaching	0		
Non-Teaching	XX.X	XX.X , XX.X	0.XXX
Number of beds in the critical care unit (per additional bed)*	XX.X	XX.X , XX.X	0.XXX
Number of CCU admissions receiving Level 3 care staying at least 48hr during the pre-trial period,1 April 2014 to 31 March 2015 (per additional 100 admissions)*	XX.X	XX.X , XX.X	0.XXX
Allocated treatment group:			
Usual care	0		
Intervention	XX.X	XX.X , XX.X	0.XXX
Fixed effects at the patient level:			
Time period:			
Baseline period	0		
Intervention period	XX.X	XX.X , XX.X	0.XXX
Interaction between time period and treatment group:			
Intervention period * Intervention group	XX.X	XX.X , XX.X	0.XXX
Age in years (restricted cubic splines, 4 knots)			
Age spline 1	XX.X	XX.X , XX.X	0.XXX
Age spline 2	XX.X	XX.X , XX.X	
Age spline 3	XX.X	XX.X , XX.X	
Gender:			
Male	0		
Females	XX.X	XX.X , XX.X	0.XXX
Ethnicity:			0.XXX
White, n (%)	0		
Mixed, n (%)	XX.X	XX.X , XX.X	
Asian/Asian British, n (%)	XX.X	XX.X , XX.X	
Black/Black British, n (%)	XX.X	XX.X , XX.X	
Others, n (%)	XX.X	XX.X , XX.X	
Quintile of IMD 2015:			0.XXX
1 - Least deprived, n (%)	0		
2, n (%)	XX.X	XX.X , XX.X	
3, n (%)	XX.X	XX.X , XX.X	
4, n (%)	XX.X	XX.X , XX.X	
5 - Most deprived, n (%)	XX.X	XX.X , XX.X	
Pre-existing anxiety/depression:			0.XXX
Anxiety, n(%)	0		
Depression, n(%)	XX.X	XX.X , XX.X	
Both, n(%)	XX.X	XX.X , XX.X	
None, n(%)	XX.X	XX.X , XX.X	
Planned admission to the CCU following elective/schedule surgery			
Yes, n(%)	0		

No, n(%)	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score from the first 24h following admission to the critical care unit (restricted cubic splines, 4 knots)			
ICNARC Physiology Score spline 1	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score spline 2	XX.X	XX.X , XX.X	
ICNARC Physiology Score spline 3	XX.X	XX.X , XX.X	
Random Effects			
Site	XX.X	XX.X , XX.X	-

CI: Confidence interval.

* - Covariates used to balance treatment allocation

Table 4b: Linear mixed effect model for duration of critical care unit stay

Variables	Coefficient	95% CI	P-value
Fixed effects at the site level*:			
Teaching status of hospital*:			
Teaching	0		
Non-Teaching	XX.X	XX.X , XX.X	0.XXX
Number of beds in the critical care unit (per additional bed)*	XX.X	XX.X , XX.X	0.XXX
Number of CCU admissions receiving Level 3 care staying at least 48hr during the pre-trial period,1 April 2014 to 31 March 2015 (per additional 100 admissions)*	XX.X	XX.X , XX.X	0.XXX
Allocated treatment group:			
Usual care	0		
Intervention	XX.X	XX.X , XX.X	0.XXX
Fixed effects at the patient level:			
Time period:			
Baseline period	0		
Intervention period	XX.X	XX.X , XX.X	0.XXX
Interaction between time period and treatment group:			
Intervention period * Intervention group	XX.X	XX.X , XX.X	0.XXX
Age in years (restricted cubic splines, 4 knots)			
Age spline 1	XX.X	XX.X , XX.X	0.XXX
Age spline 2	XX.X	XX.X , XX.X	
Age spline 3	XX.X	XX.X , XX.X	
Gender:			
Male	0		
Females	XX.X	XX.X , XX.X	0.XXX
Ethnicity:			0.XXX
White, n (%)	0		
Mixed, n (%)	XX.X	XX.X , XX.X	
Asian/Asian British, n (%)	XX.X	XX.X , XX.X	
Black/Black British, n (%)	XX.X	XX.X , XX.X	
Others, n (%)	XX.X	XX.X , XX.X	
Quintile of IMD 2015:			0.XXX
1 - Least deprived, n (%)	0		
2, n (%)	XX.X	XX.X , XX.X	
3, n (%)	XX.X	XX.X , XX.X	
4, n (%)	XX.X	XX.X , XX.X	
5 - Most deprived, n (%)	XX.X	XX.X , XX.X	
Pre-existing anxiety/depression:			0.XXX
Anxiety, n(%)	0		
Depression, n(%)	XX.X	XX.X , XX.X	
Both, n(%)	XX.X	XX.X , XX.X	
None, n(%)	XX.X	XX.X , XX.X	
Planned admission to the CCU following elective/schedule surgery			
Yes, n(%)	0		

No, n(%)	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score from the first 24h following admission to the critical care unit (restricted cubic splines, 4 knots)			
ICNARC Physiology Score spline 1	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score spline 2	XX.X	XX.X , XX.X	
ICNARC Physiology Score spline 3	XX.X	XX.X , XX.X	
Random Effects			
Site	XX.X	XX.X , XX.X	-

CI: Confidence interval.

* - Covariates used to balance treatment allocation

Table 4c: Logistic mixed effect model for PSS-SR greater than 18 points at six months

Variables	Odds ratio	95% CI	P-value
Fixed effects at the site level*:			
Teaching status of hospital*:			
Teaching	0		
Non-Teaching	XX.X	XX.X , XX.X	0.XXX
Number of beds in the critical care unit (per additional bed)*	XX.X	XX.X , XX.X	0.XXX
Number of CCU admissions receiving Level 3 care staying at least 48hr during the pre-trial period,1 April 2014 to 31 March 2015 (per additional 100 admissions)*	XX.X	XX.X , XX.X	0.XXX
Allocated treatment group:			
Usual care	0		
Intervention	XX.X	XX.X , XX.X	0.XXX
Fixed effects at the patient level:			
Time period:			
Baseline period	0		
Intervention period	XX.X	XX.X , XX.X	0.XXX
Interaction between time period and treatment group:			
Intervention period * Intervention group	XX.X	XX.X , XX.X	0.XXX
Age in years (restricted cubic splines, 4 knots)			
Age spline 1	XX.X	XX.X , XX.X	0.XXX
Age spline 2	XX.X	XX.X , XX.X	
Age spline 3	XX.X	XX.X , XX.X	
Gender:			
Male	0		
Females	XX.X	XX.X , XX.X	0.XXX
Ethnicity:			0.XXX
White, n (%)	0		
Mixed, n (%)	XX.X	XX.X , XX.X	
Asian/Asian British, n (%)	XX.X	XX.X , XX.X	
Black/Black British, n (%)	XX.X	XX.X , XX.X	
Others, n (%)	XX.X	XX.X , XX.X	
Quintile of IMD 2015:			0.XXX
1 - Least deprived, n (%)	0		
2, n (%)	XX.X	XX.X , XX.X	
3, n (%)	XX.X	XX.X , XX.X	
4, n (%)	XX.X	XX.X , XX.X	
5 - Most deprived, n (%)	XX.X	XX.X , XX.X	
Pre-existing anxiety/depression:			0.XXX
Anxiety, n(%)	0		
Depression, n(%)	XX.X	XX.X , XX.X	
Both, n(%)	XX.X	XX.X , XX.X	
None, n(%)	XX.X	XX.X , XX.X	
Planned admission to the CCU following elective/schedule surgery			
Yes, n(%)	0		

No, n(%)	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score from the first 24h following admission to the critical care unit (restricted cubic splines, 4 knots)			
ICNARC Physiology Score spline 1	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score spline 2	XX.X	XX.X , XX.X	
ICNARC Physiology Score spline 3	XX.X	XX.X , XX.X	
Random Effects			
Site	XX.X	XX.X , XX.X	-

CI: Confidence interval.

* - Covariates used to balance treatment allocation

Table 4d: Linear mixed effect model for HADS depression score at six month

Variables	Coefficient	95% CI	P-value
Fixed effects at the site level*:			
Teaching status of hospital*:			
Teaching	0		
Non-Teaching	XX.X	XX.X , XX.X	0.XXX
Number of beds in the critical care unit (per additional bed)*	XX.X	XX.X , XX.X	0.XXX
Number of CCU admissions receiving Level 3 care staying at least 48hr during the pre-trial period,1 April 2014 to 31 March 2015 (per additional 100 admissions)*	XX.X	XX.X , XX.X	0.XXX
Allocated treatment group:			
Usual care	0		
Intervention	XX.X	XX.X , XX.X	0.XXX
Fixed effects at the patient level:			
Time period:			
Baseline period	0		
Intervention period	XX.X	XX.X , XX.X	0.XXX
Interaction between time period and treatment group:			
Intervention period * Intervention group	XX.X	XX.X , XX.X	0.XXX
Age in years (restricted cubic splines, 4 knots)			
Age spline 1	XX.X	XX.X , XX.X	0.XXX
Age spline 2	XX.X	XX.X , XX.X	
Age spline 3	XX.X	XX.X , XX.X	
Gender:			
Male	0		
Females	XX.X	XX.X , XX.X	0.XXX
Ethnicity:			0.XXX
White, n (%)	0		
Mixed, n (%)	XX.X	XX.X , XX.X	
Asian/Asian British, n (%)	XX.X	XX.X , XX.X	
Black/Black British, n (%)	XX.X	XX.X , XX.X	
Others, n (%)	XX.X	XX.X , XX.X	
Quintile of IMD 2015:			0.XXX
1 - Least deprived, n (%)	0		
2, n (%)	XX.X	XX.X , XX.X	
3, n (%)	XX.X	XX.X , XX.X	
4, n (%)	XX.X	XX.X , XX.X	
5 - Most deprived, n (%)	XX.X	XX.X , XX.X	
Pre-existing anxiety/depression:			0.XXX
Anxiety, n(%)	0		
Depression, n(%)	XX.X	XX.X , XX.X	
Both, n(%)	XX.X	XX.X , XX.X	
None, n(%)	XX.X	XX.X , XX.X	
Planned admission to the CCU following elective/schedule surgery			
Yes, n(%)	0		

No, n(%)	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score from the first 24h following admission to the critical care unit (restricted cubic splines, 4 knots)			
ICNARC Physiology Score spline 1	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score spline 2	XX.X	XX.X , XX.X	
ICNARC Physiology Score spline 3	XX.X	XX.X , XX.X	
Random Effects			
Site	XX.X	XX.X , XX.X	-

CI: Confidence interval.

* - Covariates used to balance treatment allocation

Table 4e: Linear mixed effect model for HADS anxiety score at six months

Variables	Coefficient	95% CI	P-value
Fixed effects at the site level*:			
Teaching status of hospital*:			
Teaching	0		
Non-Teaching	XX.X	XX.X , XX.X	0.XXX
Number of beds in the critical care unit (per additional bed)*	XX.X	XX.X , XX.X	0.XXX
Number of CCU admissions receiving Level 3 care staying at least 48hr during the pre-trial period,1 April 2014 to 31 March 2015 (per additional 100 admissions)*	XX.X	XX.X , XX.X	0.XXX
Allocated treatment group:			
Usual care	0		
Intervention	XX.X	XX.X , XX.X	0.XXX
Fixed effects at the patient level:			
Time period:			
Baseline period	0		
Intervention period	XX.X	XX.X , XX.X	0.XXX
Interaction between time period and treatment group:			
Intervention period * Intervention group	XX.X	XX.X , XX.X	0.XXX
Age in years (restricted cubic splines, 4 knots)			
Age spline 1	XX.X	XX.X , XX.X	0.XXX
Age spline 2	XX.X	XX.X , XX.X	
Age spline 3	XX.X	XX.X , XX.X	
Gender:			
Male	0		
Females	XX.X	XX.X , XX.X	0.XXX
Ethnicity:			0.XXX
White, n (%)	0		
Mixed, n (%)	XX.X	XX.X , XX.X	
Asian/Asian British, n (%)	XX.X	XX.X , XX.X	
Black/Black British, n (%)	XX.X	XX.X , XX.X	
Others, n (%)	XX.X	XX.X , XX.X	
Quintile of IMD 2015:			0.XXX
1 - Least deprived, n (%)	0		
2, n (%)	XX.X	XX.X , XX.X	
3, n (%)	XX.X	XX.X , XX.X	
4, n (%)	XX.X	XX.X , XX.X	
5 - Most deprived, n (%)	XX.X	XX.X , XX.X	
Pre-existing anxiety/depression:			0.XXX
Anxiety, n(%)	0		
Depression, n(%)	XX.X	XX.X , XX.X	
Both, n(%)	XX.X	XX.X , XX.X	
None, n(%)	XX.X	XX.X , XX.X	
Planned admission to the CCU following elective/schedule surgery			
Yes, n(%)	0		

No, n(%)	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score from the first 24h following admission to the critical care unit (restricted cubic splines, 4 knots)			
ICNARC Physiology Score spline 1	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score spline 2	XX.X	XX.X , XX.X	
ICNARC Physiology Score spline 3	XX.X	XX.X , XX.X	
Random Effects			
Site	XX.X	XX.X , XX.X	-

CI: Confidence interval.

* - Covariates used to balance treatment allocation

Table 4f: Linear mixed effect model for health related quality of life at six months

Variables	Coefficient	95% CI	P-value
Fixed effects at the site level*:			
Teaching status of hospital*:			
Teaching	0		
Non-Teaching	XX.X	XX.X , XX.X	0.XXX
Number of beds in the critical care unit (per additional bed)*	XX.X	XX.X , XX.X	0.XXX
Number of CCU admissions receiving Level 3 care staying at least 48hr during the pre-trial period,1 April 2014 to 31 March 2015 (per additional 100 admissions)*	XX.X	XX.X , XX.X	0.XXX
Allocated treatment group:			
Usual care	0		
Intervention	XX.X	XX.X , XX.X	0.XXX
Fixed effects at the patient level:			
Time period:			
Baseline period	0		
Intervention period	XX.X	XX.X , XX.X	0.XXX
Interaction between time period and treatment group:			
Intervention period * Intervention group	XX.X	XX.X , XX.X	0.XXX
Age in years (restricted cubic splines, 4 knots)			
Age spline 1	XX.X	XX.X , XX.X	0.XXX
Age spline 2	XX.X	XX.X , XX.X	
Age spline 3	XX.X	XX.X , XX.X	
Gender:			
Male	0		
Females	XX.X	XX.X , XX.X	0.XXX
Ethnicity:			0.XXX
White, n (%)	0		
Mixed, n (%)	XX.X	XX.X , XX.X	
Asian/Asian British, n (%)	XX.X	XX.X , XX.X	
Black/Black British, n (%)	XX.X	XX.X , XX.X	
Others, n (%)	XX.X	XX.X , XX.X	
Quintile of IMD 2015:			0.XXX
1 - Least deprived, n (%)	0		
2, n (%)	XX.X	XX.X , XX.X	
3, n (%)	XX.X	XX.X , XX.X	
4, n (%)	XX.X	XX.X , XX.X	
5 - Most deprived, n (%)	XX.X	XX.X , XX.X	
Pre-existing anxiety/depression:			0.XXX
Anxiety, n(%)	0		
Depression, n(%)	XX.X	XX.X , XX.X	
Both, n(%)	XX.X	XX.X , XX.X	
None, n(%)	XX.X	XX.X , XX.X	
Planned admission to the CCU following elective/schedule surgery			
Yes, n(%)	0		

No, n(%)	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score from the first 24h following admission to the critical care unit (restricted cubic splines, 4 knots)			
ICNARC Physiology Score spline 1	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score spline 2	XX.X	XX.X , XX.X	
ICNARC Physiology Score spline 3	XX.X	XX.X , XX.X	
Random Effects			
Site	XX.X	XX.X , XX.X	-

CI: Confidence interval.

* - Covariates used to balance treatment allocation

Table 5: Structural mean models for PSS-SR at six months using randomised allocated treatment as an instrumental variable

Variables	Coefficient	95% CI	P-value
Fixed effects at the site level*:			
Teaching status of hospital*:			
Teaching	0		
Non-Teaching	XX.X	XX.X , XX.X	0.XXX
Number of beds in the critical care unit (per additional bed)*	XX.X	XX.X , XX.X	0.XXX
Number of CCU admissions receiving Level 3 care staying at least 48hr during the pre-trial period,1 April 2014 to 31 March 2015 (per additional 100 admissions)*	XX.X	XX.X , XX.X	0.XXX
Allocated treatment group:			
Usual care	0		
Intervention	XX.X	XX.X , XX.X	0.XXX
Fixed effects at the patient level:			
Time period:			
Baseline period	0		
Intervention period	XX.X	XX.X , XX.X	0.XXX
Interaction between time period and treatment group:			
Intervention period * Intervention group	XX.X	XX.X , XX.X	0.XXX
Age in years (restricted cubic splines, 4 knots)			
Age spline 1	XX.X	XX.X , XX.X	0.XXX
Age spline 2	XX.X	XX.X , XX.X	
Age spline 3	XX.X	XX.X , XX.X	
Gender:			
Male	0		
Females	XX.X	XX.X , XX.X	0.XXX
Ethnicity:			0.XXX
White, n (%)	0		
Mixed, n (%)	XX.X	XX.X , XX.X	
Asian/Asian British, n (%)	XX.X	XX.X , XX.X	
Black/Black British, n (%)	XX.X	XX.X , XX.X	
Others, n (%)	XX.X	XX.X , XX.X	
Quintile of IMD 2015:			0.XXX
1 - Least deprived, n (%)	0		
2, n (%)	XX.X	XX.X , XX.X	
3, n (%)	XX.X	XX.X , XX.X	
4, n (%)	XX.X	XX.X , XX.X	
5 - Most deprived, n (%)	XX.X	XX.X , XX.X	
Pre-existing anxiety/depression:			0.XXX
Anxiety, n(%)	0		
Depression, n(%)	XX.X	XX.X , XX.X	
Both, n(%)	XX.X	XX.X , XX.X	
None, n(%)	XX.X	XX.X , XX.X	
Planned admission to the CCU following elective/schedule surgery			
Yes, n(%)	0		

No, n(%)	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score from the first 24h following admission to the critical care unit (restricted cubic splines, 4 knots)			
ICNARC Physiology Score spline 1	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score spline 2	XX.X	XX.X , XX.X	
ICNARC Physiology Score spline 3	XX.X	XX.X , XX.X	
Random Effects			
Site	XX.X	XX.X , XX.X	-

6.2. Economic evaluation tables

Table 6: Parameter estimates of the parametric survival models used for extrapolating survival curves

	Parameter estimates	
Distribution	**Scale/Rate**	**Shape**
Exponential	xx.x	N/A
Weibull	xx.x	xx.x
Lognormal(sdlog/meanlog)	xx.x	xx.x
Log-logistic	xx.x	xx.x
Gompertz	xx.x	xx.x

Table 7: Survival probabilities of the parametric survival models

Time (Years)	Exponential	Weibull	Lognormal	Log-logistic	Gompertz
0	1	1	1	1	1
1	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
2	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
3	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
.	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
.	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
.	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
.	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
.	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
.	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
.	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
.	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
.	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
.	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
98	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
99	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
100	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx

Table 8: Rank of Goodness of fit estimates (AIC and BIC) for parametric survival models

Distribution	AIC	BIC	Ranking
Exponential	xxx.x	xxx.x	x
Weibull	xxx.x	xxx.x	x
Lognormal	xxx.x	xxx.x	x
Log-logistic	xxx.x	xxx.x	x
Gompertz	xxx.x	xxx.x	x

6.3. Figures

Figure 1: CONSORT flow diagram

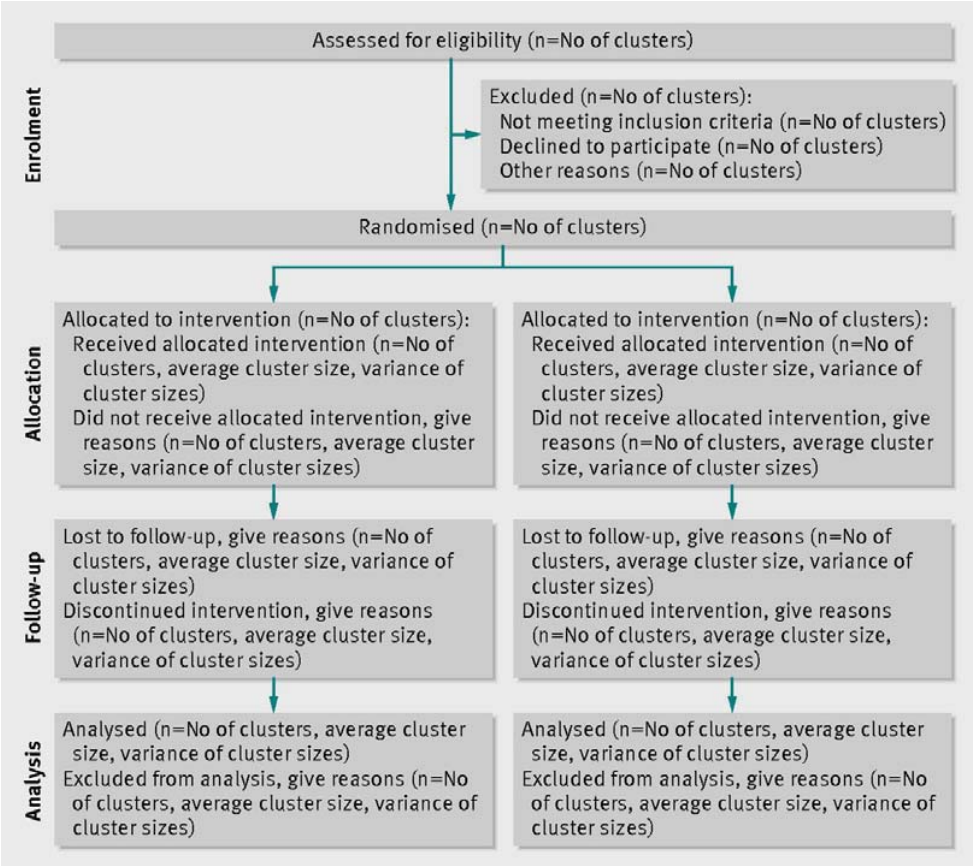


Figure 2: Kaplan-Meier plot of comparing intervention and control groups during intervention period

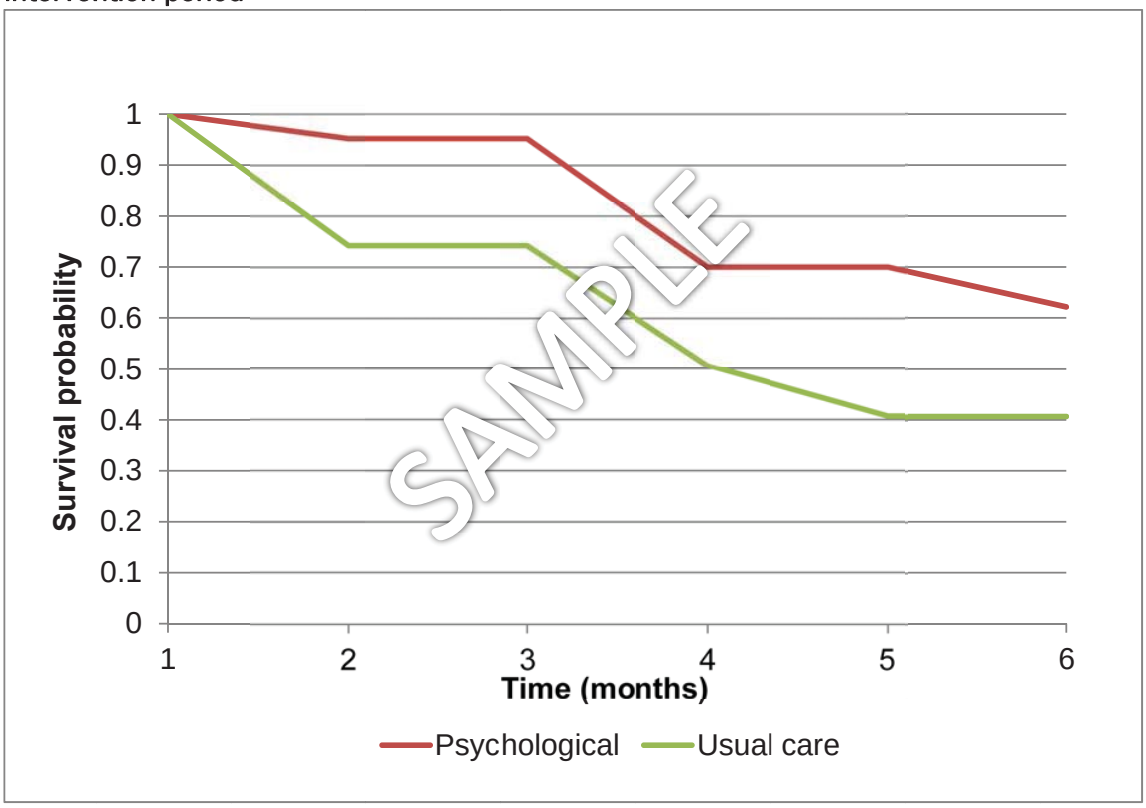
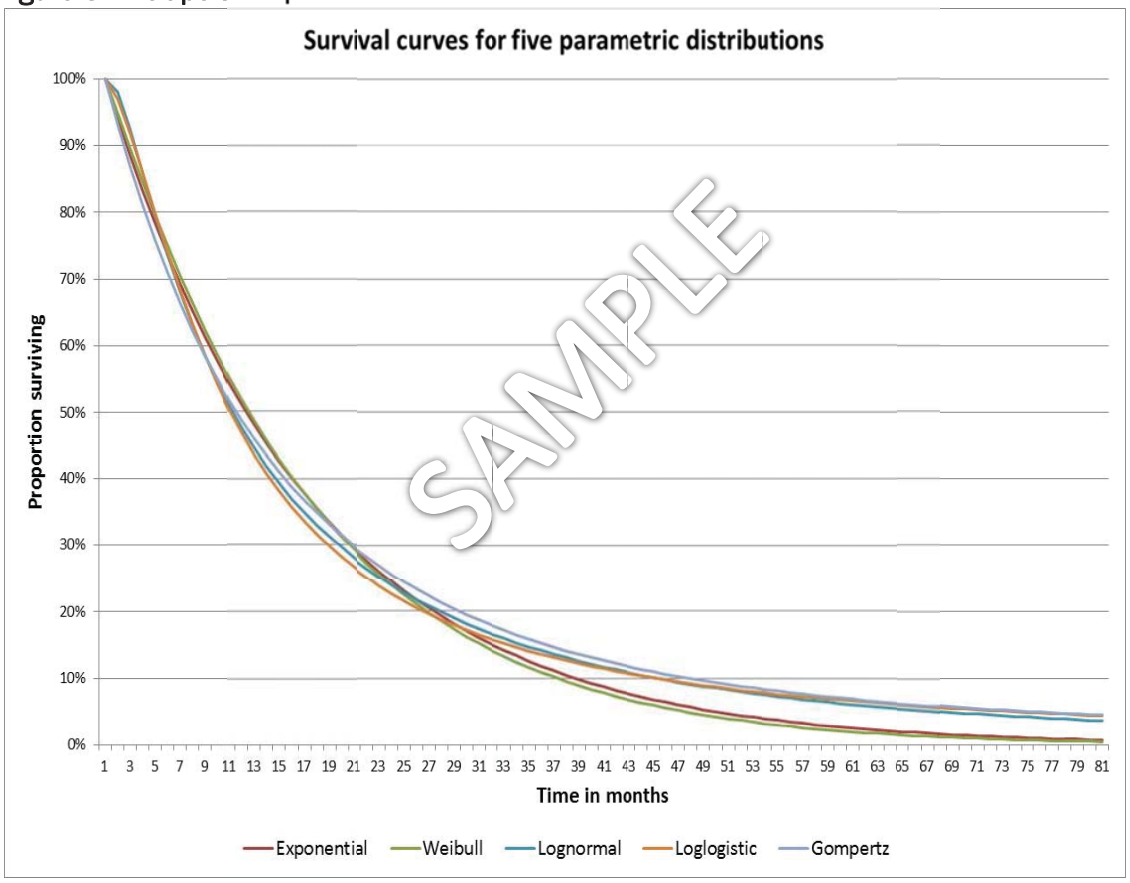


Figure 3: Extrapolated parametric survival curves for five distributions



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POPPI

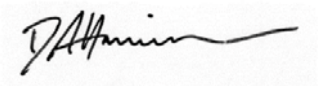
Provision Of Psychological support
to People in Intensive care

Psychological Outcomes following a nurse-led Preventative Psychological Intervention for critically ill patients (POPPI) trial

Statistical Analysis Plan

Version 1.1, 28/11/2017

REC number:	15/SC/0287
Trial sponsor:	ICNARC
Trial sponsor reference:	ICNARC/01/03/14
Trial funder:	NIHR HS&DR Programme
Funder reference:	12/64/124
ISRCTN number:	ISRCTN53448131
NIHR CRN Portfolio ID number:	18940
Author:	Dr Jerome Wulff

Role, Name and Position	**Signature**	**Date**
Chief investigator: Prof Kathryn Rowan (Director of Scientific & Strategic Development/CTU Director, ICNARC)		28/11/2017
Senior Statistician: Dr David Harrison (Head Statistician, ICNARC)		28/11/2017

Version history

Version number	Date	Summary of main changes from previous versions
1.0	10/08/2017	N/A
1.1	27/11/2017	Minor typographical corrections and changes to references; inclusion of baseline/resource use covariates in MI (4.1.4); addition of adherence variable to MI model (4.1.4)

Abbreviations

AIC	Akaike Information Criteria
BIC	Bayesian Information Criteria
CAM-ICU	Confusion Assessment Method for the Intensive Care Unit
CEA	Cost Effectiveness Analysis
CI	Confidence Interval
Cluster-RCT	Cluster-Randomised Controlled Trial
CMP	Case Mix Programme
EQ-5D	EuroQol 5-dimension quality of life questionnaire
GCS	Glasgow Coma Scale
GLMM	Generalised Linear Mixed Model
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health Related Quality of Life
ICNARC	Intensive Care National Audit and Research Centre
IMD	Index of Multiple Deprivation
IPAT	Intensive care Psychological Assessment Tool
ITT	Intent-to-treat
NHS	National Health Service
NMB	Net Monetary Benefit
POPPI	Psychological Outcomes following a nurse-led Preventative Psychological Intervention for critically ill patients
PSS-SR	PTSD Symptom Scale – Self Report version
PTSD	Post-Traumatic Stress Disorder
QALYs	Quality Adjusted Life Years
RASS	Richmond Agitation Sedation Scale
RCT	Randomised Controlled Trial
SAP	Statistical Analysis Plan
STAI	State Trait Anxiety Inventory

Table of contents

1. Background and rationale

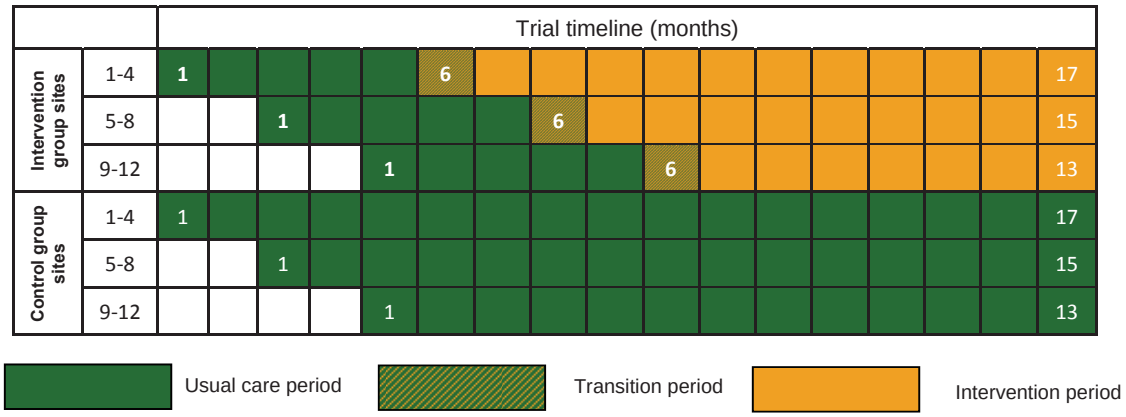
The POPPI (Psychological Outcomes following a nurse-led Preventative Psychological Intervention for critically ill patients) trial ("the Trial") is a cluster-randomised controlled trial (cluster-RCT) comparing a complex nurse-led preventative psychological intervention with usual care in reducing patient-reported post-traumatic stress disorder (PTSD) symptom severity, and other reported psychological morbidities at six months.

The study design (Figure 1) is of 24 sites, randomly assigned to either intervention or control (usual care) groups, each recruiting for between 13 and 17 months, with a staggered start to allow for roll-out of the intervention. The end of the Trial will be when the final patient has completed their six months follow-up.

The purpose of this Statistical Analysis Plan (SAP) is to document the planned analyses to be carried out to support the completion of the Final Report to the study funder and for inclusion in manuscripts for publication in the scientific literature. Additional exploratory analyses, not necessarily identified in this SAP, may also be performed. Any post-hoc or unplanned analyses not identified in this SAP will be clearly identified as such in the respective Report/manuscript.

This SAP has been agreed in advance of inspecting any outcome data from the intervention period of the Trial, so that data-derived decisions in the analyses are avoided.

Figure 1. Cluster-RCT schedule



2. Aim and objectives

2.1. Aim

The aim of the Trial is to evaluate the clinical and cost-effectiveness of a complex nurse-led preventative psychological intervention in reducing patient-reported PTSD[1] symptom severity, and other reported psychological morbidities at six months.

2.2. Objectives

The specific objectives are:

i. To evaluate the effect of the complex intervention on patient-reported PTSD symptom severity and other psychological morbidities and quality of life at six months; and
ii. To estimate, in an integrated economic analysis, the cost-effectiveness of the intervention.

An integrated process evaluation will be conducted to assess the fidelity and quality of the implementation of the intervention, and identify important contextual factors to better understand how the intervention works.

3. Methods

3.1. Trial design

Parallel group cluster-RCT, with staggered opening and a baseline (pre-intervention) period.

3.2. Setting

Twenty-four NHS adult, general critical care units in the UK ("sites").

3.3. Inclusion and exclusion criteria

The inclusion and exclusion criteria of this study are as described below.

3.3.1. Eligibility criteria for sites (clusters)

The following criteria must be met for a site to participate in the Trial. A site must:

i. show that recruitment to target, timely data collection, and delivery of the complex intervention are feasible - via completion of a site feasibility questionnaire;
ii. commit to dedicate adequate resources to carry out the complex intervention;
iii. agree to adhere to randomisation into either the control group or the intervention group;
iv. have two Joint Principal Investigators (PIs) identified to lead POPPI at the site (a lead nurse and a lead clinician);
v. agree, where possible, to recruit all eligible patients to POPPI and to maintain a POPPI Screening Log to include reasons why eligible patients were not recruited
vi. agree to use the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)[2] for assessing delirium and Richmond Agitation Sedation Scale (RASS)[3] for assessing sedation status for the duration of the trial; and
vii. be actively participating in the Case Mix Programme (CMP) – the national clinical audit for critical care units coordinated by ICNARC.

Sites that have taken part as an intervention site in the POPPI Feasibility Study (ISRCTN61088114) were not be eligible for selection.

3.3.1. Inclusion criteria for patients

Patients must meet all of the following criteria:

viii. age 18 years or greater;
ix. greater than 48 hours in the critical care unit;
x. receipt of Level 3 critical care (for any period of time) during first 48 hours in the critical care unit;

xi. between +1 and -1 on the RASS;
xii. Glasgow Coma Scale score of 15;
xiii. English-speaking; and
xiv. ability to communicate orally.

3.3.2. Exclusion criteria for patients

Patients must not meet any of the following criteria:

i. pre-existing chronic cognitive impairment, such as dementia;
ii. pre-existing psychotic illness, such as schizophrenia;
iii. pre-existing chronic posttraumatic stress disorder;
iv. receiving end-of-life care; or
v. previously recruited to POPPI.

3.4. Outcomes

All outcomes will be assessed and reported at the individual patient level.

3.4.1. Primary outcomes

The primary outcome for the clinical evaluation will be patient-reported PTSD symptom severity at six months, measured using the PTSD Symptom Scale – Self Report version (PSS-SR), which conforms to all DSM-IV diagnostic criteria for PTSD and which has been validated for use in critical care unit survivors.[4]

The primary outcomes for the economic evaluation will be incremental costs, quality-adjusted life years (QALYs) and net monetary benefit at six months.

3.4.2. Secondary outcomes

The secondary outcomes will be:

i. days alive and free from sedation to day 30;
ii. duration of critical care unit stay;
iii. PSS-SR greater than 18 points at six months;
iv. depression at six months, measured using the Hospital Anxiety and Depression Scale (HADS)[5];
v. anxiety at six months, measured using the HADS[5]; and
vi. health-related quality of life (HRQoL) at six months, measured by the EuroQol (EQ-5D-5L) questionnaire.

3.5. Power calculation

The initial power calculation for the POPPI cluster-RCT was calculated for the original grant submission and prior to conducting the POPPI feasibility study. It was based on very limited data to inform it – available at that time – namely, routine non-specific (with respect to the proposed POPPI trial population) data from the ICNARC Case Mix Programme (the national clinical audit for adult critical care in the UK) and more specific outcome data but only from a single-centre study of 100 patients. Despite this, to ensure a smooth transition from the POPPI feasibility study to the POPPI cluster-RCT (in the eventuality that feasibility was demonstrated), the initial pre-feasibility study power calculation formed the basis for the original ethics application for the POPPI cluster-RCT.

Following completion of the POPPI feasibility study, the assumptions underlying the initial pre-feasibility study power calculation were reviewed using the results from the feasibility study to ensure the proposed design retained adequate power – to produce the pre-cluster-RCT power calculation. The amount of additional information on which to update the assumptions, however, remained small – with only two critical care units having participated in the RCT processes and procedures feasibility study (providing information on the outcome measure) and a further two critical care units having participated in the delivery of the intervention feasibility study (providing information on rates of consent and patients assessed as being at high risk).

Finally, during the early phase of recruitment to the POPPI cluster-RCT, the assumptions underlying the pre-cluster-RCT power calculation were reviewed again once outcome data became available from the baseline (pre-intervention) period for 20 (of the 24) sites.

Details of these three stages are set out below.

3.5.1. Initial pre-feasibility study power calculation

The original POPPI cluster-RCT design, prior to conducting the POPPI feasibility study, was for 24 sites each recruiting eligible admissions for eleven months. The eleven months consisted of a five-month baseline period during which both intervention and control sites delivered usual care, a one-month transition period (to be excluded from the primary analysis of the cluster-RCT) during which intervention sites were trained and began to deliver the intervention, and a five-month intervention period during which intervention sites delivered the intervention. Control sites continued to deliver usual care throughout the baseline, transition and intervention periods. This design was selected to provide at least 90% power,

based on the method of Hussey and Hughes for a general, multi-period, cluster-randomised controlled trial[6] with a type I error rate of 0.05 and based on the following assumptions:

- a mean of 14 points and standard deviation of 12 points for the PSS-SR (primary outcome measure) for control group patients and for intervention group patients during the baseline period – estimated from patients receiving usual care in a previous single-centre study[7];
- an estimated intra-cluster correlation (ICC) of 0.254 – estimated, as there was no multicentre data available for the PSS-SR, by making a conservative assumption of 0.5 for the between-site coefficient of variation[8] (corresponding to a between-site standard deviation of 7 points);
- a detectable treatment effect of a reduction of 4 points on the PSS-SR based on a difference between groups equivalent to the reliable change index for the PSS-SR[9] (of 8 points) being observed in 50% of eligible patients assessed as being at high risk of psychological morbidity using the IPAT[10] in intervention sites during the intervention period; and
- an estimated harmonic mean of the number of patients completing follow-up of 76 per site per annum (corresponding to 32 in each five-month period) – estimated using data from the ICNARC Case Mix Programme for potentially eligible patients admitted to adult, general critical care units across England, Wales and Northern Ireland, assuming 10% mortality at six months following recruitment and 80% follow-up among survivors.

It was anticipated that, with the above design and assumptions, the estimated total number of patients recruited would be 2,904 (based on Case Mix Programme data). Staged roll-out in three staggers, each of eight sites (four intervention and four control) two months apart, was planned solely for practical delivery of the training for the intervention.

The above initial pre-feasibility study power calculation was included in the original trial protocol submitted for ethical approval (submitted during the feasibility study due to the need to transition rapidly from feasibility study to cluster-RCT) and was in place at the start of recruitment to the POPPI cluster-RCT.

3.5.2. Pre-cluster-RCT power calculation

Following completion of the feasibility study and prior to the start of recruitment to the cluster-RCT, the assumptions underlying the initial pre-feasibility study power calculation were reviewed using results from the feasibility study, resulting in the following assumptions:

- a mean of 6 points and standard deviation of 7.5 points for the PSS-SR (primary outcome measure);

- an estimated ICC of 0.138 – estimated by retaining a conservative assumption of 0.5 for the between-site coefficient of variation (corresponding to a between-site standard deviation of 3 points);
- a detectable treatment effect of a reduction of 2.9 points on the PSS-SR based on a difference between groups equivalent to a re-estimated reliable change index for the PSS-SR (of 8.6 points) being observed in 40% of eligible patients assessed as being at high risk of psychological morbidity using the IPAT, with 16% of recruited patients declining the intervention;
- an estimated harmonic mean of the number of patients completing follow-up of 52 per site per annum (corresponding to 22 in each five-month period) – re-estimated using data from the ICNARC Case Mix Programme for potentially eligible patients admitted to the 24 critical care units participating in the POPPI cluster-RCT, and retaining the assumptions, supported by data from the feasibility study, of 10% mortality at six months following recruitment and 80% follow-up among survivors.

This power calculation review established that the planned design retained greater than 90% power under these revised assumptions. It was anticipated that, with the above design and assumptions, the estimated total number of patients recruited would be 1,914 (based on Case Mix Programme data) in the 24 sites.

3.5.3. Final review of assumptions in pre-cluster-RCT power calculation

During the early phase of recruitment to the cluster-RCT, the day-to-day Trial Management Group noted that the recruitment rate was below anticipated. A decision was taken, in consultation with the Independent Chairs and members of the Trial Steering Committee and the Data Monitoring and Ethics Committee, to undertake a further review of the assumptions underlying the pre-cluster-RCT power calculation once outcome data were available for patients recruited during the five-month baseline period in both intervention and control sites. This review, undertaken using data available on 9 August 2016 (in month 12 of study recruitment), identified:

- a mean of 10.3 points and standard deviation of 10.8 points for the PSS-SR (primary outcome measure);
- an ICC of 0.087 (95% confidence interval 0 to 0.192) for the PSS-SR;
  [with mean, standard deviation and ICC estimated using all available data from the previous observational study, the feasibility study and the baseline period of the cluster-RCT]
- a detectable treatment effect of a reduction of 4.2 points on the PSS-SR – estimated by retaining the same effect size as a multiple of the within-site standard deviation;

- an harmonic mean of the number of patients completing follow-up of 30.7 per site per annum (corresponding to 12.8 in each five-month period) – estimated using observed data from the baseline period.

This review of assumptions established that the planned design had an anticipated 78% power under the observed parameter estimates (and, allowing for uncertainty in the between-site variation, between 73% and 85% power).

Consequently, the decision was taken to extend recruitment in stagger 1 and 2 sites to the end of planned recruitment in stagger 3 sites (corresponding to an harmonic mean of 16.5 patients completing follow-up per site during the intervention period, allowing for the variation from five to nine months duration across staggers). With this extension to recruitment, the planned design had an anticipated 85% power (and, allowing for uncertainty in the between-site variation, between 79% and 91% power). It was anticipated that, with this extension to recruitment, the estimated total number of patients recruited would be 1,378.

Recruitment continued to be monitored closely to ensure 1,378 (or more) patients were recruited and, to ensure this, a further extension to recruitment for an additional two months in all sites was approved by the Independent Chairs and members of the Trial Steering Committee and the Data Monitoring and Ethics Committee.

3.6. Allocation of sites

Participating sites were allocated to intervention or control groups using a restricted randomisation approach. A full enumeration approach to minimising imbalance[11] was selected to ensure balance across the arms in geographical location, teaching status and size of unit. Balance on geographical location was ensured by grouping the sites within each stagger according to location. We performed simulations of alternative ways to balance on size of unit comparing:

i. Balancing on teaching status and number of beds
ii. Balancing on teaching status and number of level 3 admissions
iii. Balancing on teaching status, number of beds and number of level 3 admissions

The best combination of balancing on the above three factors (balance on teaching status and number of level 3 admissions) was used to perform the final random allocation. Each stagger was made up of 8 sites and allocated 4 each to the intervention and control groups. The site allocations were done during the second month of recruitment for each stagger, on 3 November 2015, 16 December 2015 and 17 February 2016, respectively.

4. Statistical methods

4.1. General analysis issues

4.1.1. Analysis population

All analyses will be based on the intention to treat principle. The patients will be analysed according to the group they were randomised to, irrespective of whether the treatment allocated was received.

4.1.2. Sequence of planned analyses

All final, planned, analyses identified in the protocol and in this SAP will be performed only after the last patient has completed his/her treatment and the outcome measures have been recorded. A blinded data review meeting may be held prior to database lock and completion of the final analyses. In addition, the database will not be unlocked, random code unblinded or analyses completed until this SAP has been approved.

As the duration of follow-up for the primary outcome (6 months) is long relative to the duration of recruitment (intervention period between 7 and 11 months), no interim analysis of effectiveness was planned.

4.1.3. Analysis software

Analyses will be performed using Stata/SE Version 14.2 for Windows 64-bit x86-64 (StataCorp LP, College Station, Texas, USA). Multiple imputation will be performed in R Version 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria).[12]

4.1.4. Methods for withdrawals and missing data

All the patients who provided informed consent will be accounted for in the report of the Trial. Mortality at six months is anticipated to be 10% and loss to follow-up for the primary outcome is anticipated to be 20% among survivors. Loss-to follow-up for mortality at six months is anticipated to be <1%. Patients that withdraw from the trial and do not give permission for data collected prior to withdrawal will be used in the final analysis, those that die before six months and those lost to follow-up for mortality will be excluded from the analysis of six month psychological outcomes. Patients recruited during the transition period will also be excluded from the analysis. All other recruited patients will be included in the primary analysis, with outcomes imputed.

Loss to follow-up will be reported by treatment group. Reasons for withdrawal and loss to follow-up will be reported, when known.

Multiple imputation will be used to complete missing baseline and resource use covariates and non and partial responses for the PSS-SR, HADS and EQ-5D-5L, under the assumption that responses are missing at random (MAR) conditional on the observed data.[13] Two-level imputation (patients nested in sites) will be implemented using the 'jomo' package in R.[14] The overall scores on each measure will be imputed, not individual item responses. The imputation model will include the following covariates:

- Site level covariates (* denotes covariates used to balance treatment allocation):
    - Teaching status of hospital (teaching, non-teaching)*
    - Number of beds in the critical care unit (linear)
    - Number of critical care unit admissions receiving Level 3 care staying at least 48h during the pre-trial period,1 April 2014 to 31 March 2015 (linear)*
    - Allocated treatment group (intervention, control)
- Patient level covariates:
    - Time period (baseline, intervention) and interaction with treatment group
    - Age in years (linear)
    - Gender (female, male)
    - Ethnicity (white, non-white)
    - Quintile of Index of Multiple Deprivation (IMD) 2015[15] (categorical)
    - Documented pre-existing anxiety and/or depression prior to hospital admission (anxiety, depression, both, none)
    - Planned admission to the critical care unit following elective/scheduled surgery (yes, no)
    - ICNARC Physiology Score[16] from the first 24h following admission to the critical care unit (linear)
    - Last National Early Warning Score (NEWS)[17] prior to consent (linear)
    - Health-related quality of life (HRQOL) at time of consent, assessed as health thermometer score from 0 to 100 (linear)
    - Short-form State-Trait Anxiety Inventory (STAI-6)[18] at time of consent, scored from 6 to 24 (linear)
    - Duration of stay in the critical care unit in days (linear)
    - Number of days of delirium, as assessed by the CAM-ICU[2], in the critical care unit (linear)
    - Number of days receiving sedatives/anxiolytics/anaesthetics in the critical care unit (linear)
    - Number of days receiving sleep medications in the critical care unit (linear)

- Receipt of benzodiazepines in the critical care unit (yes, no)
- Number of days receiving antipsychotics in the critical care unit (linear)
- Number of days receiving analgesics in the critical care unit (linear)
- Number of days receiving antidepressants in the critical care unit (linear)
- Number of days receiving vasoactive agents in the critical care unit (linear)
- Number of days receiving mechanical ventilation in the critical care unit (linear)
- Duration of stay in hospital following discharge from the critical care unit (linear)
- Adherence to intervention (binary)
- PSS-SR at six months (linear)
- HADS at six months (linear)
- EQ-5D-5L at six months (linear)

Twenty multiply imputed datasets will be generated using Markov Chain Monte Carlo (MCMC) drawing a sample every 1000 iterations, following an initial 1000 iteration burn-in. The random number seed will be set to 6627.

For the primary clinical and cost effectiveness outcomes two sensitivity analyses will be used to address alternative assumptions regarding the missing data mechanism: missing completely at random (MCAR) and missing not at random (MNAR).

To evaluate the results under the assumption of MCAR, the analyses will be repeated using complete case data (i.e. only those patients returning a completed questionnaire).

To evaluate the results under the assumption that responses are MNAR, i.e. the probability of missing data depends on the patient's outcome after conditioning on the observed data; a pattern-mixture model approach[19] will be used. Pattern-mixture models allow the outcome to be modelled differently according to whether it is observed or missing. To inform the assumptions about the parameters for the missing pattern that cannot be estimated from the data (sensitivity parameters), expert opinion about outcome differences between patients with missing versus complete data will be elicited from a representative sample of the clinical staff involved with the POPPI trial across the different trial centres and other interested experts.[20]

4.1.5. Data transformation

If applicable, appropriate method of transformation (e.g. log, squared, cubic, square root, etc.) will be use to transform non-normally distributed continuous variables.

4.1.6. Multiple comparisons and multiplicity

No adjustment will be made to account for multiple endpoints or multiple subgroups; P<0.05 will be taken to represent a statistically significant result. The results of subgroup analyses will be interpreted taking into account the number of significant findings that would have been expected by chance alone.

4.2. Statistical analyses

4.2.1. Screening and recruitment

Screening, recruitment and follow-up will be presented in the form of a CONSORT diagram, based on the CONSORT extension for cluster-randomised trials.[21]

Descriptive statistics will be performed using the screening logs completed by all the participating sites during patient recruitment period. Patients' data recorded which will be summarized are as follows:

1. Total patients admitted
2. Total patients who stayed >48 hrs (Yes/No) – n (% of total admitted)
3. Total patients completed screening (patients with a final status) – n
4. Total patients not completed screening (patients without final status) – n
5. Patients who met stable criteria (Yes/No) – n (% of total completed screening)
    a. Reason did not meet stable criteria:
        i. No level 3 care in 1st 48 hrs – n (% of those not meeting stable criteria)
        ii. Not aged ≥ 18 yrs – n (% of those not meeting stable criteria)
        iii. Not English speaking – n (% of those not meeting stable criteria)
        iv. Previous recruited to POPPI – n (% of those not meeting stable criteria)
        v. Pre-existing chronic cognitive impairment – n (% of those not meeting stable criteria)
        vi. Pre-existing chronic PTSD – n (% of those not meeting stable criteria)
        vii. Pre-existing psychotic illness – n (% of those not meeting stable criteria)
6. Met daily transient criteria (Yes/No) – n (% of those meeting stable criteria)
    (To work out Yes: Met stable criteria = Yes AND Final status = Not eligible)
7. Reason did not meet transient criteria:
    a. Able to communicate orally - n (% of those not meeting transient criteria

b. Between +1 and -1 on the RASS - n (% of those not meeting transient criteria)
c. GCS of 15 - n (% of those not meeting transient criteria)
d. Not receiving end of life care - n (% of those not meeting transient criteria)
e. Able to consent - n (% of those not meeting transient criteria)

8. Potentially eligible patients (enrolled, refused, eligible not enrolled, other AND eligibility unknown)
   a. Missed – n (%)
   b. Eligibility unknown (%)
9. Approached (enrolled AND refused consent) (Yes/No) – n (% of potentially eligible)
   a. Enrolled – n (% of approached)
   b. Refused consent – n (% of approached)
10. Patient level indicators (to be produced overall and per month):
   a. How many times each patient underwent daily screening
      i. When screening ended for each patient (date of admission + day last screened)
   b. Percentage of days screening not occurring (e.g. weekends)

4.2.2. Demographic and baseline characteristics

Baseline demographic and clinical data will be summarised for the ITT population, for each of the two treatment groups in each of the two time periods. Continuous variables will be summarized as mean (standard deviation) and median (interquartile range) whilst categorical variables will be summarized as number (percent). There will be no statistical testing for any of the summary measures whilst comparing the baseline variables between the treatment groups. The following baseline variables will be compared between the two treatment groups.

i. Age in years
ii. Gender (female, male)
iii. Ethnicity (white, mixed, Asian, black, other, not stated)
iv. Quintile of IMD 2015 (1=least deprived to 5=most deprived)
i. Documented pre-existing anxiety/depression (anxiety, depression, both, none)
ii. Planned admission to the critical care unit following elective/scheduled surgery (yes, no)
iii. ICNARC Physiology Score from the first 24h following admission to the critical care unit
iv. APACHE II score from the first 24h following admission to the critical care unit
v. Duration of stay in the critical care unit prior to consent

vi. Number of days experiencing delirium in the critical care unit prior to consent
vii. Last NEWS prior to consent
viii. STAI-6 at time of consent
ix. HRQOL at time of consent (health thermometer score)

4.2.3. Treatments received in the critical care unit

Treatments received in the critical care unit will be summarised for the ITT population, for each of the two treatment groups in each of the two time periods. Treatments received will be summarised as number (percent) of patients receiving the treatment, the median (interquartile range) number of days on which the treatment was received (among those receiving the treatment) and the mean (standard deviation) number of days on which the treatment was received (for all patients, including those that did not receive the treatment). There will be no statistical testing for any of the summary measures whilst comparing the treatment variables between the treatment groups. The following treatment variables will be compared between the two treatment groups:

i. Sedatives/anxiolytics/anaesthetics
ii. Sleep medications
iii. Benzodiazepines (note that benzodiazepines will also be included as either sedatives/anxiolytics/anaesthetics or sleep medications, as appropriate)
iv. Antipsychotics
v. Analgesics
vi. Antidepressants
vii. Vasoactive agents
viii. Mechanical ventilation

4.2.4. Delivery of the intervention

Uptake of the POPPI Online Training will be reported for intervention sites over time as the percentage of the enumerated critical care unit staff that had completed the training course by month against a target of >80% completion.

Delivery of the intervention at a patient level will be summarised for patients in the intervention group during the intervention period. The following will be reported for all patients:

i. Number (percent) of patients consenting to assessment using the Intensive care Psychological Assessment Tool (IPAT)
ii. Among those consenting, number (percent) of patients assessed using the IPAT
iii. Median (interquartile range) IPAT score
iv. Number (percent) of patients with IPAT score ≥ 7

The following will be reported for patients with IPAT score ≥ 7:

v. Number (percent) of patients by number of stress support sessions received (0, 1, 2, 3)
vi. Reasons for not receiving all three stress support sessions
vii. Number of patients receiving tablet computer (percent of those receiving stress support session one)
viii. Number of patients reporting using tablet computer (percent of those receiving tablet computer)
ix. Numbers of patients receiving Relax and Recover DVD and Getting well, staying well booklet (percent of patients receiving stress support session two)

4.2.5. Clinical effectiveness analysis – primary outcome

The primary analysis for the clinical evaluation will examine if there is a significant difference in the mean PSS-SR at six months between patients recruited to the intervention group compared to the control group using a generalised linear mixed model (GLMM) at the individual patient level (patients nested within sites and within treatment group/time period).

The model will include the following terms:

- Fixed effects at the site level (* denotes covariates used to balance treatment allocation):
    - Teaching status of hospital (teaching, non-teaching)*
    - Number of beds in the critical care unit (linear)
    - Number of critical care unit admissions receiving Level 3 care staying at least 48h during the pre-trial period,1 April 2014 to 31 March 2015 (linear)*
    - Allocated treatment group (intervention, control)
- Fixed effects at the patient level:
    - Time period (baseline, intervention) and interaction with treatment group
    - Age in years (restricted cubic splines, 4 knots)
    - Gender (female, male)
    - Ethnicity (white, non-white)
    - Quintile of IMD 2015 (categorical)
    - Documented pre-existing anxiety and/or depression prior to hospital admission (anxiety, depression, both, none)
    - Planned admission to the critical care unit following elective/scheduled surgery (yes, no)
    - ICNARC Physiology Score from the first 24h following admission to the critical care unit (restricted cubic splines, 4 knots)

- Random effects (intercepts) at the following levels:
    - Site

The identity link (i.e. linear regression) will be used as the link function for the model and robust variance estimation[22] will be used to estimate the standard errors of the covariates as it adjusts for possible deviations from the model's assumptions. Rubin's rules will be used to combine estimates from the multiply imputed datasets. The coefficients with their 95% confidence intervals (CI) and p-values will be presented for the fixed effect covariates whilst only the coefficients with their 95% CI will be reported for the random effect variables. The primary effect estimate will be the interaction (difference in difference) between treatment group and time period. Similar models will be developed for the secondary outcomes.

A secondary analysis will use structural mean models with an instrumental variable of randomised allocated treatment to estimate the efficacy (adherence adjusted causal effect) of the stress support sessions among those patients consenting to psychological assessment and stress support sessions, assessed as being at high risk of psychological morbidity (IPAT score ≥ 7) and receiving at least two stress support sessions.[23]

A sensitivity analysis allowing the missing PSS-SR to be MNAR will use Bayesian pattern-mixture models, consistent with the specification for the primary analysis. All priors will be 'minimally informative', except those governing the differences between the observed and missing outcomes which will be informed by expert opinion. The sensitivity of the results to a full range of diversity of opinion will be examined through a comparison of pooled and individual priors. Posterior probabilities and 95% credible intervals will be reported.

4.2.6. Clinical effectiveness analysis – secondary outcomes

Analyses of the secondary outcomes will also be performed using GLMMs (like the primary outcome analysis), with identity link (i.e. linear regression) for continuous secondary outcomes (reported as difference in means with 95% CI and p-value) and logit link (i.e. logistic regression) for binary secondary outcomes (reported as odds ratio with 95% CI and p-value). Robust variance estimation method will be used to estimate the standard errors of the covariates in both the mixed linear and logistic regression models.

4.2.7. Sub-group analyses

There are planned subgroups and interaction analyses proposed for this study. The a priori identified subgroups that will be used for the subgroup analyses are as follows:

i. Age
    - Quartiles

ii. Gender
    - Male versus Female
iii. Socio-economic status - Quintile of IMD 2015
    - 1 - Least deprived vs 2 vs 3 vs 4 vs 5 - Most deprived
iv. Duration of delirium
    - No delirium vs Delirium < median duration vs Delirium ≥ median duration
v. State trait anxiety inventory score (STAI)
    - Quartiles
vi. Surgical status
    - Emergency/urgent surgery vs Elective/scheduled surgery vs Non-surgical
vii. Overall site engagement (from process evaluation work)
    - Low vs Medium vs High
viii. Heterogeneity of treatment effect
    - Derivation of a risk prediction model for the primary outcome using the usual care patients' data adjusting for a priori important covariates (age, gender, socioeconomic status, duration of delirium, STAI, surgical status) and then grouping patients based on quintiles of predicted risk of outcome

The evaluation of the treatment effect on the primary outcome of this study will be carried out using a formal test of interaction which will be obtained from the linear mixed effect regression models.[24] The linear mixed effect model will contain a main effect term denoting the specific subgroup of interest, a main effect term for treatment group and a subgroup x treatment interaction term.

4.2.8. Process evaluation

Analysis of the process evaluation will use a combination of qualitative and quantitative methods to assess and describe the variation in the delivery of the intervention across sites. Analysis of the process evaluation will be conducted independent of the Trial team before the outcome evaluation to avoid any bias in the interpretation of the process data and to generate hypotheses that may be subsequently tested in statistical analyses of integrated process and outcome data. The structural mean models described above will be extended to incorporate additional potential mediator variables on the causal pathway between treatment allocation and treatment effect identified by the independent process evaluation team, e.g. nurse competence following training, adherence to the therapeutic approach, adherence to therapy and overall site engagement.[25]

4.2.9. Economic evaluation

A full CEA will be undertaken to assess the relative cost-effectiveness of psychological assessment followed by stress support sessions for those assessed as being at high risk of psychological morbidity versus usual care. Resource use and outcome data collected as part of the cluster-RCT will be used to report cost-effectiveness at six months and to project the lifetime cost-effectiveness of each strategy.

The cost analysis will take a health and personal health services perspective.[26] Cost will be calculated from patient level resource use data on length of stay in critical care and hospital, for the index admission and any readmission before six months (recorded in the trial dataset), use of personal health services after hospital discharge and within six months post-randomisation (collected through patient questionnaire), and additional staff time required to deliver the interventions (collected from site visits). Resource use data from the site visits, cluster-RCT dataset and six-month questionnaires will be combined with unit costs from the NHS Payment by Results database and from local Trust Finance Departments, to report the total costs per patient at six months for intervention versus usual care.[27,28]

HRQoL data from the EQ-5D-5L questionnaires at six months will be combined with survival data to report QALYs at six months. QALY will be calculated by valuing each patient's survival time by their health-related QOL at six months according to the 'area under the curve' approach.[29] For six month survivors, QALYs will be calculated using the EQ-5D scores at six months, assuming an EQ-5D score of zero at randomisation, and a linear interpolation between randomisation and six months. For decedents between randomisation and six months, we will assume zero QALYs.

The CEA will follow the intention-to-treat principle and report the mean (95% confidence interval) incremental costs, QALYs and net monetary benefit (NMB) at six months. Missing data in resource use and HRQoL will be handled with multiple imputation methods as described in the clinical analysis section. As a sensitivity analysis, Bayesian pattern-mixture models will be used to allow departures from MAR for the missing HRQoL, using a similar approach to that for the clinical effectiveness primary outcome.

The CEA will use GLMMs that allow for clustering of patients[30] including site as a random effect variable and period as a fixed effect variable. The analysis will adjust for pre-specified baseline covariates at both patient and site level. The primary effect estimate will be the interaction (difference in difference) between treatment groups and time period. The cost-effectiveness analysis will use this model to estimate the effect of the intervention on mean

cost and mean QALY (allowing for the correlation between the costs and QALY at the individual and cluster level).

Lifetime cost-effectiveness will be projected by summarising the relative effects of alternative strategies on long-term survival and HRQoL, informed by extrapolations of patient survival data.[31,32] The long-term modelling will extrapolate from the cluster-RCT data by fitting alternative parametric survival curves (e.g. Weibull, exponential, lognormal, log logistic and Gompertz) to the maximum available survival data recorded in the trial dataset. The chosen method of survival extrapolation for the base case analysis will be the one judged most plausible[33] according to model fit (Akaike information criteria (AIC) or Bayesian information criteria (BIC)), and in comparison with age-gender matched all-cause mortality. Quality of life generally deteriorates after critical care discharge for up to 6 months and then slowly improves over time but remains lower than that in the general population over long-term.[34] In the base case analysis, quality of life decrement of the study population compared with age-gender matched population[35] at six months will be applied allowing for improvement in quality of life over the years of excess mortality. After period of excess mortality, quality of life from age-gender matched general population will be applied. Lifetime costs attributable to initial episode of critical illness will be estimated by utilising longer term readmission costs data to patients who were randomised early. The longer term costs will be applied over the period of excess mortality. Predicted survival and HRQoL will be combined to report lifetime QALYs, and to project lifetime incremental costs, incremental QALYs, and incremental net benefits for the alternative strategies of care. Sensitivity analyses will test whether the results are robust to methodological assumptions (e.g. specification of the statistical model, extrapolation approach, alternative HRQoL assumptions, and learning curve effects).

Adherence adjusted analysis and subgroup analysis will be undertaken for the pre-specified subgroups as per the analysis of clinical effectiveness.

5. Reporting conventions

The following reporting conventions will be adopted for the SAP. These conventions will enhance the review of the study report and help to standardize presentation with common notations.

i. Sample sizes will be presented for each treatment group as totals in the column header as “(N = xxx)”, where appropriate.

ii. Sample sizes shown with summary statistics are the samples sizes (n) of patients with non-missing values.

iii. All summaries for categorical variables will include all categories that were available and will not be restricted to those with at least one response.

iv. Summaries for continuous variables that are approximately normally distributed will be reported as n, mean and standard deviation.

v. Summaries for continuous variables that are not normally distributed will be reported as n, median and quartiles.

vi. All percentages will be rounded and reported to a single decimal place (xx.x%). A percentage of 0% will be reported as “0%”; a percentage of 100% will be reported as “100%”.

vii. Summaries that include P-values will report the P-value to three decimal places with a leading zero (0.xxx). P-values of less than 0.0005 will be reported as “<0.001” not “0.000”.

viii. Missing values for both numeric and string variables will be presented as dashes (“---”) or as “Not available” / “Not applicable” / “Not reported” (as appropriate) in tables or data listings.

6. Proposed tables and figures

6.1. Clinical evaluation tables

Table 1: Baseline demographic and clinical variables by treatment groups

Variables	Baseline period		Intervention period	
	Intervention	Usual Care	Intervention	Usual Care
	N = XXX	N = XXX	N = XXX	N = XXX
Demography				
Age (years):				
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)
Gender:				
Female, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Male, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Ethnicity:				
White, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Mixed, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Asian/Asian British, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Black/Black British, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Not stated, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Quintile of IMD 2015:				
1 - Least deprived, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
2, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
3, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
4, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
5 - Most deprived, n (%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Documented pre-existing anxiety/depression:				
Anxiety, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Depression, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Both, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
None, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Planned admission to the critical care unit following elective/schedule surgery				
Yes, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
No, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
ICNARC Physiology Score:				
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)
APACHE II score:				
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)

n: Number of patients; %: Percentage of patients; N: Total number of patients
SD: Standard deviation; IQR: Inter-quartile range; BMI: Body mass index.

Table 1: Con't

Variables	Baseline period		Intervention period	
	Intervention	Usual Care	Intervention	Usual Care
	N = XXX	N = XXX	N = XXX	N = XXX
Duration of critical care unit stay prior to consent:				
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)
Number of days experiencing delirium in the critical care unit prior to consent				
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)
Last NEWS prior to consent				
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)
STAI-6 at time of consent				
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)
HRQOL (health thermometer score) at time of consent:				
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)	XX (XX,XX)

Table 2: Concomitant medications used by treatment groups

Variables	Baseline period		Intervention period	
	Intervention	Usual Care	Intervention	Usual Care
	N = XXX	N = XXX	N = XXX	N = XXX
Sedatives/anxiolytics/anaesthetics received:				
Chlordiazepoxide, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Clobazam, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Clonidine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Desflurane, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Dexmedetomidine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Diazepam, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Etomidate, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Halothane, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Isoflurane, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Ketamine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Lorazepam, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Midazolam, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Propofol, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Sevoflurane, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Thiopentone, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Sleep medication received:				
Flurazepam, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Lormetazepam, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Nitrazepam, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Temazepam, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Zolpidem, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Zopiclone, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Benzodiazepines	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Antipsychotic medication received:				
Chlorpromazine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Clozapine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Flupentixol, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Haloperidol, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Olanzapine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Quetiapine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Risperidone, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)

Table 2: Con't

Variables	Baseline period		Intervention period	
	Intervention	Usual Care	Intervention	Usual Care
	N = XXX	N = XXX	N = XXX	N = XXX
Analgesics received:				
Alfentanil, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Co-codamol, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Codeine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Co-dydramol, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Diamorphine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Dihydrocodeine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Fentanyl, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Morphine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Oxycodone, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Remifentanil, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Tramadol, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Antidepressants received:				
Amitriptyline, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Citalopram, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Fluoxetine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Mirtazapine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Paroxetine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Reboxetine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Sertraline, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Venlafaxine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Actual vasoactive agent received:				
Adrenaline, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Dobutamine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Dopamine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Dopexamine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Metaraminol, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Noradrenaline, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Phenylephrine, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Vasopressin, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
Other, n(%)	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)

n: number of patients; %: percentage of patients; N: total number of patients

Table 3: Linear mixed effect model for PSS-SR at six months – primary analysis

Variables	Coefficient	95% CI	P-value
Fixed effects at the site level*:			
Teaching status of hospital*:			
Teaching	0		
Non-Teaching	XX.X	XX.X , XX.X	0.XXX
Number of beds in the critical care unit (per additional bed)*	XX.X	XX.X , XX.X	0.XXX
Number of CCU admissions receiving Level 3 care staying at least 48hr during the pre-trial period,1 April 2014 to 31 March 2015 (per additional 100 admissions)*	XX.X	XX.X , XX.X	0.XXX
Allocated treatment group:			
Usual care	0		
Intervention	XX.X	XX.X , XX.X	0.XXX
Fixed effects at the patient level:			
Time period:			
Baseline period	0		
Intervention period	XX.X	XX.X , XX.X	0.XXX
Interaction between time period and treatment group:			
Intervention period * Intervention group	XX.X	XX.X , XX.X	0.XXX
Age in years (restricted cubic splines, 4 knots)			
Age spline 1	XX.X	XX.X , XX.X	0.XXX
Age spline 2	XX.X	XX.X , XX.X	
Age spline 3	XX.X	XX.X , XX.X	
Gender:			
Male	0		
Females	XX.X	XX.X , XX.X	0.XXX
Ethnicity:			0.XXX
White, n (%)	0		
Mixed, n (%)	XX.X	XX.X , XX.X	
Asian/Asian British, n (%)	XX.X	XX.X , XX.X	
Black/Black British, n (%)	XX.X	XX.X , XX.X	
Others, n (%)	XX.X	XX.X , XX.X	
Quintile of IMD 2015:			0.XXX
1 - Least deprived, n (%)	0		
2, n (%)	XX.X	XX.X , XX.X	
3, n (%)	XX.X	XX.X , XX.X	
4, n (%)	XX.X	XX.X , XX.X	
5 - Most deprived, n (%)	XX.X	XX.X , XX.X	
Pre-existing anxiety/depression:			0.XXX
Anxiety, n(%)	0		
Depression, n(%)	XX.X	XX.X , XX.X	
Both, n(%)	XX.X	XX.X , XX.X	
None, n(%)	XX.X	XX.X , XX.X	
Planned admission to the CCU following elective/schedule surgery			
Yes, n(%)	0		

No, n(%)	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score from the first 24h following admission to the critical care unit (restricted cubic splines, 4 knots)			
ICNARC Physiology Score spline 1	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score spline 2	XX.X	XX.X , XX.X	
ICNARC Physiology Score spline 3	XX.X	XX.X , XX.X	
Random Effects			
Site	XX.X	XX.X , XX.X	-

CI: Confidence interval.

* - Covariates used to balance treatment allocation

Table 4a: Linear mixed effect model for days alive and free from sedation to day 30

Variables	Coefficient	95% CI	P-value
Fixed effects at the site level*:			
Teaching status of hospital*:			
Teaching	0		
Non-Teaching	XX.X	XX.X , XX.X	0.XXX
Number of beds in the critical care unit (per additional bed)*	XX.X	XX.X , XX.X	0.XXX
Number of CCU admissions receiving Level 3 care staying at least 48hr during the pre-trial period,1 April 2014 to 31 March 2015 (per additional 100 admissions)*	XX.X	XX.X , XX.X	0.XXX
Allocated treatment group:			
Usual care	0		
Intervention	XX.X	XX.X , XX.X	0.XXX
Fixed effects at the patient level:			
Time period:			
Baseline period	0		
Intervention period	XX.X	XX.X , XX.X	0.XXX
Interaction between time period and treatment group:			
Intervention period * Intervention group	XX.X	XX.X , XX.X	0.XXX
Age in years (restricted cubic splines, 4 knots)			
Age spline 1	XX.X	XX.X , XX.X	0.XXX
Age spline 2	XX.X	XX.X , XX.X	
Age spline 3	XX.X	XX.X , XX.X	
Gender:			
Male	0		
Females	XX.X	XX.X , XX.X	0.XXX
Ethnicity:			0.XXX
White, n (%)	0		
Mixed, n (%)	XX.X	XX.X , XX.X	
Asian/Asian British, n (%)	XX.X	XX.X , XX.X	
Black/Black British, n (%)	XX.X	XX.X , XX.X	
Others, n (%)	XX.X	XX.X , XX.X	
Quintile of IMD 2015:			0.XXX
1 - Least deprived, n (%)	0		
2, n (%)	XX.X	XX.X , XX.X	
3, n (%)	XX.X	XX.X , XX.X	
4, n (%)	XX.X	XX.X , XX.X	
5 - Most deprived, n (%)	XX.X	XX.X , XX.X	
Pre-existing anxiety/depression:			0.XXX
Anxiety, n(%)	0		
Depression, n(%)	XX.X	XX.X , XX.X	
Both, n(%)	XX.X	XX.X , XX.X	
None, n(%)	XX.X	XX.X , XX.X	
Planned admission to the CCU following elective/schedule surgery			
Yes, n(%)	0		

No, n(%)	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score from the first 24h following admission to the critical care unit (restricted cubic splines, 4 knots)			
ICNARC Physiology Score spline 1	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score spline 2	XX.X	XX.X , XX.X	
ICNARC Physiology Score spline 3	XX.X	XX.X , XX.X	
Random Effects			
Site	XX.X	XX.X , XX.X	-

CI: Confidence interval.

* - Covariates used to balance treatment allocation

Table 4b: Linear mixed effect model for duration of critical care unit stay

Variables	Coefficient	95% CI	P-value
Fixed effects at the site level*:			
Teaching status of hospital*:			
Teaching	0		
Non-Teaching	XX.X	XX.X , XX.X	0.XXX
Number of beds in the critical care unit (per additional bed)*	XX.X	XX.X , XX.X	0.XXX
Number of CCU admissions receiving Level 3 care staying at least 48hr during the pre-trial period,1 April 2014 to 31 March 2015 (per additional 100 admissions)*	XX.X	XX.X , XX.X	0.XXX
Allocated treatment group:			
Usual care	0		
Intervention	XX.X	XX.X , XX.X	0.XXX
Fixed effects at the patient level:			
Time period:			
Baseline period	0		
Intervention period	XX.X	XX.X , XX.X	0.XXX
Interaction between time period and treatment group:			
Intervention period * Intervention group	XX.X	XX.X , XX.X	0.XXX
Age in years (restricted cubic splines, 4 knots)			
Age spline 1	XX.X	XX.X , XX.X	0.XXX
Age spline 2	XX.X	XX.X , XX.X	
Age spline 3	XX.X	XX.X , XX.X	
Gender:			
Male	0		
Females	XX.X	XX.X , XX.X	0.XXX
Ethnicity:			0.XXX
White, n (%)	0		
Mixed, n (%)	XX.X	XX.X , XX.X	
Asian/Asian British, n (%)	XX.X	XX.X , XX.X	
Black/Black British, n (%)	XX.X	XX.X , XX.X	
Others, n (%)	XX.X	XX.X , XX.X	
Quintile of IMD 2015:			0.XXX
1 - Least deprived, n (%)	0		
2, n (%)	XX.X	XX.X , XX.X	
3, n (%)	XX.X	XX.X , XX.X	
4, n (%)	XX.X	XX.X , XX.X	
5 - Most deprived, n (%)	XX.X	XX.X , XX.X	
Pre-existing anxiety/depression:			0.XXX
Anxiety, n(%)	0		
Depression, n(%)	XX.X	XX.X , XX.X	
Both, n(%)	XX.X	XX.X , XX.X	
None, n(%)	XX.X	XX.X , XX.X	
Planned admission to the CCU following elective/schedule surgery			
Yes, n(%)	0		

No, n(%)	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score from the first 24h following admission to the critical care unit (restricted cubic splines, 4 knots)			
ICNARC Physiology Score spline 1	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score spline 2	XX.X	XX.X , XX.X	
ICNARC Physiology Score spline 3	XX.X	XX.X , XX.X	
Random Effects			
Site	XX.X	XX.X , XX.X	-

CI: Confidence interval.

* - Covariates used to balance treatment allocation

Table 4c: Logistic mixed effect model for PSS-SR greater than 18 points at six months

Variables	Odds ratio	95% CI	P-value
Fixed effects at the site level*:			
Teaching status of hospital*:			
Teaching	0		
Non-Teaching	XX.X	XX.X , XX.X	0.XXX
Number of beds in the critical care unit (per additional bed)*	XX.X	XX.X , XX.X	0.XXX
Number of CCU admissions receiving Level 3 care staying at least 48hr during the pre-trial period,1 April 2014 to 31 March 2015 (per additional 100 admissions)*	XX.X	XX.X , XX.X	0.XXX
Allocated treatment group:			
Usual care	0		
Intervention	XX.X	XX.X , XX.X	0.XXX
Fixed effects at the patient level:			
Time period:			
Baseline period	0		
Intervention period	XX.X	XX.X , XX.X	0.XXX
Interaction between time period and treatment group:			
Intervention period * Intervention group	XX.X	XX.X , XX.X	0.XXX
Age in years (restricted cubic splines, 4 knots)			
Age spline 1	XX.X	XX.X , XX.X	0.XXX
Age spline 2	XX.X	XX.X , XX.X	
Age spline 3	XX.X	XX.X , XX.X	
Gender:			
Male	0		
Females	XX.X	XX.X , XX.X	0.XXX
Ethnicity:			0.XXX
White, n (%)	0		
Mixed, n (%)	XX.X	XX.X , XX.X	
Asian/Asian British, n (%)	XX.X	XX.X , XX.X	
Black/Black British, n (%)	XX.X	XX.X , XX.X	
Others, n (%)	XX.X	XX.X , XX.X	
Quintile of IMD 2015:			0.XXX
1 - Least deprived, n (%)	0		
2, n (%)	XX.X	XX.X , XX.X	
3, n (%)	XX.X	XX.X , XX.X	
4, n (%)	XX.X	XX.X , XX.X	
5 - Most deprived, n (%)	XX.X	XX.X , XX.X	
Pre-existing anxiety/depression:			0.XXX
Anxiety, n(%)	0		
Depression, n(%)	XX.X	XX.X , XX.X	
Both, n(%)	XX.X	XX.X , XX.X	
None, n(%)	XX.X	XX.X , XX.X	
Planned admission to the CCU following elective/schedule surgery			
Yes, n(%)	0		

No, n(%)	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score from the first 24h following admission to the critical care unit (restricted cubic splines, 4 knots)			
ICNARC Physiology Score spline 1	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score spline 2	XX.X	XX.X , XX.X	
ICNARC Physiology Score spline 3	XX.X	XX.X , XX.X	
Random Effects			
Site	XX.X	XX.X , XX.X	-

CI: Confidence interval.

* - Covariates used to balance treatment allocation

Table 4d: Linear mixed effect model for HADS depression score at six month

Variables	Coefficient	95% CI	P-value
Fixed effects at the site level*:			
Teaching status of hospital*:			
Teaching	0		
Non-Teaching	XX.X	XX.X , XX.X	0.XXX
Number of beds in the critical care unit (per additional bed)*	XX.X	XX.X , XX.X	0.XXX
Number of CCU admissions receiving Level 3 care staying at least 48hr during the pre-trial period,1 April 2014 to 31 March 2015 (per additional 100 admissions)*	XX.X	XX.X , XX.X	0.XXX
Allocated treatment group:			
Usual care	0		
Intervention	XX.X	XX.X , XX.X	0.XXX
Fixed effects at the patient level:			
Time period:			
Baseline period	0		
Intervention period	XX.X	XX.X , XX.X	0.XXX
Interaction between time period and treatment group:			
Intervention period * Intervention group	XX.X	XX.X , XX.X	0.XXX
Age in years (restricted cubic splines, 4 knots)			
Age spline 1	XX.X	XX.X , XX.X	0.XXX
Age spline 2	XX.X	XX.X , XX.X	
Age spline 3	XX.X	XX.X , XX.X	
Gender:			
Male	0		
Females	XX.X	XX.X , XX.X	0.XXX
Ethnicity:			0.XXX
White, n (%)	0		
Mixed, n (%)	XX.X	XX.X , XX.X	
Asian/Asian British, n (%)	XX.X	XX.X , XX.X	
Black/Black British, n (%)	XX.X	XX.X , XX.X	
Others, n (%)	XX.X	XX.X , XX.X	
Quintile of IMD 2015:			0.XXX
1 - Least deprived, n (%)	0		
2, n (%)	XX.X	XX.X , XX.X	
3, n (%)	XX.X	XX.X , XX.X	
4, n (%)	XX.X	XX.X , XX.X	
5 - Most deprived, n (%)	XX.X	XX.X , XX.X	
Pre-existing anxiety/depression:			0.XXX
Anxiety, n(%)	0		
Depression, n(%)	XX.X	XX.X , XX.X	
Both, n(%)	XX.X	XX.X , XX.X	
None, n(%)	XX.X	XX.X , XX.X	
Planned admission to the CCU following elective/schedule surgery			
Yes, n(%)	0		

No, n(%)	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score from the first 24h following admission to the critical care unit (restricted cubic splines, 4 knots)			
ICNARC Physiology Score spline 1	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score spline 2	XX.X	XX.X , XX.X	
ICNARC Physiology Score spline 3	XX.X	XX.X , XX.X	
Random Effects			
Site	XX.X	XX.X , XX.X	-

CI: Confidence interval.

* - Covariates used to balance treatment allocation

Table 4e: Linear mixed effect model for HADS anxiety score at six months

Variables	Coefficient	95% CI	P-value
Fixed effects at the site level*:			
Teaching status of hospital*:			
Teaching	0		
Non-Teaching	XX.X	XX.X , XX.X	0.XXX
Number of beds in the critical care unit (per additional bed)*	XX.X	XX.X , XX.X	0.XXX
Number of CCU admissions receiving Level 3 care staying at least 48hr during the pre-trial period,1 April 2014 to 31 March 2015 (per additional 100 admissions)*	XX.X	XX.X , XX.X	0.XXX
Allocated treatment group:			
Usual care	0		
Intervention	XX.X	XX.X , XX.X	0.XXX
Fixed effects at the patient level:			
Time period:			
Baseline period	0		
Intervention period	XX.X	XX.X , XX.X	0.XXX
Interaction between time period and treatment group:			
Intervention period * Intervention group	XX.X	XX.X , XX.X	0.XXX
Age in years (restricted cubic splines, 4 knots)			
Age spline 1	XX.X	XX.X , XX.X	0.XXX
Age spline 2	XX.X	XX.X , XX.X	
Age spline 3	XX.X	XX.X , XX.X	
Gender:			
Male	0		
Females	XX.X	XX.X , XX.X	0.XXX
Ethnicity:			0.XXX
White, n (%)	0		
Mixed, n (%)	XX.X	XX.X , XX.X	
Asian/Asian British, n (%)	XX.X	XX.X , XX.X	
Black/Black British, n (%)	XX.X	XX.X , XX.X	
Others, n (%)	XX.X	XX.X , XX.X	
Quintile of IMD 2015:			0.XXX
1 - Least deprived, n (%)	0		
2, n (%)	XX.X	XX.X , XX.X	
3, n (%)	XX.X	XX.X , XX.X	
4, n (%)	XX.X	XX.X , XX.X	
5 - Most deprived, n (%)	XX.X	XX.X , XX.X	
Pre-existing anxiety/depression:			0.XXX
Anxiety, n(%)	0		
Depression, n(%)	XX.X	XX.X , XX.X	
Both, n(%)	XX.X	XX.X , XX.X	
None, n(%)	XX.X	XX.X , XX.X	
Planned admission to the CCU following elective/schedule surgery			
Yes, n(%)	0		

No, n(%)	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score from the first 24h following admission to the critical care unit (restricted cubic splines, 4 knots)			
ICNARC Physiology Score spline 1	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score spline 2	XX.X	XX.X , XX.X	
ICNARC Physiology Score spline 3	XX.X	XX.X , XX.X	
Random Effects			
Site	XX.X	XX.X , XX.X	-

CI: Confidence interval.

* - Covariates used to balance treatment allocation

Table 4f: Linear mixed effect model for health related quality of life at six months

Variables	Coefficient	95% CI	P-value
Fixed effects at the site level*:			
Teaching status of hospital*:			
Teaching	0		
Non-Teaching	XX.X	XX.X , XX.X	0.XXX
Number of beds in the critical care unit (per additional bed)*	XX.X	XX.X , XX.X	0.XXX
Number of CCU admissions receiving Level 3 care staying at least 48hr during the pre-trial period,1 April 2014 to 31 March 2015 (per additional 100 admissions)*	XX.X	XX.X , XX.X	0.XXX
Allocated treatment group:			
Usual care	0		
Intervention	XX.X	XX.X , XX.X	0.XXX
Fixed effects at the patient level:			
Time period:			
Baseline period	0		
Intervention period	XX.X	XX.X , XX.X	0.XXX
Interaction between time period and treatment group:			
Intervention period * Intervention group	XX.X	XX.X , XX.X	0.XXX
Age in years (restricted cubic splines, 4 knots)			
Age spline 1	XX.X	XX.X , XX.X	0.XXX
Age spline 2	XX.X	XX.X , XX.X	
Age spline 3	XX.X	XX.X , XX.X	
Gender:			
Male	0		
Females	XX.X	XX.X , XX.X	0.XXX
Ethnicity:			0.XXX
White, n (%)	0		
Mixed, n (%)	XX.X	XX.X , XX.X	
Asian/Asian British, n (%)	XX.X	XX.X , XX.X	
Black/Black British, n (%)	XX.X	XX.X , XX.X	
Others, n (%)	XX.X	XX.X , XX.X	
Quintile of IMD 2015:			0.XXX
1 - Least deprived, n (%)	0		
2, n (%)	XX.X	XX.X , XX.X	
3, n (%)	XX.X	XX.X , XX.X	
4, n (%)	XX.X	XX.X , XX.X	
5 - Most deprived, n (%)	XX.X	XX.X , XX.X	
Pre-existing anxiety/depression:			0.XXX
Anxiety, n(%)	0		
Depression, n(%)	XX.X	XX.X , XX.X	
Both, n(%)	XX.X	XX.X , XX.X	
None, n(%)	XX.X	XX.X , XX.X	
Planned admission to the CCU following elective/schedule surgery			
Yes, n(%)	0		

No, n(%)	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score from the first 24h following admission to the critical care unit (restricted cubic splines, 4 knots)			
ICNARC Physiology Score spline 1	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score spline 2	XX.X	XX.X , XX.X	
ICNARC Physiology Score spline 3	XX.X	XX.X , XX.X	
Random Effects			
Site	XX.X	XX.X , XX.X	-

CI: Confidence interval.

* - Covariates used to balance treatment allocation

Table 5: Structural mean models for PSS-SR at six months using randomised allocated treatment as an instrumental variable

Variables	Coefficient	95% CI	P-value
Fixed effects at the site level*:			
Teaching status of hospital*:			
Teaching	0		
Non-Teaching	XX.X	XX.X , XX.X	0.XXX
Number of beds in the critical care unit (per additional bed)*	XX.X	XX.X , XX.X	0.XXX
Number of CCU admissions receiving Level 3 care staying at least 48hr during the pre-trial period,1 April 2014 to 31 March 2015 (per additional 100 admissions)*	XX.X	XX.X , XX.X	0.XXX
Allocated treatment group:			
Usual care	0		
Intervention	XX.X	XX.X , XX.X	0.XXX
Fixed effects at the patient level:			
Time period:			
Baseline period	0		
Intervention period	XX.X	XX.X , XX.X	0.XXX
Interaction between time period and treatment group:			
Intervention period * Intervention group	XX.X	XX.X , XX.X	0.XXX
Age in years (restricted cubic splines, 4 knots)			
Age spline 1	XX.X	XX.X , XX.X	0.XXX
Age spline 2	XX.X	XX.X , XX.X	
Age spline 3	XX.X	XX.X , XX.X	
Gender:			
Male	0		
Females	XX.X	XX.X , XX.X	0.XXX
Ethnicity:			0.XXX
White, n (%)	0		
Mixed, n (%)	XX.X	XX.X , XX.X	
Asian/Asian British, n (%)	XX.X	XX.X , XX.X	
Black/Black British, n (%)	XX.X	XX.X , XX.X	
Others, n (%)	XX.X	XX.X , XX.X	
Quintile of IMD 2015:			0.XXX
1 - Least deprived, n (%)	0		
2, n (%)	XX.X	XX.X , XX.X	
3, n (%)	XX.X	XX.X , XX.X	
4, n (%)	XX.X	XX.X , XX.X	
5 - Most deprived, n (%)	XX.X	XX.X , XX.X	
Pre-existing anxiety/depression:			0.XXX
Anxiety, n(%)	0		
Depression, n(%)	XX.X	XX.X , XX.X	
Both, n(%)	XX.X	XX.X , XX.X	
None, n(%)	XX.X	XX.X , XX.X	
Planned admission to the CCU following elective/schedule surgery			
Yes, n(%)	0		

No, n(%)	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score from the first 24h following admission to the critical care unit (restricted cubic splines, 4 knots)			
ICNARC Physiology Score spline 1	XX.X	XX.X , XX.X	0.XXX
ICNARC Physiology Score spline 2	XX.X	XX.X , XX.X	
ICNARC Physiology Score spline 3	XX.X	XX.X , XX.X	
Random Effects			
Site	XX.X	XX.X , XX.X	-

6.2. Economic evaluation tables

Table 6: Parameter estimates of the parametric survival models used for extrapolating survival curves

	Parameter estimates	
Distribution	**Scale/Rate**	**Shape**
Exponential	xx.x	N/A
Weibull	xx.x	xx.x
Lognormal(sdlog/meanlog)	xx.x	xx.x
Log-logistic	xx.x	xx.x
Gompertz	xx.x	xx.x

Table 7: Survival probabilities of the parametric survival models

Time (Years)	Exponential	Weibull	Lognormal	Log-logistic	Gompertz
0	1	1	1	1	1
1	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
2	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
3	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
.	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
.	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
.	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
.	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
.	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
.	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
.	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
.	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
.	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
.	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
98	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
99	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
100	x.xxx	x.xxx	x.xxx	x.xxx	x.xxx

Table 8: Rank of Goodness of fit estimates (AIC and BIC) for parametric survival models

Distribution	AIC	BIC	Ranking
Exponential	xxx.x	xxx.x	x
Weibull	xxx.x	xxx.x	x
Lognormal	xxx.x	xxx.x	x
Log-logistic	xxx.x	xxx.x	x
Gompertz	xxx.x	xxx.x	x

6.3. Figures

Figure 1: CONSORT flow diagram

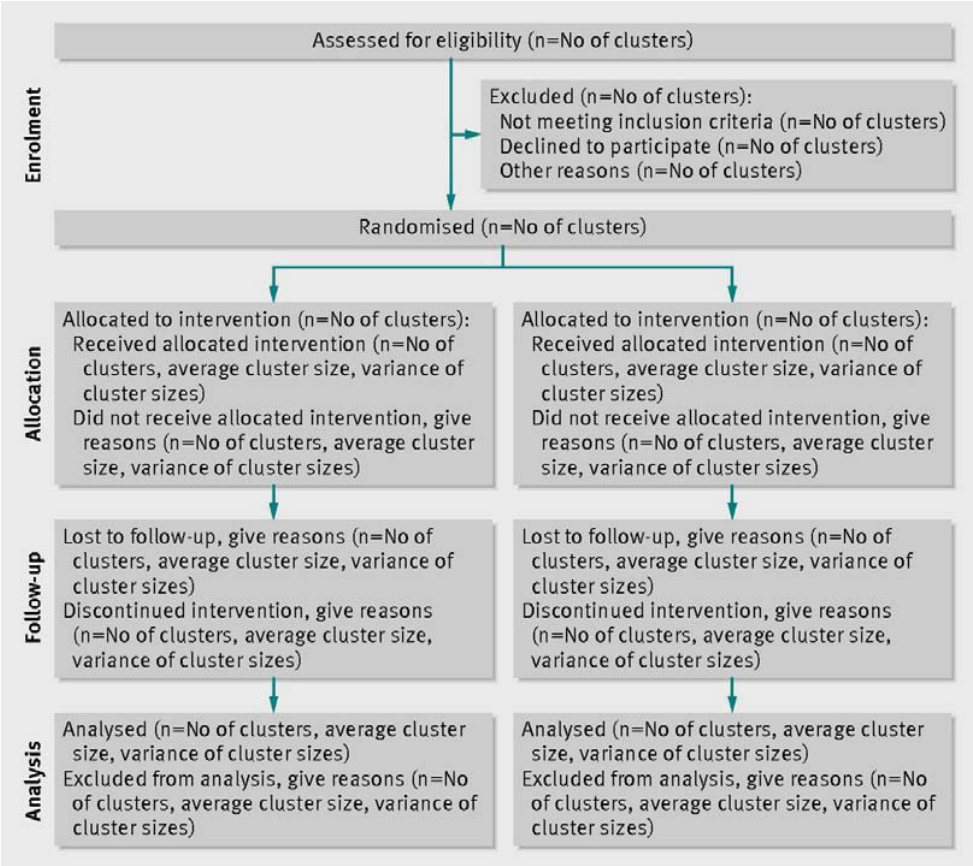


Figure 2: Kaplan-Meier plot of comparing intervention and control groups during intervention period

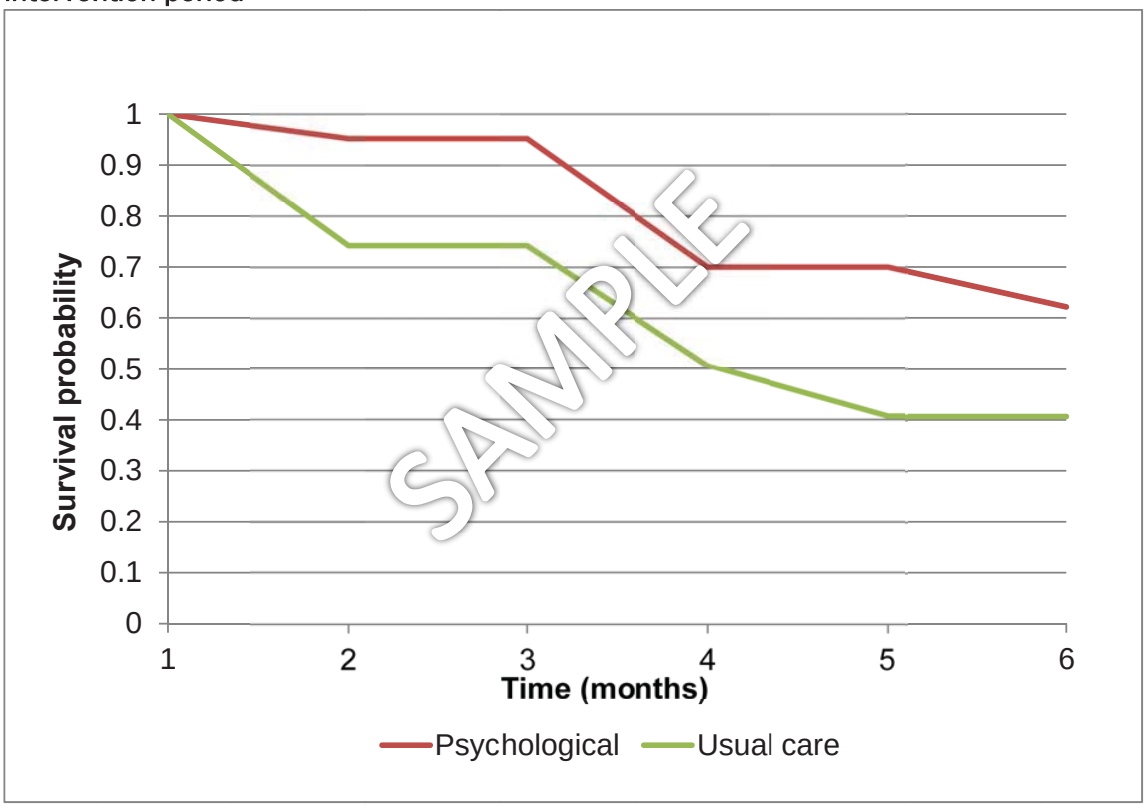
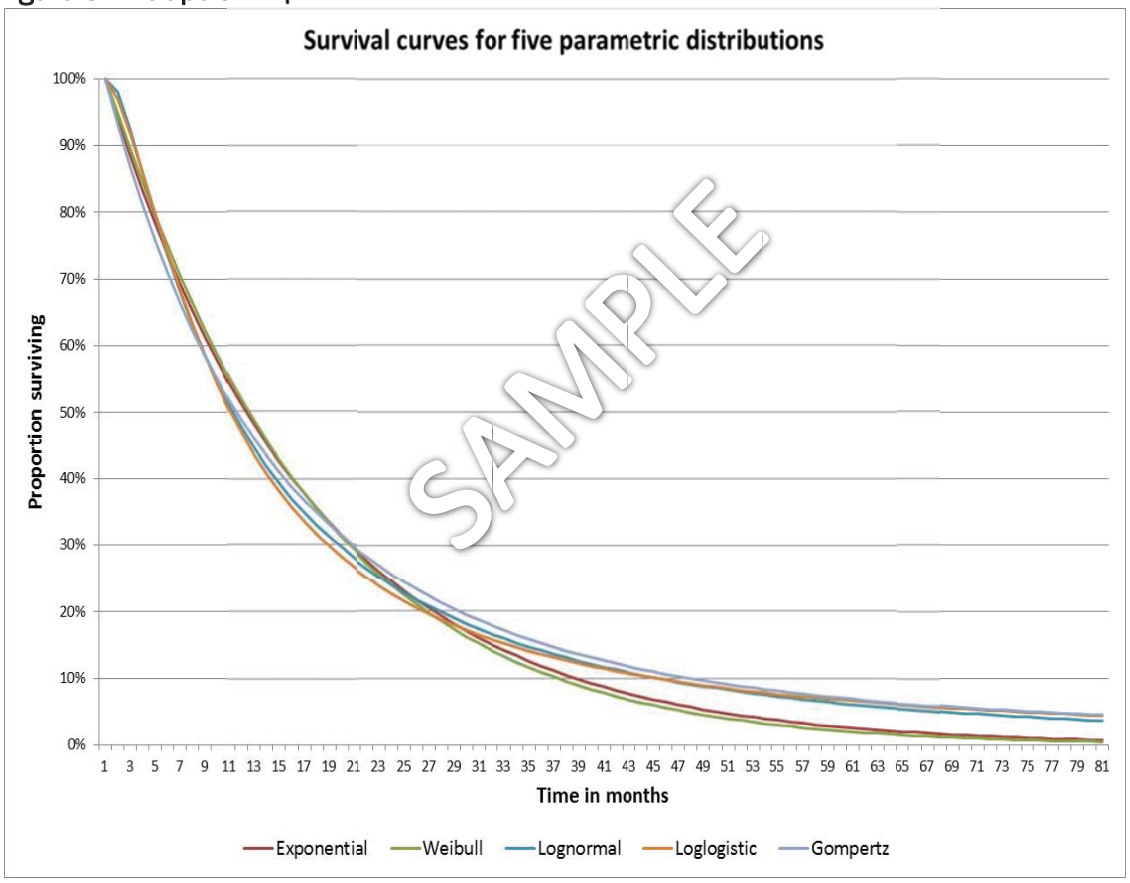


Figure 3: Extrapolated parametric survival curves for five distributions



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Statistical analysis plan summary of changes

Statistical analysis plan v1.0, 10 August 2017

Original statistical analysis plan

Statistical analysis plan v1.1, 27 November 2017

1) Inclusion of baseline/resource use covariates in multiple imputation (MI).
2) Addition of adherence variable to MI model.
3) Minor typographical and reference changes.

Annexe: Deviations from the SAP

Section	Change	Justification
4.1.4	Multiple imputation was undertaken using the package ‘mice’ rather than ‘jomo’	The mice package also supports multilevel imputation and allows predictive mean matching which is suitable for imputing data with irregular distributions
4.1.4	Length of stay in general medical wards, costs of ICU stay and costs from the Health Services Questionnaire were included in the imputation models	Omission
4.1.4	50 imputed datasets were generated rather than 20	Larger than anticipated amount of missing data for costs
4.2.1	Information on daily screening was not reported	Adequate detailed daily screening data were not available from all sites
4.2.2	Additional baseline characteristics were reported on reasons for ICU admission	Requested by reviewer
4.2.2	Additional baseline characteristics were reported on time from ICU admission to consent and proportion of patients consented in ICU	Higher than anticipated proportion of patients consented after ICU discharge
4.2.4	Additional intervention data were reported on the location of the stress support sessions and the STAI-6 before and after the sessions	To provide additional detail on delivery of the intervention
4.2.8	Structural mean models incorporating process evaluation findings have yet to be produced	Likely to form the basis of a future PhD