Evaluation of a Rehabilitation Complex Intervention for patients following Intensive Care Discharge.
The RECOVER study

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The RECOVER study. Study Protocol version 7. 30/01/2012
Lay Summary

Patients who survive intensive care (ICU) are often disabled after discharge. They experience physical, psychological and social problems that impair recovery to pre-illness quality of life. A recent NICE guideline highlighted the need to undertake research in this area and improve current standards of care.

We have developed an intervention to enhance physical rehabilitation following ICU discharge. The intervention utilises a generic rehabilitation assistant to deliver coordinated enhanced treatment to patients throughout the hospital and provide support after hospital discharge, under the supervision of existing multidisciplinary teams. In a randomised trial design we will compare this novel approach with current standard care in 240 ICU survivors who required \( \geq 2 \) days ventilation in ICU. Our primary outcome is patient disability 3 months post-randomisation, but we will measure a range of other relevant secondary outcomes at 3, 6, and 12 months post-randomisation. We will also undertake a qualitative study with patients/carers and a cost-effectiveness analysis.
### Clinical Trial Summary

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<th>ClinicalTrials.gov identifier</th>
<th>ISRCTN09412438</th>
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**Study hypothesis**

Patients who survive intensive care (ICU) and their carers cope with severe disability during a protracted and often incomplete recovery. The problems suffered include physical, psychological, and social problems, which are prevalent and often severe. Health related quality of life (HRQoL) is reduced and recovers slowly, and the direct (health care) and indirect (carers/family) costs during this period are probably high but are not well studied. A recent report ("Quality Critical Care")(DoH, 2005), and a NICE guideline (NICE, 2009) have highlighted the need to improve rehabilitation for this patient group.

The aim of this study is to evaluate the outcome of enhanced ward-based rehabilitation, compared to current standard care, on patient's physical function at 3, 6 and 12 months after intensive care discharge. The intervention utilises a generic healthcare assistant (GRA) to deliver coordinated enhanced treatment to patients throughout the hospital and provide support after hospital discharge, under the supervision of existing multidisciplinary teams. A feasibility randomised controlled trial of enhanced physiotherapy and dietetic management using a GRA demonstrated markedly enhanced levels of treatments could be successfully delivered with this model.

Our focus is on assessing the clinical and cost effectiveness of service reorganisation that better achieves the recommendations in the NICE guideline, and delivers greater physical and dietetic rehabilitation treatments.

**Ethics approval**

The Scotland Research Ethics Committee (REC) A approved on the 8th June 2010 (ref: 10/MRE00/18)

**Study design**

Multicentre prospective randomised controlled parallel group trial with concealment of outcome assessment

**Countries of recruitment**

United Kingdom

**Disease/condition/study domain**

Rehabilitation; intensive care

**Participants – inclusion criteria**

- The patient has required ≥ 48 hours of continuous invasive (via an endotracheal and/or tracheostomy tube) mechanical ventilation in the intensive care unit (ICU)
- The consultant in charge of the patient considers them fit for discharge from the ICU

**Participants - exclusion criteria**

- Primary neurological admission diagnosis (brain trauma; intracerebral bleed; stroke; Guillain-Barre syndrome)
- The clinician in charge of care anticipates withdrawing or limiting all active treatment (except palliative care) within the next 24 hours.
The RECOVER study. Study Protocol version 7. 30/01/2012

Patient currently receiving palliative care (active life support has been discontinued)
Patients currently receiving home ventilation or planning to commence a program of home ventilation
The patient is expected to be discharged from ICU to a non-study hospital where the intervention cannot be received
Gaining informed consent, following the intervention or follow-up is not feasible, despite resources available, due to communication difficulties
Patient currently enrolled in another RCT with similar endpoints
Patient aged <18 years at time of screening

Target number of participants
240 patients from 2 centres in Scotland

Interventions
Participants will be randomised into one of two groups:
Intervention group: Standard ward-based care delivered by the NHS service with additional access to enhanced rehabilitation during ward stay and telephone contact after discharge, based around a GRA working with existing NHS clinical teams.
Control group: Standard ward-based care delivered by the current NHS service

Total duration of intervention is from randomisation to 3 months post-randomisation.
The total duration of follow-up is 12 months from randomisation for both groups.

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Chief Investigator: Prof. Timothy S. Walsh

Western General Hospital
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Primary outcome measure(s)
Rivermead Mobility Index, assessed at 3 months

Secondary outcome measure(s)
The impact of the complex intervention on physical, psychological and social functioning will be measured at 3 months using:
1. Total, Physical Component Score, and Mental Component Score SF12v2
2. Hospital Anxiety and Depression (HAD) questionnaire
3. Davidson’s Trauma Scale score (DTS)
4. Nutritional Status (subjective global assessment of nutrition; SGA nutrition, physical component)
5. Hand grip strength strength (HG dynamometry)
6. 2m timed up and go time
7. Visual analogue scores (fatigue, appetite, breathlessness, joint stiffness, pain)
8. Patient Satisfaction measure
9. Health economic questionnaire
10. Process measures
11. Research Log of Generic Rehabilitation Assistants

Assessments at 6 and 12 months - Rivermead Mobility Index, SF12v2, HAD, DTS and health economic questionnaires, visual analogue scores.
Additional outcomes:
To compare patient and carer experiences between usual care and the new strategy (Focus group study)
To evaluate the cost-effectiveness of the novel approach
1 Introduction

This document is a clinical protocol for a human research study. The trial is not a Clinical Trial of an Investigational Medicinal Product (CTIMP), but investigates the impact of a complex healthcare intervention on patient outcomes following intensive care. This study is to be conducted according to international standards of Good Clinical Practice (International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Of the 10,000 patients admitted annually to 25 intensive care units (ICUs) across Scotland, 20% die in the ICU and up to 40% within 12 months. Survivors and their carers cope with severe disability during a protracted and often incomplete recovery. The disability suffered includes physical, psychological, and social problems, which are common and often severe. Health related quality of life (HRQoL) is reduced and recovers slowly. The direct (health care) and indirect (carers/family) costs during this period are probably high, but are not well-studied. A recent report ("Quality Critical Care") and a NICE guideline have highlighted the need to improve rehabilitation for this patient group. The systematic review undertaken during NICE guideline development indicated a lack of high quality research concerning what interventions improve rehabilitation of these patients, and their clinical and cost-effectiveness. Recommended future research questions included: "For patients at high risk of critical illness-associated morbidity, what is the clinical effectiveness and cost effectiveness of organised critical care rehabilitation versus usual care on physical and psychological functioning, participation and quality of life?" Our proposed trial directly addresses this question.

Based on our literature review, the NICE guideline, and our own experience we identify the following key issues in this area:

Patients health problems are wide-ranging: The health problems that follow critical illness have been called the "post-ICU syndrome". Physical impairment is typified by malnutrition, which is worsened by poor appetite and nausea. Patients can lose 10-30% of their body mass during critical illness. Recovery is further delayed by joint stiffness, pain and neuropathies; levels of fatigue and breathlessness are high. Muscle weakness is particularly common and strongly associated with poor outcome. Problems with psychological health and social functioning are also common. Anxiety, depression, and post-traumatic stress reactions (such as post-traumatic stress disorder, PTSD) are reported in 10-40% of patients.

Patient rehabilitation is currently not co-ordinated: Survivors are currently managed with inconsistent fragmented strategies post-ICU discharge. Typically, specialty-based teams lead care and patients are widely dispersed within the hospital. Importantly, patients effectively "compete" with less sick patient groups (e.g. elective surgery patients) for limited rehabilitation resource. We found that 70% of patients were discharged directly home from the acute hospital without clearly planned rehabilitation. Coordination with primary care services is poor and inconsistent, and knowledge of the specific problems faced by the post-ICU patient is very limited. The NICE guideline and our own experience suggest this is the current "usual care" service model in NHS hospitals.

Patients are major users of acute hospital resource: Intensive care costs £1500 per day, and 50,000 ICU bed days are utilised annually across Scotland. Patients with a length of stay ≥2 days comprise 30-40% of all admissions, but utilise 70-80% of ICU bed days, and continue to utilise enormous hospital resource post-ICU discharge. For example, in 2006 we found an additional 4166 non-ICU hospital bed days were utilised in the Royal Infirmary of Edinburgh after ICU discharge by the 20% of patients who required ≥4 days in ICU, equivalent to an 11-12 bed ward fully occupied throughout the year. Across Scotland ~20,000 acute bed days are utilised annually by such patients after ICU discharge. Numbers of patients are projected to increase by up to three-fold by 2031 as a result of the aging "baby-boomer" population (K Rowan personal communication).

Patient outcomes are poor: Many patients report poor pre-ICU HRQoL and have chronic health problems prior to ICU admission, but HRQoL is significantly reduced in most patients following ICU discharge. Impaired physical function is particularly common during the first 3-6 months after discharge. Typically, recovery of HRQoL takes at least 12 months. Over 50% of patients are below retirement age and only
half of those previously working have returned to work by 12 months. Patients have an excess risk of death compared to age and sex matched population for up to 5 years after discharge\textsuperscript{6}.

Remarkably little research has evaluated interventions to improve outcomes following ICU discharge. A small randomised controlled trial showed that self-help manuals, supported by a researcher, improved physical function at 6 months\textsuperscript{12}. A recent RCT found improvements in physical function at hospital discharge associated with early mobilisation in the ICU, but this has already become standard care in many UK ICUs and the study did not address longer term patient benefits or report cost-effectiveness\textsuperscript{13}. Most existing UK service models are based on nurse led follow up clinics at 3-12 months post hospital discharge, with little emphasis on the early recovery phase. No agreed or validated model for these services exists, and clinics only exist in 30\% of UK ICUs\textsuperscript{14}. A recent CSO funded RCT (the PRaCTiCaL study) compared usual care with a nurse led intervention that included provision of a self help manual and clinic review at 3 and 9 months post-hospital discharge.\textsuperscript{11} The intervention did not improve HRQoL (SF-36) or psychological morbidity at 6 or 12 months, but it is uncertain whether unmeasured benefits occurred.

The NICE guideline identified little high quality evidence to guide recommendations, which were based largely on expert opinion\textsuperscript{8}. Several key principles relevant to “best practice” and future research design were identified: first, the use of screening tools to identify patients at risk of different problems; second, the need for early intervention during recovery; third, an emphasis on communication between health care professionals and with patients and carers; fourth, structured multidisciplinary rehabilitation programmes that address individual patient needs, involve the patient in decision-making and goal setting, and are regularly reviewed during the patient journey; fifth, better coordination of health care professionals during the patient journey (including post-hospital discharge). We plan to evaluate an enhanced rehabilitation programme starting when ICU discharge is planned and lasting until a 3 months follow up point, with further 6 months follow up. Our focus is on assessing the clinical and cost effectiveness of service reorganisation that better achieves the recommendations in the NICE guideline, and delivers greater physical and dietetic rehabilitation treatments. We recognise that other studies will need to examine psychological and other potentially useful interventions, and longer term rehabilitation.

1.2 Summary of published trials of rehabilitation following critical illness

1.3 Pre-Trial Work

A qualitative interview based study evaluating the experience of 20 survivors of long-term ventilation (>14 days) during the 6 months following ICU discharge (PhD thesis; Ramsay, co-applicant) found patients experienced profound debilitation during the ward phase of recovery and were frustrated by fragmented or specialty-led care, which seemed neither to take account of their individual needs nor issues specific to critical illness. Many were distressed by a perceived indifference amongst busy ward staff towards their significant dependence and needs. Concerns focused on the brevity and perceived inadequacy of rehabilitative provision (especially physiotherapy), while others felt “outside” the rehabilitation process, in terms of their individual contribution and longer term goals and strategies. Many patients were discharged home with limited understanding of the nature or severity of their critical illness, which contributed to unrealistic expectations of recovery. In general, patients were ill-equipped to manage their own recovery following hospital discharge and had limited access to clinicians in order to address their concerns.

A prospective audit of physiotherapy and dietetic intervention between ICU and hospital discharge found that mobility problems and poor nutrition were highly prevalent and persisted at discharge home. Despite this, key mobility elements, such as transfers and walking were only taught/supervised by a physiotherapist on average once a week. Individualised exercises for strengthening and training were rarely undertaken, and goal setting was unusual. Dietetic review was undertaken on average only once weekly, recommendations were rarely monitored, and implementation was therefore inconsistent. Mobility levels at hospital discharge were very poor (Median (IQR) Rivermead mobility index 7 (2.5-10); normal value 15). Calorie and protein intakes levels were only 87\% (IQR 60-105) and 83\% (62-99) of required intake respectively, implying nutritional status was worsening rather than improving in many cases. A key limitation was lack of staff dedicated to these patients.

A prospective observational study of physical function and HRQoL for up to 6 months post ICU (N = 68) confirmed poor HRQoL, especially in physical domains. Importantly, many patients had
marked physical disability throughout the study (for example: 6 minute walk test at 3 months: 20/44 patients unable to attempt, mean (SD) distance achieved in other 24 patients 367 (130)m) and high levels of fatigue (mean score on 0-10 Visual Analogue Scale (VAS) 5 (IQR 3-7) at both 3 and 6 months).

We developed a service model based around a generic rehabilitation assistant to coordinate and deliver rehabilitation for these patients throughout their hospital stay and maintain contact after hospital discharge. In our model, rehabilitation is planned and supervised by “hard-stretched” specialist staff based on multidisciplinary meetings, but delivered by a single dedicated assistant. We undertook a **feasibility randomised controlled trial of enhanced physiotherapy and dietetic management** using a generic rehabilitation assistant (N = 16 patients), and demonstrated markedly enhanced levels of treatments could be successfully delivered with this model. The generic rehabilitation assistant successfully worked autonomously across multiple areas of the hospital with multidisciplinary supervision. We demonstrated that current standard NHS care per patient comprises 4-5 visits per week (100 minutes treatment/week). The generic rehabilitation assistant increased this to 14-15 visits per week (3-400 minutes treatment/week). Using these data we estimated that, allowing for annual leave, 2.5 WTE Band 4 generic rehabilitation assistants are required to deliver continuous care to 100 patients across the two hospitals during the study (2-3 weeks inpatient stay per patient; 4-6 patients undergoing treatment at any time; cost ≈£950 per treated patient).

2 Study Objectives

**Primary Objective**
To evaluate the impact on physical, psychological and social functioning of a novel strategy to enhance delivery of physical and nutritional rehabilitation to patients during the three months following ICU discharge.

**Secondary Objectives**
To evaluate the cost-effectiveness of the novel approach.
To compare patient and carer experiences and satisfaction between usual care and the new strategy.

3 Study Design

3.1 **General Design**
Prospective, randomised, parallel group, controlled trial with concealment of outcome assessment.

A schematic diagram describing the trial structure is shown in figure 1:
3.2 Primary Study Endpoint
Rivermead mobility index at 3 months post-randomisation

3.3 Secondary Study Endpoints

**Patient outcomes:**

*In hospital:*
1. Hospital length of stay
2. ICU readmission rate
3. Survival to hospital discharge
4. Rivermead mobility index (weekly assessment)
5. Visual analogue score (fatigue; breathlessness; appetite; pain; joint stiffness) (weekly assessment)
6. Confusion-Agitation Method for ICU (CAM-ICU; a validated delirium measure) (weekly assessment)
7. Hand grip strength (HG dynamometry; weekly)

*At 3 months:*
1. Survival
2. Total, Physical Component Score, and Mental Component Score SF-12 score,
3. Visual analogue score (VAS: fatigue; breathlessness; appetite; pain; joint stiffness)
4. Patient satisfaction measure;
5. Health economic questionnaire (including return to previous employment and information on carer burden)
6. Hospital Anxiety and Depression (HAD) questionnaire
7. Nutritional status (subjective global assessment of nutrition; SGA nutrition, physical component)
8. Weight/BMI
9. Hand grip strength (HG dynamometry)
10. 2m timed up-and-go time
11. Davidson’s Trauma Scale score (DTS)
At 6 months:
1. Rivermead Mobility Index (RMI)
2. Survival
3. Total, Physical Component Score, and Mental Component Score SF-12 score,
4. Visual analogue score (fatigue; breathlessness; appetite; pain; joint stiffness)
5. Health economic questionnaire (including return to previous employment)
6. Hospital Anxiety and Depression (HAD) questionnaire
7. Davidson’s Trauma Scale score (DTS)

At 12 months:
1. Rivermead Mobility Index (RMI)
2. Survival
3. Total, Physical Component Score, and Mental Component Score SF-12 score,
4. Visual analogue score (fatigue; breathlessness; appetite; pain; joint stiffness)
5. Health economic questionnaire (including return to previous employment)
6. Hospital Anxiety and Depression (HAD) questionnaire
7. Davidson’s Trauma Scale score (DTS)

Note: Order of administration of outcome measures will be as documented above at each time point.

Survival up to 10 years will be ascertained through linkage to the Information and Statistics Division (ISD) database through the Scottish Intensive Care Society Audit Group data base.

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

1. The patient has required ≥ 48 hours of continuous invasive (via an endotracheal and/or tracheostomy tube) mechanical ventilation in the intensive care unit (ICU)
2. The consultant in charge of the patient considers them fit for discharge from the ICU

4.2 Exclusion Criteria

1. Primary neurological admission diagnosis (brain trauma; intracerebral bleed; stroke; Guillain-Barre syndrome)
2. The clinician in charge of care has agreed with the patient and/or family that only palliative care will be provided.
3. Patients currently receiving home ventilation or planning to commence a program of home ventilation
4. The patient is expected to be discharged from ICU to a non-study hospital where the intervention cannot be received
5. Gaining informed consent, following the intervention or follow-up is not feasible, despite resources available, due to communication difficulties
6. Patient currently enrolled in another RCT with similar endpoints
7. Patient aged <18 years at time of screening
4.3 Subject Screening, Recruitment, and Consent

4.3.1 Screening of patients
All patients being admitted to the participating ICUs will be screened from 48 hours of continuous ventilation onwards. Readmissions to ICU will be rescreened only if circumstances regarding eligibility have changed and they are now eligible or if we are now in a position to approach for consent. If patient has been approached previously and refused consent they should not be rescreened. The recruitment window will start when the consultant in charge of the patient has deemed the patient fit for ICU discharge (defined as discharge from level 3 care). The recruitment window will be up to seven days from the time the patient fulfills entry criteria. This long recruitment window has been chosen to maximise recruitment rates, allow for fewer research team staff at weekends, and allow sufficient time for patients and/or relatives/welfare attorneys to consider participation. Pilot work indicates that patients will spend a median of 14 days (mean 20.7 SD 19.8 days) in hospital following ICU discharge, so we do not anticipate the prolonged recruitment window will significantly reduce exposure to the intervention strategy.

4.3.2 Consent
Eligible patients will be approached for consent to be included in the trial if capacitated at the time of eligibility. Patients deemed to lack mental capacity by caring clinicians or experienced members of the research team will still be eligible for inclusion, but welfare attorney or next of kin will be approached for consent, ideally at a face to face interview.
If welfare attorneys or next of kin are unable to travel to the hospital we will contact them by telephone to discuss the study and answer any questions they may have. Verbal consent will be sought and a letter confirming this will be posted to the welfare attorney or next of kin. A relative information sheet and consent form will also be enclosed in order to obtain written consent.
When patients lack capacity at the time of recruitment they will be approached for consent to continue participation in the trial as soon as possible after they regain capacity. The decision regarding capacity will be determined by ICU clinicians involved in the trial or by experienced members of the research team.
A small number of participants in the intervention group will be approached for consent to make digital voice recordings of the discussion with the ICU clinician following ICU discharge. Only participants that have given their own consent for the RECOVER study will be approached.
Specific information sheets and consent forms will be provided and completed for each stage of the consent process.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects
All recruited patients will be included in the intention to treat analysis. Patients (or their relatives during the period of incapacity) will be able to withdraw from the study at any time. As the trial is an evaluation of a complex intervention comprising elements of both health service re-organisation and enhanced rehabilitation there will be no withdrawal due to protocol non-compliance. Study logs will capture the numbers of patients who are unwilling to accept elements of the rehabilitation package, but this will not be considered protocol non-compliance.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects
Patients who choose to withdraw from the study during the intervention period will be managed as follows. Patients in the usual care group will receive standard NHS treatment such that withdrawal will not alter their care. Patients in the intervention group will continue to be offered the intervention delivered by the generic assistant at regular intervals. If this is refused they will receive usual NHS care as a minimum standard of care. In both cases the research team will specifically ask permission to perform the follow up at 3, 6 and 12 months. If full assessment at follow up is declined then permission to measure the primary outcome alone (RMI) will be sought.

The RECOVER study. Study Protocol version 7. 30/01/2012
5 Study Intervention

5.1 Duration of the study intervention
The study intervention will start from the time of patient randomisation. All patients will be randomised within 48 hours of consent. The intervention will last from the time of randomisation to 3 months post-randomisation. Day 1 of the intervention will be defined as the first full day after randomisation. The intervention will be divided into two periods: (a) the period between randomisation and acute hospital discharge, and (b) the period between acute hospital discharge and 3 months post-randomisation assessment time point. The duration of each of these periods will vary between patients according to individual need. Some patients may remain in the acute hospital at the three months assessment time point. Patients remaining in hospital at 3 months post-randomisation will revert to usual hospital care for the remainder of their hospital stay. This will only alter care for the enhanced rehabilitation care group, but will effectively return this group to current standard care at this time point.

5.2 Method for Assigning Subjects to Treatment Groups
Patients will be randomised 1:1 to receive either existing usual care or an enhanced physical rehabilitation strategy. Randomisation will be by a remote computer based telephone system. At randomisation minimisation with a random element will be used to balance the following baseline variables:
1. age (>65 versus ≤65 years),
2. disability at study entry (Rivermead mobility index (RMI) 0-5 versus 6-10 versus 11-15)
3. nutritional status at randomisation (Physical assessment element of the Subjective Global Assessment (SGA) of nutrition: malnourished versus well-nourished),
4. the presence/absence of delirium (using CAM-ICU), and
5. the ward destination of patient (surgical versus medical).

5.3 Subject Compliance Monitoring
This is a pragmatic complex intervention trial. The control group will receive usual care, based on existing NHS resource. Key elements of rehabilitation will be defined in the usual care group, designed to reflect a reasonable adherence to the principles set out in the NICE guideline. These will be collected systematically. For the intervention group these key elements will also be recorded, and in addition the receipt of components of the enhanced complex intervention will be recorded. The emphasis will therefore be on measuring and accurately recording the pre-defined processes received in each group to enable comparison of the treatments actually received. There will be no definition of non-compliance, because the intervention is primarily a service re-design with enhanced, but individualised, rehabilitation.

5.4 Pre-trial ICU therapy
It is widely acknowledged that key aspects of clinical service influence outcomes from critical illness. These are currently the basis of quality improvement initiatives in many health care systems including NHS Lothian, where this trial will be undertaken. Uncertainties regarding non-intervention aspects of ICU care can limit, or create uncertainty around the findings of intervention trials in critical care, especially for small trials. This arises because of the heterogeneity of the study population and the potential for heterogeneity in non-trial treatments. Compliance with a “ventilator bundle” of key aspects of clinical care is one quality indicator, and is the basis of the Scottish Patient Safety Initiative currently ongoing in the participating ICUs. In order to describe baseline care quality in ICU prior to trial entry we will use the following routinely collected data for the periods of patient recruitment:
1. Compliance with bundle elements during the trial recruitment from audit cycles (DVT prophylaxis; head up position; oral chlorhexidine; “wake up and wean”; stress ulcer prophylaxis)
2. SMR (versus APACHE II scoring system) for all patients admitted during the recruitment period (from Wardwatcher database and SICSAG data)
Descriptive audit data gathered as part of routine practice will be used to describe the ICU environment in which the trial took place, rather than individual participant compliance.
5.5 Consort Diagram

We will record data concerning all ICU admissions to construct an accurate CONSORT diagram for the ICUs. The proposed CONSORT diagram is shown in figure 2:
5.6 Baseline Patient Status and Characteristics

Data will be collected to enable a description of the baseline status of patients entering the trial. These data will be used to describe the population overall (to enable external validity to other populations to be assessed) and will enable *a priori* planned subgroup analyses:

At ICU admission: Age, Gender, Social class (postcode based), Functional Co-morbidity Index (based on pre-hospital admission data), ICU diagnosis (SICS code), APACHE II score

At randomisation: ICU length of stay, Total hospital length of stay, Days of mechanical ventilation, vasopressor use, and renal replacement therapy on ICU pre-randomisation, source of nutrition at study entry (parenteral; enteral tube feeding; oral intake); Sequential Organ Failure Assessment (SOFA) score at randomization (cardiovascular, respiratory, renal, haematologic, hepatic, and neurological component, and total SOFA score), delirium at randomization (CAM-ICU tool); RMI, Physical component of SGA nutrition

6 Study Procedures

The aim of the study is to evaluate the clinical and cost effectiveness of the additional intervention compared with usual care. As this is a complex intervention an adequately detailed description of the relevant care actually received by both groups is essential to understand the treatment difference between the groups, and also to assess the external validity of any outcome differences.
There is no universally agreed definition of usual care for the rehabilitation of patients after ICU discharge. The NICE guideline highlights current deficiencies in care and makes recommendations concerning best practice, but acknowledges that the majority of recommendations are not based on high quality evidence for clinical or cost-effectiveness. For the RECOVER study, therefore, the investigators have defined the key relevant components of usual practice by consensus using currently available evidence and in consultation with members of the NICE guideline group. The usual practice group is considered representative of current practice in the majority of NHS hospitals in the UK, accepting that wide variation probably exists. The components of the intervention group have been defined to represent a significant increase in rehabilitation efforts over current usual practice in the majority of NHS hospitals in the UK. Specifically, the use of a generic rehabilitation assistant to deliver enhanced rehabilitation to this patient group is not current practice.

6.1 Stages of the Patient Pathway

In order to describe the processes/treatments received by patients during the 3 months intervention period four key stages of the patient pathway have been identified. For each of these, key components of rehabilitation have been identified and for each component interventions have been defined. This approach enables a clear description of the treatment received and a pre-defined plan for the intervention group to be described a priori.

A diagram summarising the four stages and the components of rehabilitation is shown in figure 3

6.2 Usual Care Group

There is no agreed definition of usual care for this patient group during the rehabilitation phase. It is likely that wide variation in usual care exists both within and between different NHS institutions. Our own data suggest the intensity of physical and nutritional rehabilitation is currently low in NHS Lothian, in significant part because of service pressures. The NICE guideline makes recommendations regarding best practice, but acknowledges that these are largely expert/opinion based, or based on extrapolation from other rehabilitation settings. The lack of evidence for clinical and cost-effectiveness questions the justification of considering full adherence to these recommendations as “usual care” at the current time. The strongest evidence for effectiveness on physical recovery was provision of a self-help manual, supported by expert staff, during the weeks after ICU discharge.

For the purpose of RECOVER we require “usual care” to be externally valid as representative of practice in the NHS (or other health care systems). We have described in detail usual care in one of the study hospitals. This did not include the provision of an ICU recovery manual. As data exist to support this intervention, we will include an ICU recovery manual as part of “usual care” to ensure the relevance of the trial findings. The ICU manual will be given to all participants in the study by the research team after consent has been obtained. Otherwise rehabilitation will be provided by NHS multidisciplinary teams using the current arrangements in NHS Lothian. Generic rehabilitation assistants will not be included in this service model, as this role is not part of existing service.

A matrix describing the rehabilitation strategy for usual care is summarised in table 1.
### Stage in Patient Pathway

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<thead>
<tr>
<th>Stage 1: ICU discharge</th>
<th>Usual Care Group</th>
<th>Intervention Group</th>
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<tr>
<td>Within 1 week of ICU discharge according to individual patient characteristics</td>
<td>Provision of ICU recovery manual</td>
<td>Visit by ICU staff member</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 2: Ward based rehabilitation</th>
<th>Usual care pattern of multidisciplinary team input</th>
<th>No involvement by generic rehabilitation assistant</th>
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</thead>
<tbody>
<tr>
<td>Ongoing until hospital discharge</td>
<td>Weekly goal setting</td>
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<td></td>
<td>Daily visits from generic rehabilitation assistant to deliver agreed strategy to achieve goals</td>
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<td></td>
<td>Active problem identification and solving using screening tools and triggers</td>
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<tr>
<th>Stage 3: Hospital discharge planning</th>
<th>Usual care pattern of discharge planning by parent teams</th>
<th>Planning with input from generic rehabilitation assistant to needs assessment</th>
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<td>Around time of planned discharge</td>
<td>ICU visit as determined by parent teams</td>
<td>Coordinated provision of critical illness specific information to GP</td>
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<td>ICU visit prior to discharge</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 4: Post Hospital discharge</th>
<th>Usual care with no specific ICU based input</th>
<th>Provision of generic rehabilitation assistant contact details to all patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>From hospital discharge to up to 3 months follow up point</td>
<td>At least one telephone contact within one week of discharge</td>
<td>Other input according to individual patient preference</td>
</tr>
</tbody>
</table>

**Figure 3: Stages in the patient pathway, with key events in each trial group**
Table 1: Matrix to describe “usual care” patient pathway, the process measures to describe it, and the method of acquiring process data.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Component</th>
<th>Procedure</th>
<th>Process measure (type of data)</th>
<th>Data recorded</th>
</tr>
</thead>
<tbody>
<tr>
<td>One:</td>
<td>Post-ICU discharge</td>
<td>Visit by ICU clinician  Provision of post-ICU rehabilitation manual</td>
<td>Visit documented in notes (binary) Relative was present (binary) Rehabilitation manual provided (binary)</td>
<td>Research nurse from medical notes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Visits at discretion of clinical staff  2. Provision of manual by research team</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two:</td>
<td>Ward based rehabilitation</td>
<td>Rehabilitation Treatments/visits received by week:  Week one  Week two etc</td>
<td>1. Number of agreed patient-centred goals documented  2. Number of physiotherapy sessions  3. Number of specific elements of physiotherapy  4. Number of dietetic visits  5. Number of food diaries completed/analysed  6. Number of visits (and content) by occupational therapy, SLT, and other non-parent specialty staff</td>
<td>Counts for different elements (continuous data)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three:</td>
<td>Hospital discharge</td>
<td>Discharge planning</td>
<td>1. Patient discharged to rehabilitation facility  For patients discharged to home/community:  2. Home assessment occurred  3. Direct contact with GP occurred</td>
<td>Each element occurred (binary)</td>
</tr>
<tr>
<td>Four:</td>
<td>Post hospital discharge to 3 month outcome measure</td>
<td>No formal component currently exists</td>
<td>1. Any outpatient contact with hospital or hospital team  2. Contacts with primary care  3. Hospital readmissions</td>
<td>Health economic questionnaire</td>
</tr>
</tbody>
</table>
6.3 Intervention Group

The key changes in the intervention group are twofold:

1. A generic rehabilitation assistant will be employed under the supervision of the multidisciplinary rehabilitation team. The generic rehabilitation assistant will receive a pre-defined and documented programme of training, to an agreed job description, prior to starting the study. This will include knowledge of intensive care, the common complications of intensive care, the common rehabilitation needs of ICU patients, and the rehabilitation strategies proposed. These will focus on physiotherapy and dietetics, but will include some elements of Speech and Language Therapy, Occupational Therapy, and Psychology relevant to the patient group. The use of systematic screening tools will be included for common problems. The training programme will be summarised (and potentially published) as part of the trial documentation.

2. The Generic Rehabilitation Assistant will deliver an enhanced and coordinated rehabilitation under the supervision of the multidisciplinary specialists. Key elements will include:
   a. Weekly individualised goal setting with each patient in a range of areas. These goals will be determined in conjunction with the patient on an individualised basis.
   b. A clear plan of exercises and nutrition interventions aimed at achieving the goals.
   c. Regular systematic screening by the generic rehabilitation assistant for anticipated problems relating to nutrition and physical disability using tools agreed with physiotherapy, dietetic, occupational therapy, and speech and language therapy teams. Triggering for specialist input using these tools and pre-defined thresholds or criteria.

3. A lay summary will be produced by an ICU consultant or nominated member of medical staff and made available to patients, their relatives and relevant healthcare professionals providing a brief summary of key events that occurred during the patient’s stay in intensive care. This will take the form of an A4 sheet that will provided to patients at the visit described below. A proforma, which will be pre-defined, will be used to ensure similar information is provided to all participants.

4. All patients will receive a visit from a Critical Care consultant or nominated deputy. The GRA will arrange this at an appropriate time mutually convenient to the patient, the consultant, and the patient’s relative (if they wish to attend). The GRA will also attend this meeting whenever feasible. A pre-defined topic guide will be used to cover key aspects of the critical illness pathway and will include possible short and long term complications.

5. After discharge home the generic rehabilitation assistant will contact the patient within the first week to enquire how they are managing at home and whether there are any issues that have arisen and may follow this up if appropriate. A copy of the lay summary may be posted to the patient if requested. The patient will be provided with a telephone number at discharge, on which they can contact the generic rehabilitation assistant to discuss any issues.

A matrix describing the rehabilitation strategy for the intervention group is summarised in table 2.

At the beginning of the study 4 pilot participants will receive the intervention but will not be included in the intention-to-treat analysis. This run-in phase will allow the new generic rehabilitation assistants employed for the trial to become familiar with their role.

6.4 Process measures

As this is an evaluation of a complex intervention, measurement of process is important. The occurrence of a pre-defined range of processes will be recorded from the patient case notes. Process assessment will include binary measures (whether the component of rehabilitation occurred or not) and frequency measures (the number of visits made or treatments administered). During the ward based period of care, when it is anticipated the majority of rehabilitation will occur, process measures will be summarised in week epochs. The numbers of patients exposed to ward based rehabilitation will decline over the three months as patients are discharged from hospital.
In addition to pre-defined process measures, the generic rehabilitation assistants will keep a diary for each patient noting additional treatments, interventions or interactions. Data concerning key blocks and problems with delivering the intervention will also be recorded. These narrative data will be used to enrich the understanding of the complex intervention delivered, in conjunction with the planned focus groups.
Table 2: Matrix to describe “intervention” patient pathway, the process measures to describe it, and the method of acquiring process data. Key elements that are in addition to usual care are highlighted.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Component</th>
<th>Procedure</th>
<th>Process measure (type of data)</th>
<th>Data recorded by</th>
</tr>
</thead>
<tbody>
<tr>
<td>One: Post-ICU discharge</td>
<td>Visit by Generic Assistant and ICU clinician</td>
<td>1. Generic rehabilitation assistant introduced to patient and relative 2. GRA coordinates visit by ICU clinician for structured discussion using topic guide 3. Lay summary of ICU experience provided to patient and relative (offer discussion) 4. Rehabilitation manual provided by research team</td>
<td>GRA met patient Consultant discussion occurred and documented in notes (binary) Relative was present (binary) Rehabilitation manual provided (binary)</td>
<td>Research nurse from medical notes</td>
</tr>
<tr>
<td>Two: Ward based rehabilitation</td>
<td>Summary of treatments received by week: Week one Week two etc</td>
<td>1. Agreed patient centred goals documented 2. GRA visits to deliver agreed treatments (number) 3. Screening tools used to identify additional rehab needs 4. Contact relevant staff according to agreed triggers</td>
<td>1. Goals documented in notes 2. Number of visits by GRA 3. Number of physical therapy sessions by GRA or physio 4. Number of specific elements of physical therapy 5. Number of visits by non GRA AHPs 6. Number of food diaries completed/analysed</td>
<td>Research nurse from medical notes</td>
</tr>
<tr>
<td>Three: Hospital discharge</td>
<td>Discharge planning For patients discharged to home/community: 1. Patient discharged to rehabilitation facility 2. Home visit occurred 3. Letter sent to patient’s GP documenting status at hospital discharge (for all patients)</td>
<td>Each element occurred (binary)</td>
<td>Research nurse from medical notes</td>
<td></td>
</tr>
<tr>
<td>Four: Post hospital discharge to 3 month outcome measure</td>
<td>Contact with GRA</td>
<td>1. Number of contacts with GRA 2. Any outpatient contact with hospital or hospital team 3. Contacts with primary care 4. Hospital readmissions</td>
<td>Total contacts with GRA during post-hospital discharge period (continuous) Health economic questionnaire</td>
<td>Research nurse at 3 months assessment</td>
</tr>
</tbody>
</table>
1 Psychological: amnesia, delirium, hallucinations, PTSD symptomatology (flashbacks, etc), sleep disturbance, relocation stress
   Physical: fatigue, breathlessness, muscle wasting/weakness, CIP, painful joints, loss of appetite, weight loss, taste changes in food.
2 Dictated by member of medical staff (will require secretarial support) and potentially, discussion by same.
3. Explanation of rehab. strategy over the intervention period, including goal setting, screening tools, GHA visits. Includes provision of ICU rehab. Manual
4 Weekly meetings with ward-based clinicians to set treatment/rehab goals
5. CAM-ICU, agreed OT screening tools, MRC muscle strength

6.5 Data Collection
Data collection is summarised in table 3.

6.6 Blood sampling
A sub-study will investigate the prevalence of persisting inflammation following ICU discharge, and the relationship this has with recovery. Specifically we will explore whether persisting systemic inflammation predicts the ability of patients to respond to rehabilitation, both for all patients and specifically in the intervention group. Consent to participate in the blood sampling study will be part of the main study consent process, but patients will be able to opt out of this element if they do not wish to have additional blood samples taken. For patients who consent to additional blood sampling a 10mL blood sample will be collected at randomisation, weekly until hospital discharge, and at the 3 months visits. Plasma and serum will be frozen for later determination of a panel of pro- and anti-inflammatory markers. Assays for C-reactive protein will be undertaken at all time points. Assays for additional cytokines and inflammatory markers will be decided after the sample bank has been obtained.
Table 3: Matrix describing the data collection during the trial.

<table>
<thead>
<tr>
<th></th>
<th>Pre-Randomisation</th>
<th>Within 7 days of ICU discharge</th>
<th>From ICU discharge to hospital discharge (weekly data collection)</th>
<th>Hospital Discharge</th>
<th>Outcome assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline data collection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 months 6 months 12 months</td>
</tr>
<tr>
<td>ICU recovery manual provided?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit by ICU consultant or other ICU clinician occurred</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lay Summary of ICU stay provided?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivermead mobility index (RMI)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X X X</td>
</tr>
<tr>
<td>Handgrip Dynamometry</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Blood sample for inflammatory markers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

**Non GRA AHP staff**

|                                                                 |                   |                               |                                                               |                   |                     |
| Number of visits by physiotherapist, dietitian, occupational therapist, and SLT |                   | X                             |                                                               |                   |                     |
| Numbers of physical therapy treatments received                  |                   |                               |                                                               |                   | X                   |

**Generic Rehabilitation Assistant**

|                                                                 |                   |                               |                                                               |                   |                     |
| Number of visits by Generic Rehabilitation Assistant             |                   | X                             |                                                               |                   |                     |
| Number of different physical therapy, dietetic, occupational therapy, and SLT treatments (broken down by type) delivered |                   | X                             |                                                               |                   |                     |
| Number of agreed patient goals documented                        |                   | X                             |                                                               |                   |                     |
| Number of food charts completed                                  |                   | X                             |                                                               |                   |                     |
| Number of referrals to specialist staff                          |                   | X                             |                                                               |                   |                     |
| Summary of discharge status sent to GP ?                         |                   |                               |                                                               |                   | X                   |
| Summary of ICU, HDU, hospital length of stay and ICU readmissions |                   |                               |                                                               |                   | X                   |
| SF-12                                                            |                   |                               |                                                               |                   | X X X               |
| SGA nutrition assessment (physical component)                    |                   |                               |                                                               |                   | X                   |
| 2m timed up and go test                                          |                   |                               |                                                               |                   | X                   |
| HAD questionnaire                                                |                   |                               |                                                               |                   | X X X               |
| DTS questionnaire                                                |                   |                               |                                                               |                   | X X X               |
| VAS scores                                                       |                   |                               |                                                               |                   | X X X               |
| Patient satisfaction questionnaire                                |                   |                               |                                                               |                   | X                   |
| Health economic questionnaire (including hospital resource use and return to employment) |                   |                               |                                                               |                   | X X X               |
| Height/Weight/BMI                                                |                   |                               |                                                               |                   | X                   |

*The timing of the ICU visit and lay summary may be delayed beyond 7 days if thought appropriate for the individual patient.*
6.7 Outcome measurements

6.7.1 Hospital discharge
The following information will be recorded from the patient clinical record or hospital information system at the time of hospital discharge. Data will be extracted by research nurses unrelated to the trial intervention:

1. Survival status at hospital discharge (including date of death for deaths in hospital)
2. Hospital length of stay
3. Total ICU days, HDU days, and general ward days from randomization (using definitions of levels of care)
4. ICU readmission rate during hospital admission

6.7.2 Visit/follow-up one: 90 days post-randomisation
All patients surviving to 3 months post-randomisation will be visited by a community based research nurse from whom group allocation is concealed. The window of follow up will be from 80 days until 100 days post-randomisation. Patients’ general practitioners will be contacted to ascertain survival status if this is uncertain. Patients will then be contacted by telephone or post to arrange a visit in their own home, or at a visit to the Clinical Research Facility if they prefer. Patients who remain inpatients from the original hospital admission, or who have been readmitted to hospital will be visited in hospital by nurses from whom group allocation is concealed.

In some cases a face to face follow-up visit is not possible as it is inconvenient for the patient or they reside a considerable distance from the study hospital making a visit unfeasible. In those instances, if the patient is agreeable, the primary income measure only will be collected by phone by the community based research nurse. If the patient wishes to be withdrawn from the study the trial office will be notified and no further contact will be made or data collected.

The following outcomes will be measured:

Primary outcome
1. Rivermead mobility index

Secondary outcomes
1. Total, Physical Component Score, and Mental Component Score SF-12 score,
2. Visual analogue score (VAS: fatigue; breathlessness; appetite; pain; joint stiffness)
3. Patient satisfaction measure;
4. Health economic questionnaire (including return to previous employment and information on carer burden)
5. Hospital Anxiety and Depression (HAD) questionnaire
6. Nutritional status (subjective global assessment of nutrition; SGA nutrition, physical component)
7. Weight/BMI
8. Hand grip strength (HG dynamometry)
9. 2m timed up-and-go time
10. Davidson’s Trauma Scale score (DTS)
11. Blood sample for inflammatory markers

We will also include a question asking participants to document the group to which they believed they were allocated. This will be included because of the non-blinded nature of the trial and high probability of patients having ongoing awareness of group allocation and the rationale for the different approaches used. This introduces the potential for participation bias if there is an imbalance in outcome assessment rates between the groups and also response bias to the the outcome measures used. Recording knowledge of group allocation at 3 months will allow greater understanding of the potential importance of bias to the trial findings.

The order in which the outcomes and procedures occur will be as above.
6.7.3 Visit/follow-up two: 180 days post-randomisation
Patients will be contacted by post at 180 days post-randomisation. As at 90 days the patient’s general practitioner will be contacted to ascertain survival status if this is uncertain. Patients will be contacted initially by post with questionnaires and a pre-paid return envelope. A £5 gift voucher will be included as a token of gratitude for involvement. Patients who do not respond to postal contact will be telephoned by a member of the research team from whom group allocation is concealed. The window for contact will be from 150 to 210 days post-randomisation. The following outcomes will be ascertained by postal questionnaire or telephone interview (for those failing to respond to postal contact):

1. Rivermead Mobility Index (RMI)
2. Survival
3. Total, Physical Component Score, and Mental Component Score SF-12 score,
4. Visual analogue score (fatigue; breathlessness; appetite; pain; joint stiffness)
5. Health economic questionnaire (including return to previous employment)
6. Hospital Anxiety and Depression (HAD) questionnaire
7. Davidson’s Trauma Scale score (DTS)

6.7.4 Visit three: 12 months days post-randomisation
Patients will be contacted by post at 12 months post-randomisation. A £5 gift voucher will be included as a token of gratitude for involvement. As at 90 and 180 days the patient’s general practitioner will be contacted to ascertain survival status if this is uncertain. The same strategy for follow up will be used to the 6 months time point. Patients who do not respond to postal contact will be telephoned by a member of the research team from whom group allocation is concealed. The window for contact will be from 11 to 13 months post-randomisation. The following outcomes will be ascertained by telephone interview:

1. Rivermead Mobility Index (RMI)
2. Survival
3. Total, Physical Component Score, and Mental Component Score SF-12 score,
4. Visual analogue score (fatigue; breathlessness; appetite; pain; joint stiffness)
5. Health economic questionnaire (including return to previous employment)
6. Hospital Anxiety and Depression (HAD) questionnaire
7. Davidson’s Trauma Scale score (DTS)

Survival up to 10 years will be ascertained through linkage to the Information and Statistics Division database

6.7.5 Qualitative Outcome Assessment

Focus Groups
Focus group interviews will be conducted at each of the participating hospitals. With participants’ permission, each of the interviews will be digitally voice recorded and transcribed verbatim.

(i) Patients and carers: Using purposive sampling, we will invite 8-10 patients and carers from the “usual care” and intervention groups to participate in separate focus groups. Potential participants will be approached either by members of the RECOVER research team (who are known to participants) prior to hospital discharge (in which case survival status will be known) or the delegated Wellcome Trust Clinical Research Facility (WTCRF) nurses at the end of their blinded outcome assessment at 3 months post intervention. The WTCRF nurses have existing strategies in place to ensure survival status i.e. they contact the participant’s General Practitioner to ascertain survival prior to contacting the participant to arrange the outcome assessment
Participants will be invited to discuss their experiences of recovery and rehabilitation up to 3 months post-ICU discharge. We will explore key issues and concerns and the ways in which multi-disciplinary input impacted upon recovery both during the acute hospital phase and following discharge home. A comparative analysis between the “usual care” and intervention focus groups will explore the impact of
multi-disciplinary input and trial participation upon recovery. The interview schedule has been developed for the purposes of exploring the discrete and cumulative effects of different elements of our complex intervention upon recovery. Focus groups will occur when all participating patients and carers have completed the 3 months outcome assessment (the primary outcome assessment time point) to minimize any bias resulting from participation in the focus groups.

(ii) **Healthcare professionals:** Using purposive sampling, we will invite 8-10 representatives from key healthcare disciplines at each site to participate in focus group interviews towards the end of the recruitment period. Drawing upon our analysis of the research logs, participants will be invited to discuss barriers to the delivery and coordination of patient-led care among both groups and perceptions (including acceptability) of the generic rehabilitation assistant as a novel strategy for the rehabilitation of patients after ICU discharge.

Separate information sheets and consent forms will be used for the focus groups.

**Process Outcomes: assessment of research logs kept by Generic Rehabilitation Assistants**

Using thematic analysis, we will analyse the research logs in order to categorise (i) the principle barriers to the intervention and (ii) successful strategies in the implementation of the intervention; both in individual patients and across ward and hospital settings. These data will supplement the quantitative measurement of process outcomes and facilitate the translation of findings into routine care.

**6.7.6 Long term outcomes**

Long term survival will be ascertained through linkage to the SMR1 data set and the death registry of the Information and Statistics Division (ISD). This occurs automatically through the Scottish Intensive Care Society audit data base, in which data for all enrolled patients will be available. Approval for this linkage will be obtained from the SICSAG steering group and any additional approvals obtained through ISD.

**6.8 Steps Taken to Minimise Bias**

**6.8.1 Selection bias**

All eligible patients will be accounted for in the two participating ICUs. The ICU characteristics of eligible patients not randomised in the trial will be available from the Wardwatcher system used to collect Scottish Intensive Care Society Audit Group data. From these routinely collected data we will be able to describe age, gender, APACHE II score, and ICU length of stay. These data will be available for comparison with the study population.

**6.8.2 Treatment allocation bias**

A minimisation algorithm is included in the randomisation process to ensure balance in several pre-defined factors (see section 5.2). These have been chosen by consensus as potentially influencing the response to rehabilitation, namely age (>65 versus ≤65 years), disability at study entry (Rivermead mobility index (RMI) 0-5 versus 6-10 versus 11-15, nutritional status at randomisation (Physical component of the Subjective Global Assessment of nutrition: malnutrition versus well-nourished), the presence/absence of delirium (using CAM-ICU), and ward destination of patient (surgical versus medical).

**6.8.3 Crossover and study effects**

This is a non-blinded trial with concurrent treatment groups. It is potentially subject to crossover and study effects, especially for an improvement in “usual care” over existing practice. The following measures will be used to either minimise the chance of study effects, or at least measure and account for any effects that occurred:
1. The Generic Rehabilitation Assistant will not have any contact, or know the details of patients allocated to the usual care group. Other members of the rehabilitation team will be instructed not to discuss or request any generic rehabilitation assistant input to non-intervention group patients. The generic rehabilitation assistant will be instructed to inform the trial management team if they have any contact with any non-intervention group patients, and this will be logged.

2. Detailed process measures will be kept regarding the treatment received by both groups. This will enable a detailed description of the numbers and types of treatments received by all patients. As "usual care" for rehabilitation of patients following ICU discharge is not clearly defined it is not feasible to control management tightly in this group. It is possible that the treatment received by the "usual care" group will improve because the profile and needs of these patients will be highlighted during the trial. It is also possible that NHS clinicians may have additional time to treat the usual care group because of the contribution of the generic rehabilitation assistant in the intervention group. This effect was not observed in the pilot study, in which a significant difference in treatment intensity occurred. The current time and service pressures on NHS clinical staff also suggest this is unlikely to be a major problem. The recent NICE guideline recommendations were for care to be significantly improved in NHS hospitals so we do not anticipate that any change during the study will be if sufficient magnitude to make our "usual care" group non-representative and the process measure data will enable the treatment received to be accurately described.

3. We will be able to compare the treatment received by the "usual care" group to our data collected prior to the trial.

6.8.4 Investigator bias

There is a chance of investigator bias in any non-blinded trial, especially when the intervention is a complex strategy such as rehabilitation. We have minimised investigator bias during the intervention phase by embedding the intervention in routine NHS treatment, and minimising the involvement of the trial team in the intervention itself. However, this cannot protect fully against bias among NHS clinical staff. We will minimise bias during recording of the treatments received by using research nurses from the Clinical Research Facility, who are not involved directly in the trial, to collect the process measure data during the hospital phase of the intervention.

Bias in the outcome measures could occur if assessors were not blinded to group allocation, or had some influence on the timing of measurement (for example the time of hospital discharge). Minimising bias in outcome assessment is of central importance to this trial because group allocation cannot be truly blinded from patients, or caring clinicians, or the researchers. All outcome measures will therefore be ascertained by visits or telephone consultation by staff that are not members of the trial management team, are not involved in treating the patients, and are not aware of group allocation. Quantitative outcome data will only be available to the Data Monitoring Committee during the trial until the time the data base is locked for analysis. We have also chosen fixed times for outcome assessment (3, 6 and 12 months) which will minimise the chance of bias related to clinical decisions, such as the timing of hospital discharge.

6.8.5 Participation and Response Bias

There is potential for participation bias if there is an imbalance in the follow up rates between the groups, which might occur because patients enrolled in the intervention group feel more involved, interested, or positive about the trial. We will attempt to minimize this by aiming to achieve high rates of follow up, especially at the 3 month primary outcome assessment by using a patient visit. Several attempts to contact and visit the patients will be made. If a patient declines to have a visit, we will ask if they are prepared to complete the primary outcome measure (RMI) by telephone.

Response bias could occur if patients are aware of group allocation and adjust their responses to the outcome measures as a result of this, for example giving more positive responses when they were aware of allocation to the enhanced rehabilitation group. In this study it is difficult to avoid this potential bias due to the unblinded nature of the intervention, and possible patient beliefs that greater input will aid recovery. Interpretation is also complicated by the potential overlap between a response bias and a true benefit to
patients, given some of the outcomes relate to self-perception of health status. We will ask patients at 3 months which group they think they were allocated to in order to obtain data that will enable the potential influence of response bias to be assessed.

7 Statistical Plan

7.1 Sample Size Determination
Based on our pilot study, we estimate the mean (SD) RMI at 3 months post-randomisation will be 10 (4.3), with normal mobility being 15 on a 0 to 15 scale. Our pilot data suggest a change from baseline to 3 months in RMI of 2 (SD 5) is currently typical. We have powered the study to detect an improvement in the change from baseline RMI of 2 points at 3 months in the intervention group compared with usual care. This would be a clinically relevant difference in physical disability for patients in relation to activities of daily living and independence. To detect this difference we require 100 evaluable patients per group at 3 months (80% power; 5% significance level). Using Scottish Intensive Care Society audit data for the two ICUs for 2005-6 (24 months), we estimate that 498 eligible patients will be cared for each year; of these 309 will be discharged alive from ICU. Assuming 70% enrolment (consistent with our previous studies) we will enroll 216 patients per year (4 per week). Of these, assuming 12% death rate before 3 months (26 patients; based on pilot work) and 95% follow up of remaining patients at 3 months (facilitated by home visits by research nurses) we require to randomise 240 patients. This can be achieved in 14 months in the Edinburgh Royal Infirmary and Western General Hospital general ICUs.

7.2 Statistical Methods
The primary analysis will be performed according to the intention to treat principle. The primary outcome measure, RMI at 3 months post-randomisation, will be compared between the groups using ANCOVA to adjust for baseline RMI and for the factors included in the minimisation algorithm. A sensitivity analysis will be performed where the lowest possible value of RMI (0) is imputed for those patients who die within 3 months of randomisation. A similar approach will be used to analyse the secondary outcome measures. A priori subgroup analyses will be undertaken for the primary outcome measure using baseline RMI, SGA and age. The subgroup analyses will be performed by including appropriate interaction terms in the ANCOVA model.

7.3 Subject Population(s) for Analysis
The primary analysis will be on intention to treat for all randomised patients. As the trial is testing a complex intervention involving health service re-design, we do not propose a separate analysis of patients who did not receive any or certain elements of the intervention.

Pre-defined sub-group analyses will be undertaken for the following groups:
1. Age ≤65 years versus >65 years at study entry
2. RMI (0-5 versus 6-10 versus 11-15) at randomisation
3. SGA nutrition physical component at study entry (malnourished versus well-nourished) at randomisation

7.4 Analysis Plan
A detailed analysis plan will be written during the early phases of the trial, agreed by the trial steering committee, and provided to the data monitoring committee.
8 Safety Reporting

8.1 Adverse events

This is not a Clinical Trial of an Investigational Medicinal Product (CTIMP) and is therefore not subject to the guidelines set down in the European Clinical Trials Directive (2001/20/EC). However, this trial will be conducted in accordance with the International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines. Specifically, the research sponsors' (Edinburgh University/Lothian Health Board) guidelines for adverse event reporting policy and Standard Operating Procedures will be followed. These are consistent with adverse event reporting guidelines from the National Research Ethics Service for safety reporting in research other than clinical trials of investigational medicinal products.

Participants taking part in the study will have all been critically ill in an intensive care unit. Therefore many adverse events, and serious adverse events including death, are expected to occur during the intervention and follow up phases. The following definitions will be used:

Adverse Events

<table>
<thead>
<tr>
<th>Adverse events include</th>
<th>Adverse events do not include</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) an exacerbation of a pre-existing illness</td>
<td>a) medical or surgical procedures- the condition which leads to the procedure is the adverse event</td>
</tr>
<tr>
<td>b) an increase in frequency or intensity of a pre-existing episodic event/condition</td>
<td>b) pre-existing disease or conditions present before treatment that do not worsen</td>
</tr>
<tr>
<td>c) a condition (even though it may have been present prior to the start of the trial) detected after trial intervention</td>
<td>c) situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery</td>
</tr>
<tr>
<td>d) continuous persistent disease or symptoms present at baseline that worsens following the administration of the trial/trial treatment</td>
<td>d) overdose of medication without signs or symptoms</td>
</tr>
<tr>
<td></td>
<td>e) the disease being treated or associated symptoms/signs unless more severe than expected for the patient’s condition</td>
</tr>
</tbody>
</table>

8.2 Serious adverse event (SAE)

A SAE is an untoward and unexpected occurrence that a research participant experiences which:

1. Results in death
2. Is life threatening
3. Requires hospitalisation or results in prolongation of existing hospitalisation
4. Results in persistent or significant disability or incapacity
5. Consists of a congenital anomaly or birth defect

Note: 1 All patients in this trial will be hospitalised; 2 This is not relevant to this study population. In addition, all participants will, by enrolment criteria definitions, have life threatening illnesses that can result in death or persisting disability/incapacity.
8.3 Reporting of SAEs

We will report all deaths occurring in hospital during the first 90 days of randomization (the maximum duration of the intervention) as SAEs. Deaths occurring after hospital discharge will not be routinely reported as SAEs, but will be captured as secondary outcome measures. In addition, we will report all serious adverse events considered unexpected for this patient population and any serious adverse events that could be related to taking part in the study.

Examples of SAEs that will be reported are shown below, together with examples of SAEs that are expected to occur in this population, and are unlikely to be directly related to participation in the trial.

<table>
<thead>
<tr>
<th>SAEs that will routinely be reported</th>
<th>Examples of SAEs that should be reported</th>
<th>Examples of SAEs that are expected to occur and do not need to be reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any death in hospital within 90 days of randomization</td>
<td>Falls or other injuries resulting in significant disability or incapacity during the hospital intervention phase</td>
<td>Hospital acquired infections</td>
</tr>
<tr>
<td>Any SAE that the local PI considers may be related to participation in the trial</td>
<td>Pulmonary aspiration associated with feeding, whether enteral or oral</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>Bowel complications (for example perforation) associated with feeding interventions</td>
<td>Cardiac arrhythmias</td>
</tr>
<tr>
<td></td>
<td>Thrombotic complications that may be related to immobility (for example DVT or PE)</td>
<td>Re-admission to intensive care</td>
</tr>
</tbody>
</table>

Deaths and other unexpected SAEs will be reported on the appropriate trial form by the clinician or research staff involved with the patient, and reported locally immediately to the Principal Investigator at the centre. The PI at the centre will fax details of the SAE to the ACCORD office (fax number 0131 242 9447), within 24 hours of becoming aware of its occurrence. The ACCORD office will subsequently inform the Edinburgh Clinical Trials Unit (ECTU) of the SAE.

The local Investigator will give an opinion as to whether the event is [a] “related” (resulting from the administration of any of the research procedure), and [b] “unexpected” (the type of event is not listed in the protocol as an expected occurrence). All reported SAEs will be reviewed by the CI in a timely manner.

Any unexpected related SAE will be submitted by ACCORD to the relevant main Research Ethics Committee within 15 days of their becoming aware of the event, using the NRES report of serious adverse event form.

8.4 Institution Responsibilities

The patient will, at all times, be under the medical direction of their local clinicians. Should an adverse event occur this will be managed according to local policy.
9 Trial Management

9.1 Trial Management Group
The trial management, including financial management, will be undertaken by the Edinburgh Clinical Trials Unit (ECTU). The day-to-day management of the trial will be undertaken by a trial management group (TMG) who will meet at least every 14 days during the trial, and more frequently as appropriate. Minutes of the trial management team will be kept in the trial office. The members of the TMG are:

Prof Tim Walsh (CI)
Dr Lisa Salisbury
Ms Pam Ramsey
Dr Julia Boyd (ECTU Trial Manager)
Ms Judith Merriweather

9.2 Trial Steering Group
The trial steering group (TSG) will be responsible for reviewing the progress of the trial, and providing advice to the investigators regarding ongoing problems. The TSG will meet prior to the start of trial recruitment, after 80-100 patients have been randomized, and then at the end of the trial. More frequent meetings will be held if deemed necessary. The Chair of the TSG will be an independent clinician (Dr Steve Brett) who was Chair of the NICE guideline development group. The lay member will be Ms Vera Fletcher, a patient who required prolonged rehabilitation after severe critical illness in Edinburgh. Other independent members will be a local expert in rehabilitation medicine (Dr Ian Todd) and care of the elderly (Dr Tricia Cantley).

Membership of the trial steering group:

Dr Stephen Brett (Independent Chairman), Consultant in Intensive Care, London

Trial Team
Prof Tim Walsh (CI)
Dr Lisa Salisbury
Dr Pam Ramsey
Ms Judith Merriweather
Dr Guro Huby
Dr John Forbes
Prof Gordon Murray
Dr Steff Lewis
Dr Alasdair Hull
Dr Janice Rattray
Dr Simon Mackenzie
Dr Julia Boyd (ECTU Trial Manager)

Independent Lay Member
Ms Vera Fletcher

Independent members
Dr Patricia Cantley
Dr Ian Todd

9.3 Independent Data and Safety Monitoring Committee (DSMC)
The trial will have an independent DSMC, comprising three experienced individuals including an expert in intensive care medicine, an expert in rehabilitation, and an experienced trial statistician. All members of
the DSMC will be independent from the trial and will be required to sign statements relating to conflict of interest. The DSMC will agree a Charter describing its function as well as an analysis plan for any interim review of data. The DSMC will have the right to review interim unblinded analyses of data, which will be prepared by a statistician independent from the Trial team.

The members of the DSMC are:

Professor John Norrie (Biostatistician; Chair; expert trialist and statistician)
Robertson Centre for Biostatistics
University of Glasgow

Professor Martin Dennis (Professor of Stroke Medicine; expert in clinical trials and stroke rehabilitation)
Edinburgh University

Dr Carl Waldman (Critical Care consultant; expert in rehabilitation post critical illness)
Consultant in Critical Care

The DMSC will meet before or within 2 months of starting recruitment. Subsequent meetings will be planned after approximately 80 patients and 150 patients are recruited. Given the size and exploratory nature of the trial no formal stopping rules will apply.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan
This study will be monitored according to the Standard Operating Procedures of the Sponsor (NHS Lothian). A monitoring plan will be agreed between the TMG and the sponsor.

10.2 Auditing and Inspecting
Requirements for auditing and expecting will be agreed in accordance with the Standard Operating Procedures of the sponsor, and trial materials kept in accordance with GCP requirements

11 Ethical Considerations
Patients may be incapacitated at the time of eligibility to the trial as a result of critical illness. The commonest reason for incapacity is expected to be delirium around the time of ICU discharge. The rationale for the intervention requires that randomisation is obtained as soon as ICU discharge is planned. We therefore plan to ask responsible clinicians or experienced members of the research team to make a decision regarding mental capacity to provide consent. Patients with capacity will be approached directly. For patients lacking capacity at the time of eligibility we will approach the next of kin or welfare attorney (WA) at a face to face interview for consent to participate. If welfare attorneys or next of kin are unable to travel to the hospital we will contact them by telephone to discuss the study and answer any questions they may have. Verbal consent will be sought and a letter confirming this will be posted to the welfare attorney or next of kin. A relative information sheet and consent form will also be enclosed in order to obtain written consent.

In cases that initial consent is provided by the next of kin/WA we will approach the patient for permission to continue in the study as soon as possible after they regain mental capacity. A specific information sheet will be provided at this time and a second consent form will be completed by the patient if they agree to ongoing participation. We also plan to balance patients with delirium at the time of randomisation using minimisation.
The trial compares current usual NHS rehabilitation arrangements for patients following ICU discharge in NHS Lothian with an enhanced rehabilitation strategy. None of the patients will therefore receive care that is below the current level of standard care. We consider it likely that the usual care group may receive higher levels of rehabilitation because of the higher profile likely to be given these patients during the trial. The enhanced rehabilitation group will receive care that is not currently standard practice, specifically based around a new NHS role, the generic rehabilitation assistant. As this is not available out with the trial, we do not consider this a major ethical consideration because patients not participating in the trial will not receive this additional resource.

12 Data storage
Data will be stored in the Edinburgh Clinical Trials Unit or associated data archiving facilities. We will store data for a maximum of 15 years to enable subsequent ascertainment of long term health status from national data bases through linkage. Access will only be from members of the research team. Any additional research using the data, including linkage to other data bases to obtain long term outcome data, will only be permitted if a specific amendment is submitted to this application or a separate ethics application made.

13 Study Finances

13.1 Funding Source
This trial is being funded by the Chief Scientist’s Office, Scotland. Project ID CZH/4/531

13.2 Financial Management
The trial will be managed by the Edinburgh Clinical trials Unit in collaboration with the TMG.

14 Publication Plan
A publication plan will be agreed with investigators early in the course of the trial.

15 Key References
(8) Rehabilitation after critical illness. www.nice.org.uk/CG83. accessed 1st August 2009
## APPENDIX: Trial GANTT CHART

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Evaluation of a Rehabilitation Complex Intervention for patients following Intensive Care Discharge. The RECOVER study

ANALYSIS PLAN
Tim Walsh (Chief Investigator)

Steff Lewis (Trial Statistician)
June 2013

Chief Investigator: Professor Tim Walsh
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Regulatory Sponsor: Co-sponsored by Lothian University Hospitals Division and Edinburgh University
QMRI, 47 Little France Crescent, Edinburgh, EH16 4TJ

Funding Organisation: Chief Scientist’s Office, Scotland
Scottish Government Health Directorates
St Andrew’s House, Regent Road
Edinburgh EH1 3DG

Trial Registration numbers: NIHR CRN portfolio number: 8849 (Critical Care Specialty Group)
ISR CTN: 09412438

Ethics Committee Number: Scotland A REC 10/MRE00/18
<table>
<thead>
<tr>
<th>Contents</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial Overview</td>
<td>3</td>
</tr>
<tr>
<td>Trial Protocol</td>
<td>3</td>
</tr>
<tr>
<td>Study Design</td>
<td>3</td>
</tr>
<tr>
<td>Analysis</td>
<td>3</td>
</tr>
<tr>
<td>Analysis Principles</td>
<td>3</td>
</tr>
<tr>
<td>Trial Profile</td>
<td>4</td>
</tr>
<tr>
<td>Characteristics of Patients at Baseline</td>
<td>5</td>
</tr>
<tr>
<td>Process measures</td>
<td>6</td>
</tr>
<tr>
<td>Outcome measures</td>
<td>10</td>
</tr>
<tr>
<td>Subgroup analyses</td>
<td>14</td>
</tr>
</tbody>
</table>
**Trial Overview**
Patients who survive intensive care (ICU) are often disabled after discharge. They experience physical, psychological and social problems that impair recovery to pre-illness quality of life.

The RECOVER trial is evaluating an intervention to enhance physical rehabilitation following ICU discharge. The intervention utilises a generic rehabilitation assistant (GRA) to deliver coordinated enhanced treatment to patients throughout the hospital and provide support after hospital discharge, under the supervision of existing multidisciplinary teams. In a randomised trial design we will compare this novel approach with current standard care in 240 ICU survivors who required $\geq$2 days ventilation in ICU. Our primary outcome is patient disability 3 months post-randomisation, but we will measure a range of other relevant secondary outcomes at 3, 6, and 12 months post-randomisation. These will include measures of physical function, psychological well-being, health related quality of life (HRQoL), and variables relevant to healthcare costs. We will also undertake a qualitative study with patients/carers and a cost-effectiveness analysis.

This analysis plan describes the quantitative analysis of the trial data (but not the cost-effectiveness analysis).

**Trial Protocol**
The full RECOVER trial protocol is available at the Edinburgh Clinical Trials Unit website [http://www.clinicaltrials.ed.ac.uk](http://www.clinicaltrials.ed.ac.uk)

**Study Design**
Prospective, 1:1 randomised, parallel group, controlled trial with blinded outcome assessment.

**ANALYSIS**

**Analysis Principles**
- We will include all participants who are randomised on the intention to treat principle. By this we mean that all patients will be analysed in the group that they were allocated to, regardless of compliance with the protocol. We do not plan a per protocol analysis.
- All tests will be two-sided and the $\alpha$ will be 5%. 95% confidence intervals will be given.
- We will report absolute differences between the groups for all outcomes.
- For the primary and all the secondary outcome measures we will report the numbers of patients for whom each outcome of interest was measured for each group.
- For the primary outcome, the primary analysis will include patients who die between randomisation and three months post-randomisation by imputing an RMI value of 0 for these patients.
- For all other patient outcome measures, the primary analysis will exclude patients with missing values.
- We will not adjust the P values for the multiple tests undertaken. We have clearly defined the primary outcome measure of interest. As this is a complex intervention trial the secondary outcomes are all potentially of interest and of relevance to patients. Interpretation of the clinical significance of any differences between the groups will acknowledge the wide range of variables being measured.
- For the primary analysis, adjustment will be made for pre-defined patient level variables at baseline, namely: age (>65 versus <65 years), RMI (0-5 versus 6-10 versus 11-15), SGA nutrition category (malnourished versus well-nourished), presence of delirium (presence versus absence), and ward destination category (surgical versus medical). These variables are included in the minimisation algorithm at randomisation. If there is any missing data present within the minimisation variables then appropriate action will need to be taken to deal with it. The appropriate action will depend on the amount of missing data as if there are only a few missing data points then they may be merged into the most common category amongst the non-missing data, however if there is a vast amount then a separate missing category may need to be developed. If two minimisation variables are very strongly correlated then we will adjust for the one with the least amount of missing data.

**Trial Profile**

We will report the trial profile using a CONSORT diagram as shown in figure 1. We will report the total numbers of admissions to each of the two intensive care units, the numbers who were excluded and the reasons, the numbers of eligible patients, and the numbers for whom consent was obtained, and the number randomised. For randomised patients, we will report the numbers of patients who died during follow up, and the numbers of patients in whom the primary and secondary outcome measures were obtained at 3, 6, and 12 months post-randomisation.
Characteristics of Patients at Baseline
We will compare the following patient characteristics at baseline. Mean (SD), median (IQR), and proportions will be used as appropriate. No formal statistical comparisons will be made between baseline variables.

1. Age
2. Gender
3. Social class
4. Pre-admission weight
5. Functional Comorbidity Index Score
6. ICU admission diagnosis
   a. Surgical patients
      i. Cardiovascular
      ii. Respiratory
      iii. Gastrointestinal
      iv. Renal
      v. Trauma
      vi. Other orthopaedic
vii. Obstetrics/Gynaecology
viii. Other
b. Medical patients
   i. Cardiovascular
   ii. Respiratory
   iii. Gastrointestinal
   iv. Renal
   v. Trauma
   vi. Obstetrics/Gynaecology
   vii. Haematological
   viii. Other
7. APACHE II score
8. Pre-randomisation ICU length of stay
9. Pre-randomisation total hospital stay
10. Days of mechanical ventilation in ICU prior to randomisation
11. Vasopressor/inotropic support in ICU prior to randomisation:
    a. Proportion of patients requiring support
12. Renal replacement therapy prior to randomisation
    a. Proportion of patients requiring support
13. Time from ICU discharge to randomisation
14. Organ failure score at randomisation
    a. Total SOFA
    b. Cardiovascular score
    c. Respiratory score
    d. Renal score
    e. Haematologic score
    f. Hepatic score
    g. Neurologic score
15. RMI at randomisation
    a. Score
    b. Proportion score 0-5
    c. Proportion score 6-10
    d. Proportion score 11-15
16. Physical component of Subjective Global Assessment of nutrition
    a. Proportion severe
    b. Proportion moderate
    c. Proportion mild
17. Patients with delirium at randomisation
18. Mode of nutrition at randomisation
    a. Parenteral
    b. Enteral (feeding tube any route)
    c. Oral (with or without supplements)

Process measures
The RECOVER study is a complex intervention trial based around the
provision of a trained GRA in addition to routine rehabilitation in the context of
usual NHS care. The description of process is therefore of great importance to
understanding the treatments received by each group, and the differences
between the groups. Data will be extracted from the patient’s record and from
the treatment logs completed by the GRAs. Table 1 summarises the process measures that will be systematically recorded prospectively during the trial.

Table 1: The process measures that will be collected and reported for each group. The numbers and proportions of patients receiving processes that are binary events will be reported. For continuous variables, such as numbers of treatments, mean (SD) or median (IQR) numbers of treatments will be reported as appropriate.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stage 1: ICU discharge</th>
<th>Stage 2: ICU discharge to acute hospital discharge</th>
<th>Weekly interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients received a post-ICU discharge visit for a structured discussion</td>
<td></td>
<td>Week one post-randomisation</td>
</tr>
<tr>
<td></td>
<td>Number (%)</td>
<td></td>
<td>Number of patients remaining in acute hospital</td>
</tr>
<tr>
<td></td>
<td>Number (%) with relative/family/friend present</td>
<td></td>
<td>Visited by dietitian</td>
</tr>
<tr>
<td></td>
<td>Number (%) at which GRA was present</td>
<td></td>
<td>Visited by physiotherapist</td>
</tr>
<tr>
<td></td>
<td>Patients who received a lay summary of what happened during the ICU stay offered to patient Number (%)</td>
<td></td>
<td>Visited by occupational therapist</td>
</tr>
<tr>
<td></td>
<td>Patients accepted lay summary Number (%)</td>
<td></td>
<td>Visited by speech and language therapist</td>
</tr>
<tr>
<td></td>
<td>Patients who received an ICU rehabilitation manual</td>
<td></td>
<td>Visited by GRA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Visited by other health professional (excluding parent medical team and ward nursing staff)</td>
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<td></td>
<td></td>
<td></td>
<td>Documentation of patient-centred goals or goal setting review</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>All of the above N (%)</td>
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<td>Week two post randomisation</td>
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<td>Weeks five to hospital discharge or week 12 post randomisation</td>
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<tr>
<td>Stage 3: Hospital discharge</td>
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</tbody>
</table>
Patients discharged from acute hospital alive during 12 weeks post-randomisation
Patients who received a home assessment prior to hospital discharge
   Number (%)
Patients offered a visit to ICU prior to hospital discharge
   Number (%)
Patients who visited ICU prior to hospital discharge
   Number (%)
Patients whose GP received a study specific discharge summary of rehabilitation status
   Number (%)
Referral to Community rehabilitation teams
   Number (%)
   a. Physiotherapy
   b. Occupational therapy
   c. Dietetic
   d. Speech and language therapy
   e. Community enteral nutrition team
   f. Alcohol liaison
   g. Smoking cessation
   h. Other teams

<table>
<thead>
<tr>
<th>Stage 4: post hospital discharge to 90 days post-randomisation</th>
</tr>
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<tbody>
<tr>
<td>Patients who received at least 1 contact from GRA (number (%))</td>
</tr>
<tr>
<td>Number of contacts per patient</td>
</tr>
<tr>
<td>Contacts initiated by GRA per patient</td>
</tr>
<tr>
<td>Contacts initiated by patient/relative per patient</td>
</tr>
<tr>
<td>Contacts initiated by GP per patient</td>
</tr>
</tbody>
</table>

### Types of therapy received in hospital between randomisation and hospital discharge

Based on data recorded prospectively by dedicated research staff from the patient record using a pre-defined template the types of treatments will be summarised for the major rehabilitation categories. Treatment provided by the GRA extracted from treatment logs completed by GRAs using pre-specified proforma.

Treatments recorded from any qualified health care professional. For intervention group treatments summed for separate episodes provided by specialist staff and/or GRAs in each category.

#### Dietetic treatments
*Interventions occurring at least once during intervention period in acute hospital:*
- Estimation of nutritional requirements
- Recording of food charts
- Estimation of nutritional intake
Organisation of nutritional supplements
Period of enteral tube feeding
Period of parenteral feeding
Prescription of additional dietetic snacks

Number of days on which documented dietetic interventions occurred by dietician and/or GRA

**Physiotherapy treatments**

*Respiratory*

Number of days on which respiratory assessments occurred
Number of days on which respiratory treatments occurred

**Mobility**

Number of days on which mobility assessments occurred
Number of days on which treatments occurred relating to:
  a. Transfers
  b. Marching on the spot
  c. Walking
  d. Stairs
  e. Exercises
  f. Balance work
  g. Pedals
  h. Mobility advice
  i. Exercise bike
  j. Massage
  k. Passive range of movements
  l. Stretches
  m. Pacing
  n. Other

**Occupational Therapy Treatments**

Numbers of patients receiving the following at least once during intervention period in acute hospital:

*Assessments*
  a. Documentation of preadmission profile and/or background information
  b. Mobility assessment
  c. Transfers assessment
  d. Washing/dressing assessment
  e. Toileting/continence assessment
  f. Feeding assessment
  g. Self-care assessment
  h. Kitchen/meal preparation assessment
  i. Cognitive/memory assessment
  j. Domestic assessment
  k. Other assessment

*Treatments*
  a. Washing and dressing practice
  b. Toileting/continence practice
  c. Feeding practice
d. Self-care practice  
e. Kitchen/meal preparation practice 

Preparation for discharge  
a. Package of care arranged  
b. Aids provided  
c. Adaptations arranged/provided  
d. Home assessment/visit  
e. Environmental assessment 

**Speech and Language Therapy**  
Number of patients receiving the following at least once during intervention period in acute hospital:  
a. Swallow assessment  
b. Communication assessment  
c. Any SLT intervention  

**Outcome measures**  

**Primary outcome**  
The primary outcome measure, RMI at 3 months post-randomisation, will be compared between the groups using ANCOVA to adjust for baseline RMI. 

**Secondary outcomes**  

**A. Hospital outcomes**  
The following outcomes will be compared between the groups for the acute hospital stay:  
1. Length of acute hospital stay post-randomisation analysed using Wilcoxon Mann-Whitney test provided data is skewed.  
2. Readmissions to the ICU during the same hospital stay analysed using binary logistic regression.  
3. Survival to hospital discharge. This will be reported as proportions for each group. In addition, this will be presented as Kaplan-Meier curves, and analysed using Cox regression if the appropriate assumptions hold. Patients will be censored at discharge.  
4. RMI at hospital discharge (surviving patients only) using ANCOVA to adjust for baseline RMI.  
5. Visual analogue score at hospital discharge (10 cm visual analogue scale; last measurement prior to hospital discharge) for the following:  
  i. Fatigue  
  ii. Breathlessness  
  iii. Appetite  
  iv. Pain  
  v. Joint stiffness  
These will be analysed using linear regression, provided distributional assumptions hold.
6. Patients with delirium (CAM-ICU positive) at hospital discharge (last recorded measure in hospital). This will be analysed using binary logistic regression and adjusted for the baseline value.

7. Handgrip strength at hospital discharge (last recorded measure in hospital; mean of three values). This will be analysed using linear regression, provided distributional assumptions hold.

B. Recovery during acute hospital stay
For each weekly assessment during acute hospital admission post-randomisation, the following will be compared between the randomised groups. For each week, the numbers of patients at risk will be described, as the numbers of patients will decrease progressively as acute hospital discharge (or death post ICU discharge) occurs. We will examine the profile of the following variables across time for each patient, and provide a suitable summary measure, graphically if possible:
   a. RMI
   b. Visual analogue score for:
      i. Fatigue
      ii. Breathlessness
      iii. Appetite
      iv. Pain
      v. Joint stiffness
   c. Presence of delirium (CAM-ICU positive)
   d. Handgrip strength (mean of three values)

C. 90 day outcomes
We will compare the following variables at the 90 day time point

1. Survival to 90 days. Survival (to the end of study) will be presented as Kaplan-Meier curves, and analysed using Cox regression if the appropriate assumptions hold. 90-day survival will be estimated from these analyses.

2. Total, Physical Component Score, and Mental Component Score SF-12 score. These will be analysed using linear regression, provided distributional assumptions hold.

3. Visual analogue scores for the following:
   a. Fatigue
   b. Breathlessness
   c. Appetite
   d. Pain
   e. Joint stiffness
   These will be analysed using linear regression, provided distributional assumptions hold.

4. Patient satisfaction measure. See section F.

5. Hospital Anxiety and Depression (HAD) questionnaire
   a. Absolute scores, using linear regression provided distributional assumptions hold.
   b. Number of patients triggering anxiety and depression symptomatology [score greater or equal to 8]. These data will be descriptive only.
6. Nutritional status (subjective global assessment of nutrition, analysed using ordinal logistic regression; proportion who are malnourished versus well-nourished {descriptive only}).

7. Weight. If there are sufficient numbers of patients with data, this will be analysed using ANCOVA, adjusting for pre-ICU admission weight (recorded or estimated). Otherwise, the analysis will not adjust for pre-ICU admission weight.

8. Hand grip strength, analysed using linear regression, provided distributional assumptions hold.

9. 2m timed up-and-go time analysed using Wilcoxon Mann-Whitney tests provided data is skewed.

10. Davidson’s Trauma Scale score (DTS)
    a. Absolute scores analysed using linear regression, provided distributional assumptions hold.
    b. Number of patients triggering PTSD symptomatology [score of greater or equal to 27]. These data will be shown descriptively only.

D. 6 month outcomes
We will compare the following variables at the 6 month time point

1. RMI, using ANCOVA to adjust for baseline RMI.
2. Survival. 6 month survival will be estimated from the survival analysis presented in C1.
3. Total, Physical Component Score, and Mental Component Score SF-12 score. These will be analysed using linear regression, provided distributional assumptions hold.
4. Visual analogue scores for the following:
   a. Fatigue
   b. Breathlessness
   c. Appetite
   d. Pain
   e. Joint stiffness
   These will be analysed using linear regression, provided distributional assumptions hold.

5. Hospital Anxiety and Depression (HAD) questionnaire
   a. Absolute scores using linear regression provided distributional assumptions hold.
   b. Number of patients triggering anxiety and depression symptomatology [score greater or equal to 8]. These data will be descriptive only.

6. Davidson’s Trauma Scale score (DTS)
   a. Absolute scores analysed using linear regression, provided distributional assumptions hold.
   b. Number of patients triggering PTSD symptomatology [score greater or equal to 27]. These data will be shown descriptively only.

E. 12 month outcomes
We will compare the following variables at the 12 month time point

1. RMI, using ANCOVA to adjust for baseline RMI.
2. Survival. 12 month survival will be estimated from the survival analysis presented in C1.
3. Total, Physical Component Score, and Mental Component Score SF-12 score. These will be analysed using linear regression, provided distributional assumptions hold.
4. Visual analogue scores for the following:
   a. Fatigue
   b. Breathlessness
   c. Appetite
   d. Pain
   e. Joint stiffness
   These will be analysed using linear regression, provided distributional assumptions hold.
5. Hospital Anxiety and Depression (HAD) questionnaire
   a. Absolute scores using linear regression provided distributional assumptions hold.
   b. Number of patients triggering anxiety and depression symptomatology [score greater or equal to 8]. These data will be descriptive only.
6. Davidson’s Trauma Scale score (DTS)
   a. Absolute scores analysed using linear regression, provided distributional assumptions hold.
   b. Number of patients triggering PTSD symptomatology [score greater or equal to 27]. These data will be shown descriptively only.

F. Patient Satisfaction during 3 months intervention period (measured at 90 days follow up visit)
   We will compare Lickert scale scores (on a 10cm scale) for the following domains:
1. Transfer from Intensive Care to the ward (the first few days)
2. The ward staff’s understanding of your time in Intensive Care
3. Exercises to get you moving/back on your feet
4. Help, support and advice with being independent (in everyday things like washing and dressing yourself)
5. Help with eating and nutrition
6. Being involved in decisions about your care
7. The organisation/co-ordination of your care
8. Information about what happened in Intensive Care
9. Knowing what to expect after you got home
These will be compared descriptively only.

G. Other descriptive statistics, not specifically related to pre-specified secondary outcomes
1. Discharge destination. The number of patients in the following categories will be presented. No formal statistical analysis will be done, as this is not an outcome
   i. Own home (alone or with family/carers)
   ii. Other home with family/carers
   iii. Sheltered accommodation
   iv. Nursing home
   v. Long term NHS care
   vi. Rehabilitation hospital
   vii. Other acute hospital
   viii. Death

Subgroup analyses

Primary Outcome
For the primary outcome (RMI), subgroup analyses will be performed by adding the interaction between treatment and the subgroup variable into the ANCOVA model. A forest plot will be used to present results for the following subgroups:

1. Age ≤65 years versus >65 years at study entry
2. RMI (0-5 versus 6-10 versus 11-15) at randomisation
3. SGA nutrition physical component at study entry (severe versus moderate versus better) at randomisation

Secondary Outcomes
As this is a complex intervention trial it is acknowledged that the intervention may plausibly have differential effects on different outcomes. Several secondary outcomes may be of equal importance to patients to the primary outcome. Similarly, an effect on secondary outcomes in the presence of “no effect” on the primary functional outcome could be of importance to patients and healthcare.

Subgroup analyses will be performed for the following secondary outcomes at 90 days:

- Survival to 90 days.
- SF-12 score (Total, Physical Component Score, and Mental Component Score)
- Hospital Anxiety and Depression (HAD) questionnaire absolute score
- Davidson’s Trauma Scale score (DTS) absolute score

A forest plot will be used to present results for the following subgroups:

1. Age ≤65 years versus >65 years at study entry
2. RMI (0-5 versus 6-10 versus 11-15) at randomisation
3. SGA nutrition physical component at study entry (severe versus moderate versus better) at randomisation