Anaemia management with red Blood Cell transfusion to improve post-intensive care disability: a randomised controlled trial

(The ABC post-intensive care trial)

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Version Number and Date	Version 9 14 March 2025

Amendment classification and number:	**Summary of change(s)**
Sub-Amendment 1 17Jan2020	***Version 2 (first approved version) to Version 3*** • Addition of study logo • Addition of clarification of eligibility period (4.2 and 5.1.2) • Removal of option to have data withdrawn (5.2.3) • Addition of time window for commencement blood transfusion (6.1.2.4) • Acceptable time window for completion of follow up visits (6.2) • Comment regarding collection of research blood sample (table1) • Correction of definition for infections at day 90 to match that given for day 30 (table 1) • Research blood sample changed to optional (7.1) • Change to requirement to enter data on to paper CRF before entry on to study specific database. Method to be used by site will be identified in SDP. (7.5) • Database will be developed by ECTU using the REDCAP system
Sub-Amendment 02 28 May 2020	No changes to protocol
Sub-Amendment 03 02Sep2020	***Version 3 to Version 4*** • **Design** – removal of reference blinded outcomes - NA. • **Inc/Exc Criteria** – additions to ensure that population of interest is recruited. • **Outcomes** – reformatted & addition of PCS component of SF36. • **Data Collection** – addition of clinical frailty index – commonly used in ICU research. Removal of HADS and IES-R to reduce participant burden. • **Screening and Eligibility** - period clarified to ensure consistency across all sites and reduce impact of delayed ICU discharge. • **Consent** – updated to include/reflect MCA terminology. • **Follow-Up** – will be carried out by site teams to minimise loss to follow up. • **Deviations** – clarity regarding deviation, for consistency across sites. • **MACE** – stroke and MI diagnosis criteria. • **Transfusion Reactions** – SHOT reporting will be used to assess all transfusion related reactions.
Sub-Amendment 05	***Version 4 to Version 5*** • **Key Trial Contacts** – Trial Manager updated • **Inc/Exc Criteria** – additions to ensure that population of interest is recruited. • **Recruitment** – period extended to account for impact of COVID • **Wording** – 1, 3 & 6 month changed to 30, 90 and 180 days throughout • **Prediction variable** - and/or mobility and/or baseline severity of system inflammation (based on C Reactive Protein) added • **Follow up** – 90 & 180 day window for completion extended to 14 days and updated follow up to allow a second telephone call • **Blood sample** - : clarified blood sampling processes and that research blood samples should be taken within 48 hours of enrolment in the trial • **Health Service Utilisation Questionnaire** – correctly renamed throughout

Amendment 06	***Version 5 to Version 6*** • **Section 5.3.1 added** - Clarification surrounding Haemoglobin concentrations during screening and eligibility period • **Eligibility -** Clarification around who can confirm eligibility • **Withdrawals** - Clarification around withdrawal criteria • **Intervention Period –** clarification around assessment and management during intervention period • **Deviations** – clarification to what constitutes a deviation • **Follow up visits** – clarification around follow up visits • **Data collection** – clarification around data collection at baseline • **Sample storage** – clarified and Sample Processing SOP added to **Appendix 3** • **Minor updates to wording throughout**
Amendment 7	***Version 6 to Version 7*** • **Change to Key Contacts** – Trial manager updated • **Adjustment to site target**: from 15 sites to 20-25 sites • **Added exclusion:** prisoners added, patient due for imminent discharge added • **Video added**: the option to use a video guide to aid consenting participants • **Corrections to Table 1**: 90 day follow up window corrected to +/-14 days • **Change to window for 30 day visit follow up:** questionnaire and blood sample can be taken within the window of 7 days prior or 14 days post visit date • **Health Economics: brief text added in section 9.2.1 to clarify that data linkage for 5 years outcomes will only be performed if considered of value after analysis of the short term outcome data.** • **Comment added in section 2.3.2 on secondary endpoints, to clarify the time horizon is 180 days for the main HE evaluation instead of 90 days.**
Amendment 8	***Version 7 to Version 8*** • ***Increase in sample size from 305 to 346*** • ***Remove maximum approach limit*** • ***Inclusion of the Study Within A Trial (SWAT) to explore reasons for declining consent (section 11). Participant Information Sheets and consent forms for research staff approached for this SWAT also included.*** • ***Additional detail regarding statistical analysis added to section 9.2***

Amendment 9	***Version 8 to Version 9*** 5.1.3b: Change Hb range from 94-100 g/L to 94-99 g/L to guide decision making for transfusions for when a baseline or another Hb measurement becomes available before any transfusion has occurred.

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SUMMARY

SCIENTIFIC SUMMARY

DESIGN:

Prospective, parallel group, randomised controlled, intervention trial. Embedded prediction and mechanistic study. Health economic evaluation.

POPULATION:

1. Patient who received level 3 ICU care at any time point during the current hospital admission (defined as advanced respiratory support and/or at least two organ support)
2. Patient considered ready for discharge from the ICU by the caring clinical team
3. Hb≤94g/L when ready for ICU discharge or during the first seven days following the decision by the treating clinician that the patient is **ready for** ICU discharge
4. Age ≥16 years.
5. Patient expected to remain in study hospital until hospital discharge
6. Consent provided (by participant or in accordance with appropriate mental capacity legislation for the site)

Exclusion criteria

1. Contraindication or objection to RBC transfusion
2. Active bleeding when screened
3. Primary neurological ICU admission diagnosis, including primary brain or spinal cord injury
4. Patients discharged from the ICU following cardiac surgery
5. Currently receiving or planned to receive end-of-life care
6. Not expected by clinical team to survive to hospital discharge.
7. Patient with a proven chronic haematological disease that requires regular RBC transfusion to treat anaemia
8. Patient with dialysis-dependent chronic renal failure prior to ICU admission
9. Patient receiving regular erthyropoietin (or any erythropoiesis stimulating agent) treatment for anaemia prior to ICU admission.
10. Unable to obtain consent (from patient or in accordance with appropriate mental capacity legislation for the site)
11. Readmission to ICU during current hospitalisation episode and not enrolled following previous ICU admissions
12. Patient recovering following liver transplantation, kidney transplantation, or combined kidney/pancreas transplantation
13. Patient recovering from variceal bleeding due to chronic liver disease
14. Prisoners
15. Patient due for imminent hospital discharge within the next 24 hours

RANDOMISATION: Allocation 1:1 by remote computer randomisation (stratified by centre in blocks).

TREATMENT GROUPS:

Intervention group: All patients will receive a single unit RBC transfusion post-randomisation. Single RBC transfusions will subsequently be administered to achieve and maintain Hb 100-120g/L until hospital discharge. Hb measured at least weekly in hospital. Hb transfusion trigger <100g/L

Comparator 'usual care' group: Current usual care transfusion practice, namely single RBC transfusions when Hb less than 70g/L **(or modified according to clinician decision)** to achieve target Hb 70-90g/L. Hb measured at least weekly in hospital.

Co-interventions: all other aspects of care will be according to clinician decisions. Other treatments for anaemia, such as iron therapy, will be permitted in both groups but decided by treating clinicians.
Duration of intervention: From randomisation until acute hospital discharge (typically 2-3 weeks).

OUTCOMES:

Primary outcome: Physical Component Score (PCS) of the SF-36 HRQoL questionnaire at 90 days post-randomisation.

Secondary outcomes*:*

Patient centred outcomes:

1. Physical Component Score (PCS) of the SF-36 HRQoL questionnaire (and its four sub-domains) at 30 and 180 days post-randomisation.
2. Patient fatigue (Fatigue Severity Scale (FSS)) at 30, 90 and 180 days post-randomisation
3. Mental component score SF-36 (and its four sub-domains) at 30, 90 and 180 days post-randomisation.
4. Activities of Daily Living (ADLs) (WHODAS questionnaire[4]) at 90 days post-randomisation
5. Patients alive at 30, 90, and 180 days post-randomisation
6. Patients alive at 5 years post-randomisation derived from data linkage
7. Haemoglobin concentration at 30 days post-randomisation

Resource use and cost-effectiveness (based on data linkage and questionnaires):

1. Post-ICU length of hospital stay;
2. Care costs during 180 days post-randomisation.
3. Incremental cost per QALY at 180 days
4. Care costs derived from data linkage during 5 years post-randomisation (depending on short term analysis results)

Process and Safety outcomes:

1. Protocol compliance (during intervention index hospital stay)
2. Hb concentration (during index hospital stay)
3. RBC use (during 90 days follow up)
4. New Infections (during 90 days follow-up)
5. Transfusion-related adverse events (during 90 days follow-up)
6. Major adverse cardiovascular events (MACE; during 90 days follow-up)

DATA COLLECTION:

Baseline: age; sex; recalled SF-36 HRQoL; co-morbidity count (Functional Comorbidity Index FCI); Clinical Frailty Index prior to hospital admission; ICU admission diagnosis; ICU duration of mechanical ventilation and length of stay; baseline Hb; inflammation/erythrogenesis biomarkers.
During hospital stay: Hb; RBC transfusions; safety outcomes
30, 90, 180 days post-randomisation: SF-36 (PCS; MCS); fatigue (FSS); Health resource use; survival
90 days: *WHODAS disability questionnaire*
30 days post-randomisation: Hb; inflammation/erythrogenesis biomarkers (mediation variables).

SAMPLE SIZE

346 PATIENTS (randomised 1:1 between the two groups).

PERSONALISED MEDICINE COMPONENTS

Moderation analysis: We will use both baseline co-morbidity burden (FCI), recalled HRQoL, a measure of baseline physical function (ICU Mobility Scale), and the measures of baseline inflammation (C-reactive protein (CRP)) to explore whether and how pre-critical illness health and wellbeing, and the severity of ICU-discharge inflammation, moderate the efficacy of the intervention.
Mediation analysis: We hypothesise that ongoing impaired marrow erythrogenesis will affect the efficacy of the intervention, but whether this effect is 'positive' versus 'negative' is uncertain. IL-6 concentration, ferritin concentration, transferrin saturation, soluble transferrin receptor concentration, hepcidin concentration, erythroferrone concentration, and other key mediators of inflammation and erythrogenesis will be measured 30 days post-enrolment as markers of erythrogenesis. These will form the basis of an exploratory *mediation* analysis.

PLAIN ENGLISH SUMMARY

People who are discharged from intensive care (ICU) are often anaemic. Severe illnesses prevent new red blood cells (RBCs) being produced in the bone marrow, probably because inflammation in the body stops the bone marrow working correctly. Research has shown that during the time in ICU patients tolerate being anaemic well so we generally try not to give blood transfusions unless RBC counts are very low. However, many patients are severely anaemic when they leave ICU and we know it can take many months for anaemia to recover.
After ICU discharge patients typically feel tired and fatigued. Regaining the energy and health they once had can take a long time and be very debilitating. Tiredness and fatigue are typical symptoms of anaemia, but we currently don't know if interventions that correct anaemia can improve energy levels and recovery after ICU. We do know this can improve health for anaemic patients in other situations. ICU patients typically experience an 'acute' anaemia, which develops quickly due to their illness and, unlike patients with long-standing anaemias, their bodies may not have had time to compensate for this. The most effective way to quickly treat anaemia is to use a blood transfusion, which can return the RBC count close to normal very quickly. However, before recommending this for post-ICU patients we need to be sure that blood transfusions are benefitting patients as they are in short supply and can have complications. At present most patients remain anaemic for many weeks and months after they leave ICU, anaemia receives little attention, and doctors rarely treat it with blood transfusions. Alternative approaches such as iron therapy are also rarely used, but are unlikely to correct anaemia as quickly and effectively as blood transfusions.

Our trial will be the first to find out if an ICU patient's health can be improved by treating their anaemia using blood transfusions from the time they leave the ICU. We will compare the current approach, which is to leave people more anaemic, with a more active approach of using blood transfusions to correct anaemia during the time they spend in hospital after leaving ICU. Patients will be randomly split into two groups and the allocated approach will be used from the time they leave ICU until they are discharged from hospital. We will measure the effect that treating anaemia with blood transfusions has on important patient outcomes such as quality of life, the ability to carry out daily tasks, symptoms of fatigue, and patients' physical ability. Our trial will also explore which patients benefit most from blood transfusions and those who gain no benefit. We aim to establish which anaemic patients to treat with blood transfusions after ICU to help their recovery.

CONTENTS

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
ADL	Activity of Daily Living
CI	Chief Investigator
CRF	Case Report Form
CRP	C Reactive Protein
ECTU	Edinburgh Clinical Trials Unit
GCP	Good Clinical Practice
HRQoL	Health Related Quality of Life
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
	Intention to Treat
ISF	Investigation Site File
MA	Meta-analysis
MACE	Major Adverse Cardiovascular Event
NICE	National Institute for Care and Clinical Excellence
PI	Principal Investigator
PICS	Post Intensive Care Syndrome
QA	Quality Assurance
QALY	Quality of Life Adjusted Year
RBC	Red Blood Cell
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SOP	Standard Operating Procedure
SR	Systematic Review
TSC	Trial Steering Group

Academic and Clinical Central Office for Research and Development

WHO World Health Organisation

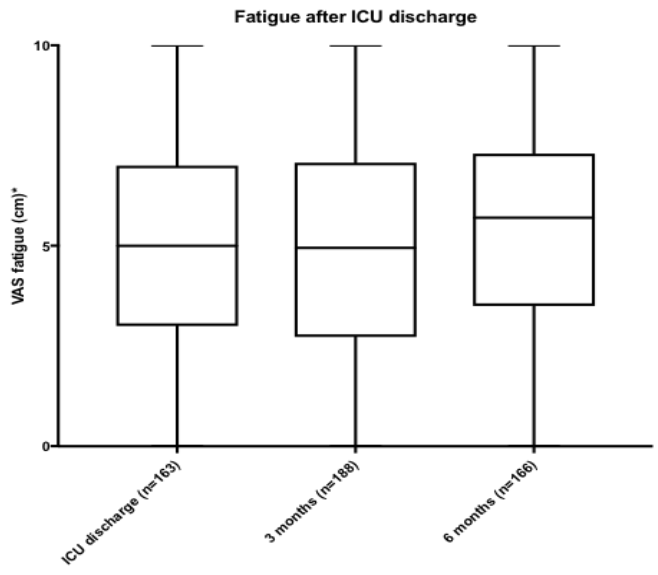
1 INTRODUCTION

1.1 BACKGROUND

1.1.1 Intensive Care (ICU) survivors frequently experience very poor health.

Around 270,000 adults require ICU care annually in the United Kingdom, of whom 75% are aged >50 years. Although around 80% of patients survive their initial critical illness, many subsequently suffer poor health for many months as a result of physical, mental, and cognitive impairments that collectively have been called a 'post intensive care syndrome (PICS)'.[1] It has been estimated around 25% of ICU survivors experience a PICS, according to the definition used and population examined. The PICS results from the systemic acute inflammation, organ failures, and neuromuscular weakness that result from critical illness, combined with the psychological and cognitive impact of acute illness. New disabilities are often superimposed on pre-existing health impairments. For example, more than 50% of ICU survivors have two or more pre-existing co-morbidities (such as diabetes, hypertension, cardiorespiratory disease)[2].

Physical function is particularly impaired during the first 2-3 months following ICU discharge. Disability, as described by the World Health Organisation (WHO) International Classification of Functioning, Disability and Health (ICF) Framework, is prevalent, and includes impaired *body function* (muscle strength, walking ability), *activity* (ability to carry out Activities of Daily Living (ADLs)), and *participation* (including health-related quality of life (HRQoL), and return to work).[3 4] Fatigue is the most prevalent symptom reported by ICU survivors, and is often severe and debilitating (figure 1)[5 6].



*Visual analogue scale for fatigue range 0 (no fatigue) to 10 (worst fatigue imaginable)

Figure 1: Box and whisker plot showing patient reported fatigue severity on a scale from 0 'no fatigue' to 10 'worst fatigue imaginable for patients who participated in a post-ICU rehabilitation trial.[2] The horizontal lines represent the median reported value; boxes represent the 25% of values above and below the median value.

ICU survivors are more likely to die compared to other hospitalised patients, and utilise substantially higher healthcare resource, especially during the first 3-6 months following ICU discharge.[7] For example, patients typically spend a further three weeks in the acute hospital

after ICU discharge, and 25% experience unplanned emergency readmission to hospital within 3 months of eventual hospital discharge.[8]

Our previous research found ICU survivors described recovery as a journey with enormous personal impact and challenges,[9] yet it receives little attention from major funders and charities. The James Lind Alliance (a patient/professional collaborative)[10] and the National Institute of Health and Care Excellence (NICE)[11] both highlight research into promoting post-ICU recovery as a priority. The post-ICU trials that have been undertaken, including by our group, have mostly evaluated the impact of exercise-based rehabilitation, but frustratingly none have demonstrated clinically important effects on patient outcome.[12] A possible contributing factor is that patients are too fatigued and weak to participate in physical rehabilitation programmes, especially during the early post-ICU period.

1.1.2 Anaemia may contribute to poor health and disability following critical illness

Acute anaemia *during* ICU care is very common, and affects around 80% of patients of whom 30-40% experience moderate-severe anaemia according to the World Health Organisation (WHO) definition of haemoglobin (Hb) ≤94g/L.[13] Anaemia has multiple causes, but impaired bone marrow RBC production (erythrogenesis) is of major importance. Inflammation is thought to impair normal erythrogenesis, because it results in low iron bioavailability, low erythropoietin levels, and direct marrow inhibition.[14 15] Around 25% of ICU survivors have moderate-severe anaemia at ICU discharge[16], and 75% still have some degree of anaemia when discharged home.[17] Up to 50% of these patients have persisting anaemia 3-6 months later, which is associated with low HRQoL and is most severe in patients with early persisting systemic inflammation.[18] We recently showed that virtually no ICU survivors receive treatment for their anaemia and most do not have their anaemia actively managed during follow-up.

In other groups of patients anaemia is strongly associated with significant fatigue and reduced HRQoL, for example in patients with chronic inflammatory diseases, cancer, chronic renal failure, and bone marrow failure. In these patient groups anaemia is typically treated actively using RBC transfusions, erythropoietin, and iron therapy because correcting anaemia is known to improve patient symptoms and HRQoL[19-21]. NICE recommends individualised blood transfusions for patients with chronic marrow failure.[22] However, despite the known association between anaemia, fatigue, disability and reduced HRQoL there are no published large clinical trials of anaemia treatment for ICU survivors.[23] Although there has been considerable justified concern about the historical safety of blood transfusions, current rigorous testing make this an extremely safe medical treatment if used for the 'right patient at the right time'.

1.1.3 Persisting inflammation may impair anaemia recovery after ICU.

Our previous research suggests persisting systemic inflammation may be a barrier to physical recovery after ICU. Inflammation is prevalent after ICU discharge[24], and in a secondary analysis of an ICU rehabilitation trial we found persisting inflammation three months after ICU discharge was associated with poor functional recovery[25]. Among the 240 patients we studied 50% had moderate-severe anaemia at ICU discharge (mean Hb 88g/L (SD 9)), and were still inflamed as assessed by circulating C-reactive protein concentrations (CRP; mean CRP 65mg/L; normal <3mg/L). This sub-group had very low physical HRQoL 3 months later (mean SF12 PCS score 35 (SD 11); normal level 50).

1.1.4 Blood transfusion as a potential treatment for anaemic ICU survivors.

Several large randomised controlled trials (RCTs) compared more liberal with restrictive RBC strategies for managing anaemia *during* ICU care. These found that survival from critical illness was similar when restrictive RBC transfusions (target Hb 70-90g/L) were used[26], but in these trials deaths mostly occurred *before ICU discharge* rather than among survivors (typically 25-30% of patients died in the ICU) and disability outcomes among survivors were not reported. The intervention in almost all of these trials also only occurred *during* ICU admission. Several recent systematic reviews (SRs) suggest that restrictive RBC transfusions may not be safe for all patients, notably those with cardiovascular disease[27] and older patients[28] in whom mortality and complications may occur more frequently. This could be important among ICU survivors, because cardiovascular disease is present in up to 25% of ICU patients[29], and around 50% are aged >65 years.

We hypothesise that the risk to benefit balance for transfusions may be different once patients have survived and are discharged. The high prevalence of anaemia, its persistence for many weeks/months, and concurrent severe fatigue and physical weakness provide biological plausibility for this hypothesis. Anaemia may limit the effectiveness of rehabilitation and delay recovery, explaining in part why rehabilitation has very limited effectiveness. The restrictive transfusion practices recommended during ICU may not be best practice among survivors, who are similar to chronically anaemic patients in whom transfusions can improve HRQoL. We hypothesise that correction of anaemia by RBC transfusion *after* ICU discharge will improve recovery.

To evaluate RBC transfusions in this setting, a careful evaluation of risk to benefit balance is required. Potential benefits include reduced fatigue, improved breathlessness and mobility, and a reduction in complications such as cardiovascular events that may be more prevalent with anaemia. Potential risks include the complications of blood transfusions, including transfusion reactions, pulmonary oedema, and infections. It is possible that the risk to benefit balance of RBC transfusions is dependent in part on the patient's status, including their pre-existing health and/or ongoing complications of critical illness. Research is needed to evaluate the risk to benefit balance of this therapy in anaemic ICU survivors, and also to explore which patients might have the most benefit in terms of balance between risks and benefits.

1.1.5 Potential alternatives to RBC transfusions

The most plausible alternatives to RBCs for treating anaemia are iron therapy and/or erythropoietin therapy. Iron therapy is likely to have limited efficacy and slow effects in ICU survivors, particularly if ongoing inflammation is prevalent.[15 24] A recent ICU based trial of intravenous iron therapy found higher hepcidin concentrations (a key regulator of iron effectiveness) were associated with systemic inflammation and poor anaemia correction supporting the importance of inflammation as a barrier to recovery.[30] Iron was only modestly successful in correcting anaemia and avoiding RBC transfusions,[31] and a SR of all published trials suggests limited effectiveness.[32] Another concern is the known association between iron therapy and infections, which are common among ICU survivors especially those who experienced sepsis.[33] Similarly, erythropoietin therapy has limited efficacy in the presence of inflammation, is unlicensed for the treatment of critical illness related anaemia, and may be associated with complications such as venous thrombo-embolism and hypertension.[34] Neither iron nor erythropoietin therapy rapidly correct anaemia (over days), and even if effective are likely to take weeks or longer.

We aim to correct anaemia over several days in order to maximise the impact on fatigue and recovery as soon as possible after ICU discharge. We believe the intervention with greatest fidelity and predictability is RBC transfusion.

1.2 WHY IS THIS RESEARCH IMPORTANT?

The approximately 50,000 patients who survive critical illness with moderate-severe anaemia annually in the UK experience physical disability and although NICE recommend offering rehabilitation to ICU survivors the evidence underpinning how best to do this is weak and inconclusive.[11] As guidelines recommend restricting RBC transfusions during ICU care, survivors are currently often discharged anaemic and remain so for many months, during which fatigue and disability are most severe.[35] We have consulted with ICU patients and their families, who helped develop our research. This group strongly support exploring interventions that might reduce fatigue and disabilities, and agreed that anaemia is an important consideration. Our research will provide the first evidence about which patients may benefit from RBC transfusions post-ICU. It is relevant to patients, healthcare professionals and providers, and blood services.

1.3 REVIEW OF RELEVANT EXISTING EVIDENCE

As noted above recent SRs and meta-analyses (MAs) conclude that overall effects on *mortality* are similar between restrictive and liberal RBC transfusion strategies[26 35], but no studies were conducted specifically in our study population. Importantly, heterogeneity of effects are emerging from recent SRs/MAs restricted to populations with co-morbidities[27 28]. Two ICU based transfusion trials measured HRQoL: a trial in septic shock patients[36], and our trial in older patients requiring prolonged mechanical ventilation[37]. The intervention in both trials occurred during ICU, and ICU mortality was high. Survivor cohorts were small, confirmed markedly reduced HRQoL, but found no differences in HRQoL. In addition to limited statistical power, these analyses did not adjust for baseline health status or other factors, which we and others have shown to be important determinants of HRQoL in heterogeneous ICU populations[38 39]. No rehabilitation trials have considered anaemia treatment either as the main intervention or as part of the intervention.[23]

A large observational literature demonstrates the high disability burden suffered by ICU survivors, especially during the first 3-6 months, but often lasting many years. This includes physical impairments, reduced Activities of Daily Living (ADLs), and mental and cognitive disability.[1 3 40] Pre-existing health status is an important determinant of post-ICU disability, but has not been widely considered in published trials, which may explain in part why the increasing number of ICU rehabilitation trials have demonstrated disappointing effects on outcomes.

1.4 RATIONALE FOR STUDY

1.4.1 Research Questions:

- Does correcting anaemia using blood transfusions improve patients' quality of life, fatigue, disability, cardiac complications, and survival after being discharged from intensive care?
- Does correcting anaemia using blood transfusions reduce the time needed in hospital after being discharged from intensive care?
- Is correcting anaemia using blood transfusions a cost-effective treatment after being discharged from intensive care?
- Are there certain groups of intensive care survivors who benefit more from correcting anaemia using blood transfusions?

1.4.2 Hypothesis:

In patients discharged from intensive care with moderate to severe anaemia, correction of anaemia using blood transfusions will improve quality of life, disability, and other measures of well-being

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

To determine whether correcting anaemia from the time of ICU discharge using blood transfusions (target Hb 100-120g/L) results in an improvement in self-reported quality of life (HRQoL) 90 days after intensive care discharge, compared with current usual care which recommends transfusions when Hb is less than 70g/L to achieve a target Hb 70-90g/L.

2.2 SECONDARY OBJECTIVES

- To determine the effect of correcting anaemia using blood transfusions on fatigue, disability, and death rate compared with current usual care
- To determine the safety of correcting anaemia with blood transfusions, compared with current usual care
- To determine which patients may benefit most from more active correction of anaemia using blood transfusions
- To determine whether more active correction of anaemia using blood transfusions is cost-effective in the NHS

2.3 ENDPOINTS

2.3.1 Primary Endpoint/Outcome

Physical Component Score (PCS) of the SF-36 HRQoL questionnaire at 90 days post-randomisation.

2.3.2 Secondary Endpoints/Outcomes

Patient centred outcomes:

1. Physical Component Score (PCS) of the SF-36 HRQoL questionnaire (and its four sub-domains) at 30 and 90 days post-randomisation.
2. Patient fatigue (Fatigue Severity Scale (FSS)) at 30, 90 and 180 days post-randomisation
3. Mental component score SF-36 (and its four sub-domains) at 30, 90 and 180 days post-randomisation.
4. Activities of Daily Living (ADLs) (WHODAS questionnaire[4]) at 90 days post-randomisation
5. Patients alive at 30, 90 and 180 days post-randomisation
6. Patients alive at 5 years post-randomisation derived from data linkage
7. Haemoglobin concentration at 30 days post-randomisation

Resource use and cost-effectiveness (based on data linkage and questionnaires):

8. Post-ICU length of hospital stay;
9. Care costs during 180 days post-randomisation.

10. Incremental cost per QALY at 180 days
11. Care costs derived from data linkage during 5 years post-randomisation (depending on results from shorter term outcome analysis)

Process and Safety outcomes:

12. Protocol compliance (during intervention index hospital stay)
13. Hb concentration (during index hospital stay)
14. RBC use (during 90 days follow up)
15. New Infections (during 90 days follow-up)
16. Transfusion-related adverse events (during 90 days follow-up)
17. Major adverse cardiovascular events (MACE; during 90 days follow-up)

3 STUDY DESIGN

3.1 STUDY DESIGN OVERVIEW

We propose a **prospective, parallel group, randomised controlled intervention trial**.

3.1.1 Personalised Medicine

We recognise the need for *personalised medicine*, especially in relation to the use of blood transfusions, and will use novel approaches to explore two key issues that will inform which patients may gain greatest benefit from this intervention:

Prediction (moderation) variables (what baseline covariates influence treatment success)**:** the importance of *baseline co-morbidity, HRQoL, mobility and/or baseline severity of systemic inflammation (based on C Reactive Protein)* will be studied within the trial, and a prediction model developed to help identify who will or will not benefit from blood transfusions.

Mediation variables (what variables measured early after randomisation are on the causal pathway for clinical benefit)**:**
the importance of *systemic inflammation* and *impaired erythrogenesis* post-ICU will be studied within the trial to improve our understanding of the causal pathway whereby transfusions may improve recovery.

These variables may be useful to identify if treatments were working, as surrogate outcomes, or to assist clinical decision-making.

3.2 STUDY SETTING

Acute hospitals managing patients discharged after a period in intensive care

3.3 RESEARCH QUESTIONS

3.3.1 'PICO' research question:

Population: ICU survivors with moderate-severe anaemia (WHO definition; Hb≤94g/L).
Intervention: RBC transfusion practice to maintain Hb at 100-120g/L during subsequent hospital stay; transfusion trigger <100g/L

Comparator: Current usual RBC transfusion practice to maintain Hb 70-90g/L; transfusion trigger <70g/L
Primary Outcome: Physical Component Score (PCS) of the SF-36 HRQoL questionnaire 90 days post-randomisation

Secondary Outcomes:
To determine whether the intervention improves: Patient fatigue; Patient disability (function and activities of daily living (ADLs)); Rates of major adverse cardiac events (MACE); Survival (up to 5 years); Health service resource use and costs (up to 5 years – according to results of the shorter term outcomes).
To evaluate if the intervention is cost-effective.

3.3.2 Personalised medicine questions:

To explore whether any of the following modify the efficacy of the intervention:
Prediction variables (moderation analyses) – baseline predictive factors

1. Pre-existing HRQoL
2. Pre-existing co-morbidities
3. Mobility status at ICU discharge
4. Baseline severity of inflammation (based on C Reactive Protein concentration)

Mechanistic factors (mediation analyses) – post ICU causal mediating factors:

5. Persisting systemic inflammation
6. Evidence of impaired erythrogenesis

3.3.3 Cost effectiveness questions:

We will estimate cost per life-year and cost per Quality-Adjusted Life Year (QALY) over the follow-up period of the study. Health service costs will rely on patient questionnaires. Depending on the results of the short-term outcomes, linkage of routinely collected healthcare data, including inpatient, outpatient, A&E, and unscheduled care may be undertaken.

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

The total sample size is 346, allocated 1:1 between the two randomised groups.

We anticipate recruitment will take place in 20-25 sites UK-wide, but more sites will be included according to interest, resources, and recruitment rates. Sites outside the UK will be considered if feasible.

4.2 INCLUSION CRITERIA

[1] Patient who received level 3 ICU care at any time point during the current hospital admission (defined as advanced respiratory support and/or at least two organ support)
[2] Patient considered ready for discharge from the ICU by the caring clinical team
[3] Hb≤94g/L when ready for ICU discharge or during the first seven days following the decision by the treating clinician that the patient is **ready for** ICU discharge
[4] Age ≥16 years.
[5] Patient expected to remain in study hospital until hospital discharge

[6] Consent provided (by participant or in accordance with appropriate mental capacity legislation for the site)

4.3 EXCLUSION CRITERIA

[1] Contraindication or objection to RBC transfusion
[2] Active bleeding when screened
[3] Primary neurological ICU admission diagnosis, including primary brain or spinal cord injury
[4] Patients discharged from the ICU following cardiac surgery
[5] Currently receiving or planned to receive end-of-life care
[6] Not expected by clinical team to survive to hospital discharge.
[7] Patient with a proven chronic haematological disease that requires regular RBC transfusion to treat anaemia
[8] Patient with dialysis-dependent chronic renal failure prior to ICU admission
[9] Patient receiving regular erthyropoietin (or any erythropoiesis stimulating agent) treatment for anaemia prior to ICU admission.
[10] Unable to obtain consent (from patient or in accordance with appropriate mental capacity legislation for the site)
[11] Readmission to ICU during current hospitalisation episode and not enrolled following previous ICU admissions
[12] Patient recovering following liver transplantation, kidney transplantation, or combined kidney/pancreas transplantation
[13] Patient recovering from variceal bleeding due to chronic liver disease
[14] Prisoners
[15] Patient due for imminent hospital discharge within the next 24 hours

4.4 CO-ENROLMENT

Co-enrolment will be permitted to other studies and trials once the following criteria and steps have been taken:

- Consideration has been made by both study Chief Investigators of issues related to study design and statistical considerations; legal and ethical considerations; biological and scientific rationale; participant considerations and; logistical and organisational issues.
- Ethical approvals for both studies, and sponsor policies for each study, allow co-enrolment
- Agreement to co-enrolment has been documented according to the policies and procedures of both sponsors
- For ACCORD, this is set out in the ACCORD Co-enrolment Policy (POL008 Co-enrolment Policy).

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

5.1.1 Screening

Patients will be screened at the time they are considered ready for ICU discharge by the clinical teams. According to local site arrangements, screening may be undertaken by the ICU clinical teams or ICU rehabilitation teams, in collaboration with research teams or other team members delegated at the local site. Members of the responsible clinical team (which could be the ICU team or ward-based team according to timing) will be asked to confirm suitability prior to any approach for consent.
Screening (and recruitment) can continue for up to seven days following ICU discharge or the patient being considered ready for discharge, whichever occurs first (the recruitment window).
All eligible patients identified from screening will be entered into the screening log, which will be kept in the Investigator Site File (ISF). The screening log, and the outcome of screening for eligible patients, will be completed and maintained by an appropriately trained member of the research team.

5.1.2 Eligibility period

The eligibility window will be from the time the patient meets inclusion criteria and has no exclusion criteria for up to seven days following the decision by the treating clinician that the patient is **ready for ICU discharge**, as long as the patient remains in the acute hospital. The aim will be for enrolment to occur as close to ICU discharge as possible, but recognises that patients are often fatigued and/or may need time to consider participation during this period.

5.1.3 Haemoglobin concentrations during screening and eligibility period

A patient can be screened as eligible for the trial based on any haemoglobin concentration during the eligibility period. If a haemoglobin concentration of 94g/L or less has been measured, and other inclusions/exclusions make the patient eligible, they can be approached for consent. Several scenarios based on the haemoglobin concentration may occur:

a. The patient provides consent without any further haemoglobin measurement being undertaken for clinical or other reasons. In this situation the patient should be immediately randomised and managed according to the allocated group. *There is no requirement to wait for the result of the baseline blood sample Hb measurement or any other Hb measurements before transfusing according to the protocol because the patient has demonstrated eligibility during the eligibility period.*
b. If the patient has been randomised, baseline blood samples have been taken, and the baseline or another Hb measurement becomes available before any transfusion has occurred, transfusion decisions should follow the protocol and group allocation using the most recent Hb concentration. *The patient should remain in the trial once randomised and not be withdrawn if the Hb concentration is above 94 g/L on repeat Hb measurement.* Transfusions should follow the protocol according to the most recent Hb measurement: for example if the Hb has increased on the baseline blood and is 94-99 g/L the patient should receive 1 unit of RBC if they are in the liberal group, with a target Hb of 100-120g/L. If they are in the restrictive group their Hb should simply be monitored, but they should not be withdrawn.
c. If a patient is being screened and fulfils all eligibility and no exclusion criteria, *but has not yet provided consent* (for example lack of capacity or patient/family are still considering taking part) the following should guide participation:

i. If a further Hb concentration is taken for clinical reasons *prior to consent being obtained*, and the result is >94 g/L, the patient is no longer eligible for the trial at that time.

ii. If after (i) above, a further Hb concentration is taken for clinical or other reasons and is again ≤94 g/L the patient is again eligible if within the 7 days recruitment window. They can then be approached for consent.

iii. Once a patient has provided consent they should be randomised immediately without waiting for further testing. Once randomised they should remain in the trial as per scenario (a) and (b) above.

5.2 CONSENTING PARTICIPANTS

It is recognised that patients may lack capacity at the time of ICU discharge, and during the days following discharge as a result of their acute illness. Reasons include delirium, severe fatigue, and cognitive impairment (that can especially impact short-term memory and the ability to retain information).

It is important to consider inclusion of all eligible patients, including those who may lack capacity, because patients lacking capacity may benefit from the trial intervention and might respond differently to those who have capacity at this time. Published studies also suggest that around 15% of patients may be delirious at the time of ICU discharge, which is likely to impair mental capacity.[2]

Eligibility can be confirmed, and patients and/or surrogate decision makers approached, by any individual delegated to do so by the local PI, including doctors, nurses, or other healthcare professionals with appropriate training in study procedures.

Wherever possible, patients should be approached when they are considered to have mental capacity. However, when the clinical and/or research teams consider that they lack mental capacity approaches appropriate to the local legal arrangements for Adults with Incapacity (AWI) should be used.

The timing is at the discretion of the research teams in consultation with clinical teams.

5.2.1 Patients with Mental Capacity

If the clinical team (ICU and/or ward based clinical team) agree for the patient to be approached, the clinical or research team will provide the patient with a Participant Information Leaflet (PIL). They may also provide access to a video describing the trial and what is involved, which can be used by the patient and their relatives to help understand the study. If the patient agrees a member of the research team will introduce and discuss the study. Patients will be allowed to consider participation during any part of the eligibility period, but will need to provide consent within 7 days of ICU discharge.

Where a patient agrees, the patient will be provided with a copy of the consent form, a copy of the form will be filed in the patient`s medical notes and a copy filed in the ISF. The informed consent process must be documented in the patient`s medical records.

5.2.2 Patients lacking Mental Capacity

5.2.2.1 In England, Wales, and Northern Ireland

An opinion/advice will be obtained in line with the legal requirements for obtaining advice in patients without capacity in England and Wales (Mental Capacity Act 2005). Northern Ireland follows common law; for the purposes of the trial, processes used in England and Wales will be used in Northern Ireland.

The researcher will seek from the opinion of a Personal Consultee (who may be a relative, partner or friend of the participant). This should normally take place during a face-to-face meeting. An authorised staff member/researcher will describe the trial to the individual, and provide them with a PIL and Personal Consultee Declaration (England/Wales and Northern Ireland). They may also provide access to a video describing the trial and what is involved, which can be used by the Personal Consultee to help understand the study. The researcher will seek their opinion about whether the patient should take part in the study. They will be asked to consider what the wishes and feelings of the patient would be if they had capacity. After the researcher has checked that the information sheet is understood, the researcher will invite the Personal Consultee to sign the form and will then countersign it. The Personal Consultee will be provided with a copy of the consent form, a copy of the form will be filed in the patient's medical notes and a copy filed in the ISF.
It is expected that in most cases of incapacity, the opinion of the Personal Consultee will be sought during a face-to-face meeting. When this is not possible, it will be allowed to discuss the study by telephone or other real-time communication media.

For patients who lack capacity, and for whom there is no personal consultee available from who to seek advice during the recruitment window, it will be possible to consult a Professional Consultee. The Professional Consultee will be a nominated individual who has relevant knowledge of the trial and the clinical area, and is not a member of the research team. If the Professional Consultee agrees, they will sign a Professional Consultee declaration form. A copy of the form will be filed in the patient's medical notes and a copy filed in the ISF.

The process must be documented in the patient`s medical records.

5.2.2.2 In Scotland

Consent will be obtained in Scotland according to the Adults With Incapacity (Scotland) Act 2000).

The researcher will seek consent from a Nearest Relative/Guardian or Welfare Attorney (who may be a relative, partner or friend of the participant). This will usually take place during a face-to-face meeting. An authorised staff member/researcher will describe the trial to the individual, and provide them with a PIL and Consent Form for Nearest Relative/Guardian or Welfare Attorney (Scotland). They may also provide access to a video describing the trial and what is involved, which can be used by the Nearest Relative/Guardian or Welfare Attorney to help understand the study. The researcher will seek their views about whether the patient should take part in the study. They will be asked to give their consent based on their opinion of the wishes and feelings of the patient if they had capacity. After the researcher has checked that the information sheet is understood, the researcher will invite the Nearest Relative/Guardian or Welfare Attorney to sign the form and will then countersign it. The Nearest Relative/ Guardian or Welfare Attorney will be provided with a copy of the consent form, a copy of the form will be filed in the patient's medical notes and a copy filed in the ISF.

It is expected that in most cases of incapacity, the opinion of the Nearest Relative/Guardian or Welfare Attorney will be sought during a face-to-face meeting. When this is not possible, it will be allowed to discuss the study by telephone or other real-time communication media.

The process for obtaining consent must be documented in the patient`s medical records.

5.2.2.3 Procedure once patients regain capacity

Once the participant has recovered from the condition causing incapacity, they will be approached by a member of the research team to obtain permission to continue in the study. The consent to continue process will include: assessment and documentation of capacity; providing the PIL and Consent Form for Participant with Recovered Capacity; allowing sufficient time for the patient to understand the material and ask questions; and, obtaining written informed consent. If the patient agrees to continue in the study they will be asked to sign the form which will then be counter signed by a member of the research team. The patient will be provided with a copy of the consent form, a copy of the form will be filed in the patient's medical notes and a copy filed in the ISF. The informed consent to continue process must be documented in the patient`s medical records.

If the participant declines on-going participation in the study the procedures for withdrawal (below) will be followed. In the rare event that the patient does not regain capacity or staff have been unable to obtain consent to continue, the consent/opinion from the Personal Consultee or Nearest Relative/ Guardian or Welfare Attorney or Professional Consultee will continue.

5.2.3 Withdrawal of Study Participants

There will be no pre-defined participant withdrawal criteria based on medical criteria.
Participants are free to withdraw from the study at any point or a participant can be withdrawn by the Investigator if this is considered clinically appropriate. In the case of incapacity, the representative of the participant can also withdraw the patient from the trial.

It is recognised that responsible clinicians may decide to suspend group allocation in certain circumstances based on their clinical judgement. Examples may include bleeding events, acute cardiovascular events, or other periods of clinical deterioration. In this situation, the patient should not be withdrawn from the trial unless the clinician specifically requests this. Ideally, the patient should be re-established on group allocation after the acute situation has resolved. *Wherever possible the patient should remain in the trial for follow-up even if a decision is made to permanently suspend group allocation (see option 1 below).*

If withdrawal occurs, the participant will have the following withdrawal options:

1. From any further study intervention only (ie the two transfusion groups). Further blood transfusions at the discretion of the clinical team. However, all follow up data collection (including the visit at 30 days if appropriate) will be completed as far as possible. The priority in this situation is the completion of the primary outcome (SF-36 PCS at 90 days).
2. From any further study intervention and data collection. All data collected until the point of withdrawal can be retained. In this situation, effort should be made to request that the primary outcome data at 90 days (SF-36 PCS) can be collected even if other

follow up is not completed. If the participant agrees, then this is re-classified as 'option 1' but restricted to primary outcome.
3. From all aspects of the trial and follow up. All research data collected to be removed from analysis.

If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case report form, if possible. The type of follow-up (if any) will be documented in the case report form.

5.3 RANDOMISATION

Patients will be randomised by remote computer to ensure allocation concealment. Allocation will be in a 1:1 ratio stratified by centre in blocks. The randomisation sequence will be generated by an independent statistician.

6 STUDY ASSESSMENTS

6.1 STUDY ASSESSMENTS AND MANAGEMENT DURING THE INTERVENTION

6.1.1 Duration on intervention

The intervention period will last from the time of enrolment until discharge from the acute hospital.

The intervention will end when one of the following occurs:

1. Patient is discharged home from hospital (or to a family member/friend who plan to provide support/care post-acute hospital discharge)
2. Patient dies during the acute hospital stay
3. Patient is discharged to a rehabilitation hospital or facility
4. Patient is discharged to an intermediate or long-term care facility

Note: If a participant is discharged to another acute care hospital from the enrolling hospital as part of the same hospitalisation, the randomisation allocation will be maintained wherever possible until discharge from that acute hospital. The site study team will attempt to provide advice to the hospital to which the patient is discharged and obtain relevant study assessment data. *Continuing to follow up these patients for primary outcome data at 90 days is the priority.*

6.1.2 Assessment and management during intervention period

The local care and research teams, in accordance with the protocol, will carry out the management of the patient during the intervention period.

6.1.2.1 Measurement of haemoglobin concentration:

Measurement of haemoglobin concentration in the acute hospital will be at the discretion of the clinical teams *unless haemoglobin concentration is not measured as part of routine care for seven consecutive days.*

If seven days have passed since the previous haemoglobin concentration measurement, the research team will request that the clinical team undertakes a measurement. This will only apply during the intervention period.

6.1.2.2 Transfusion practice during the intervention for patients randomised to the usual care transfusion practice

Patients should be managed according to current NICE guidance (see: www.nice.org.uk/guidance/ng24/chapter/Recommendations#red-blood-cells-2)

For the purpose of the trial this means:

Use restrictive red blood cell transfusion thresholds for patients who need red blood cell transfusions and who do not have major haemorrhage or have acute coronary syndrome.

Use a threshold of less than 70 g/litre and a haemoglobin concentration target of 70–90 g/litre after transfusion, unless the responsible clinician decides to modify this based on the patients' condition.

Use single-unit red blood cell transfusions for adults who do not have active bleeding and re-check Hb within 24-48 hours of the transfusion

This guidance should be followed after each haemoglobin concentration measurement undertaken during the intervention period (minimum one measurement per seven days).

6.1.2.3 Transfusion practice during the intervention for patients randomised to the intervention (more liberal) transfusion practice

Patients should be managed as follows following each haemoglobin concentration measurement undertaken during the intervention period:

If the haemoglobin concentration is ≥100g/L no transfusion should be given.

If the haemoglobin concentration is <100g/L a single-unit red blood cell transfusion should be given followed by clinical reassessment and re-checking the haemoglobin concentration.

If the haemoglobin concentration remains <100g/L further single unit red blood cell transfusions should be given until the haemoglobin concentration is 100-120g/L.

For both study groups, the haemoglobin concentration should be re-checked after each unit of red blood cells they receive unless they are bleeding (NICE Blood Transfusion Quality Statement 3: www.nice.org.uk/guidance/qs138/chapter/Quality-statements)

Haemoglobin concentration should ideally be re-checked within 24 hours of each transfusion and definitely within 48 hours. *If Haemoglobin is not re-checked within 48 hours this should be reported as a deviation.*

6.1.2.4 Transfusion prescription and patient monitoring during transfusion

Prescription of RBC transfusions should be made by a member of the clinical team using local procedures and documentation. Transfusions should be commenced **as soon as possible** after a triggering Hb result (the time the sample was taken as per the laboratory report), **and within a maximum of 48 hours**. Transfusions that do not occur or occur after 48 hours will be considered a protocol deviation (see 6.1.3). Bedside prescription checking and monitoring of patients during the transfusion period should follow locally agreed protocols and Standard Operating Procedures. This may include prescription of additional medication, such as diuretics, at the discretion of the clinical team.

6.1.3 Deviations from the allocated transfusion practice

All deviations from the recommended transfusion practice should be reported as a protocol deviation on the appropriate protocol deviation form. The following are pre-defined deviations:

- Failure to re-check Hb concentration within 48 hours of a transfusion
- Failure to administer a blood transfusion within 48 hours of the stated trigger in the allocated group (<70g/L or <100g/L)
- In the usual care group, administration of a blood transfusion at a trigger Hb ≥70g/L without the responsible clinician providing a reason for modifying the transfusion trigger.

6.1.4 Use of alternatives to blood transfusion

Patients in both study groups can receive alternatives to blood transfusion if directed by the clinical teams. However, these should be consistent with current NICE guidance concerning alternatives to blood transfusion: (see: www.nice.org.uk/guidance/ng24)

6.1.5 Other treatment and interventions during the intervention period

All other treatments and therapies provided to patients in both study groups should be at the discretion of the clinical teams.

6.2 LONG TERM FOLLOW UP ASSESSMENTS

Following randomisation, assessment will be carried out at the following time points (see also table 1) irrespective of whether the patient remains in the acute hospital (intervention still ongoing) or has been discharged from the acute hospital (intervention period completed).

For all follow up visits, vital status should be confirmed and telephone contact made at the start of the visit window to alert the participant to the follow up and arrange a suitable time and method. *To promote completeness the Physical Component Score (PCS) of the SF-36 should be done at this initial telephone contact wherever possible, especially at 90 day follow up*.

If a participant opts for postal or online follow up, *the local research team should check 7 days after the visit window opens that questionnaires have been completed*. If questionnaires are not complete, the research team should contact the participant and offer to complete via the telephone or online with assistance given over the phone if required. A second telephone call should be undertaken to remind the participant if the first telephone call does not result in the participant returning the questionnaire.

30 day follow up (7 days prior or 14 days post visit date for all aspects of the follow-up visit).

Ideally this visit will be conducted in person to allow blood sample collection. Arrange this visit with the participant before discharge if possible. In the event the participant declines blood sample, conduct visit remotely using the methods below.

- Vital status* and follow up to be carried out by the local research team.
- Follow up questionnaires
- Data collection
- Blood sampling

90 day follow up (+/- 14 days) – ***prioritise primary outcome***

- Vital status* will be checked and confirmed by the local research team. Follow up questionnaires will be undertaken by the local research team (or delegated individual).
  - Completion order as follows to ensure primary outcome is collected:
    1. Physical Component Score (PCS) of the SF-36
    2. Mental Component Score (MCS) of the SF-36
    3. Fatigue Severity Scale (FSS)
    4. WHODAS ADLs questionnaire
    5. Health Service Utilisation

  Participants should be offered several ways in which to complete and return the follow up questionnaires:
    1. **Telephone call** - the participant can complete with the aid of a member of the trial team. *This is the preferred method.*
    2. **Postal** – questionnaires will be posted out to participants for completion and return in provided envelope.
    3. **Online** – can be answered directly onto the trial database via a link provided by the central research team.

180 days follow up (+/- 14 days)

- Vital status* will be checked and confirmed by the local research team.
- Follow up questionnaires - completion will be undertaken by the local research team.
  - Completion order as follows to ensure primary endpoint is reached wherever possible:
    1. Physical Component Score (PCS) of the SF-36
    2. Mental Component Score (MCS) of the SF-36
    3. Fatigue Severity Scale (FSS)
    4. Health Service Utilisation
- Make telephone contact with the participant at the start of the visit window to alert them to the follow up and confirm the method. Wherever possible complete follow up questionnaires at this call.

  Participants will be offered several ways in which to complete and return the follow up questionnaires:
    1. **Telephone call** - the participant can complete with the aid of a member of the trial team. *This is the preferred method.*
    2. **Postal** – questionnaires will be posted out to participants for completion and return in provided envelope.
    3. **Online** – can be answered directly onto the trial database via a link provided by the central research team.

For postal and online follow-up the research team should check whether this has been completed after 7 days and attempt to prompt completion whenever possible.

Follow up with the participant will occur within a 14 day window however, questionnaires may be returned outwith this window. Questionnaires returned after 14 days will not be classed as a deviation.

Five-year follow up will be completed via data linkage. This will only be undertaken if deemed worthwhile after the main trial analysis.

*At all follow ups, before contact is with the participant is attempted, survival status will be confirmed by the participating site using local health records/systems.

Table 1: Follow-up time points and measurements

Follow-up time point	**Measurements**	**Comments**
30 days post randomisation (7 prior or 14 days post visit date)[1] (surviving patients)	1. Physical Component Score (PCS) of the SF-36 2. Mental Component Score (MCS) of the SF-36 3. Fatigue Severity Scale (FSS) 4. New Infections (defined as any clinically suspected or proven infection occurring after randomisation requiring a new course of antibiotics) 5. Major Adverse Cardiac Events (MACE), comprising: any confirmed stroke, myocardial infarction, or cardiovascular death 6. Transfusion-related adverse events Haemoglobin concentration 1. CRP (in local hospital laboratory) 2. Blood samples for erythrogenesis and inflammatory markers (for patients providing permission for this and where feasible to collect) 3. Survival 4. Health service utilisation questionnaire	Follow-up can be undertaken in any clinic (eg post-ICU follow-up clinic; routine follow-up clinic) or In a clinical Research Facility or In the patients home or current residence or In a hospital ward Follow up undertaken by local investigator team
90 days post randomisation (±14 days)[1] (surviving patients)	1. Physical Component Score (PCS) of the SF-36 2. Mental Component Score (MCS) of the SF-36 3. Fatigue Severity Scale (FSS) 4. WHODAS ADLs questionnaire 5. New Infections (defined as any clinically suspected or proven infection occurring after randomisation requiring a new course of antibiotics) 6. Major Adverse Cardiac Events (MACE), comprising: any confirmed stroke, myocardial infarction, or cardiovascular death 7. Transfusion-related adverse events 8. Survival 9. Health service utilisation questionnaire	Follow up by postal questionnaire followed by telephone consultation if required Survival determined by local team consulting electronic health record Follow up undertaken by local investigator team

180 days post randomisation (±14 days)[1] (surviving patients)	1. Physical Component Score (PCS) of the SF-36 2. Mental Component Score (MCS) of the SF-36 3. Fatigue Severity Scale (FSS) 4. Survival 5. Health service utilisation questionnaire	Follow up by postal questionnaire followed by telephone consultation if required Survival determined by local team consulting electronic health record Follow up by local investigator team
5 years post randomisation[2]	1. Survival (via data linkage) 2. Health care resource and costs (via data linkage)	Five-year outcomes determined by data linkage without needing to contact patients.

[1] If follow up in person is not possible or feasible, or is declined by the patient, then research teams should make efforts to obtain questionnaire data either by postal questionnaire or via telephone.

[2] the decision to undertake data linkage will be determined based on the results of the main trial and any effects seen.

7 DATA COLLECTION

7.1 Definition of time periods

Baseline is the day of randomisation until 23:59 that calendar day.

Study day 1 is the first calendar day after baseline from 00:00 to 23:59. All subsequent study days will follow accordingly.

Study day period is 00:00 to 23:59.

For the purpose of baseline data collection, all data will be extracted from the patient record and apply to the time leading up to randomisation (see details below)

7.2 Baseline

The following data will be collected:

Demographics: age, sex

Pre-existing health status:

- recalled SF-36 (PCS and MCS) 30 days prior to hospitalisation. Attempt to complete as close to the time of enrolment as possible. For patients lacking capacity at enrolment, this measure can be deferred until patients regain capacity
- Functional Co-morbidity Index (FCI)
- Clinical Frailty Index prior to the onset of the acute illness that resulted in this hospitalisation
- ICU Mobility Scale (IMS) at the time of randomisation
- Baseline health service utilisation questionnaire

Acute illness characteristics:

- ICU admission diagnosis
- APACHE II score
- duration of mechanical ventilation
- duration of renal replacement therapy (if required)
- SOFA score from the 24hrs period prior to the participant being ready for ICU discharge.

Blood sampling:

1. Blood required for cross matching: These samples should follow normal local procedures and are not considered research samples. Only send this sample if not available clinically and required for transfusion.
2. Hospital Laboratory (using local sampling volumes and processes): haemoglobin concentration; reticulocyte count; C Reactive Protein (CRP). These results should be collected for all trial participants. Existing results from samples taken **<24hrs** prior to randomisation can be used. It is acceptable to use the screening haemoglobin as the baseline haemoglobin if from <24 hours prior to randomisation. Use local procedures to 'add on' tests to appropriate existing clinical samples where possible (for example reticulocyte

count and CRP). If not available, the samples should be taken as part of clinical care but if not possible they should be taken as additional research samples.

Refer to section 5.1.3 for guidance on baseline Hb results and study procedures.

3. Blood sampling for mechanistic sub-study (research blood samples): For participants providing consent to participate in the mechanistic sub-study, up to 5mLs of blood should be taken, processed, and stored for: IL-6 concentration, ferritin concentration, transferrin saturation, soluble transferrin receptor concentration, hepcidin concentration, erythroferrone concentration and other inflammatory markers. (Every effort should be made to obtain this research blood sample, but it is not compulsory for inclusion. If the participant is reluctant or refuses to provide a blood sample for the mechanistic study they can still be recruited to the trial).

   Refer to Sample Processing (Research Sample) document for processing instructions (see Appendix 3).

Where an appropriate clinical result is not available, all research blood samples including the mechanistic sub-study sample should be taken within **48 hours** of randomisation in the trial.

All research samples should be taken whenever possible **before any blood transfusion** has started, for example with the cross match sample or routine blood testing. In the event the transfusion is given prior to mechanistic blood sample collection, still collect the sample.

The research blood sampling including 5ml mechanistic sub-study will be up to a maximum of 20mls.

7.3 During intervention

- Haemoglobin concentration (all measurements with date and time) – Hb concentrations used can be a formal laboratory result, or where local practice is for clinical decisions to be made using the Hb concentration from a blood gas result this can be used in the trial. *Laboratory results are preferable.*
- red blood cell transfusions (date; number of units)
- new infections (defined as clinically suspected or proven infection treated with a course of antibiotics)
- any MACE (non-fatal stroke, non-fatal myocardial infarction, cardiovascular death); Definition of stroke and myocardial infarction is ‘confirmation by the clinical team that patient has experienced a stroke or myocardial infarction’
- transfusion related adverse events.

7.4 Follow-up at 30 days, 90 days, 180 days and 5 years

Measurements as per table 1

7.5 Source Data Documentation

Source data will be the medical record at each site or the study specific questionnaires and tests according to the data variable.

7.6 Case Report Forms

Case Report Forms (CRFs) will be provided to sites, reflecting the study specific database data requirements. Site staff can complete the paper CRF (pCRF) and then enter this data on to the secure study specific database via individual logins. Alternatively, site teams can decide to enter data directly onto the study database from the source. The site specific Source Data Plan(SDP) will identify the approach to be taken and what is considered source for relevant study data..

All case report forms will be reviewed and approved by the ACCORD Monitor prior to use (see ACCORD SOP CR013 CRF Design and Implementation).

7.7 Trial database

Edinburgh Clinical Trials Unit (ECTU) will provide and maintain a secure web based database compliant to Sponsor SOPs using the REDCAP system. Data will be entered by those staff delegated to do so on the delegation log held at site.

Routine data quality checks will be carried out by ECTU in accordance with their practice.

At the end of the trial, electronic data will be archived by ECTU.

8 DATA MANAGEMENT

8.1.1 Personal Data

The following personal data will be collected as part of the research:

Patients:

Name, CHI number or other unique numeric identifiers, date of birth

Personal data will be stored by the research team in a secure locked environment. Only approved delegated members of the local research team or wider study team will have access to personal data.

Personal data will be stored for 5 years after the end of the trial.

SWAT participants (research staff):

For the SWAT participants we will collect the minimum level of personal detail. All secure data will be stored in an encrypted study folder in DataStore (The University of Edinburgh's networked storage facility). DataStore is encrypted with Veracrypt and accessed via password protected desktops or encrypted laptop. Once the data collection is complete and transcripts checked, interview recordings will be deleted.

Interviews will be recorded on a recording device with 256-bit AES encryption or an equivalent algorithm. Also, the device will have a PIN or password lock to ensure restricted access.

8.1.2 Transfer of Data

Data collected or generated by the study (including personal data) will not be transferred to any external individuals or organisations outside of the Sponsoring organisation unless part of the trial.

Specifically, the analysis of blood samples for erythrogenesis markers will be undertaken in Oxford, and samples will be transferred for analysis (co-investigators Dr Noemi Roy, Dr Hal Drakesmith, Dr Simon Stanworth). Samples should be stored at sites as per the sampling SOP until arrangements are made to transfer them for analysis.

8.1.3 Data Controller

The University of Edinburgh and NHS Lothian are joint data controllers.

8.1.4 Data Breaches

Any data breaches will be reported to the University of Edinburgh and NHS Lothian Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

9 STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION

Based on our previous research[2 18] we estimated mean PCS SF-36 at 90 days will be significantly reduced at 35-40 (normal population average value 50), with standard deviation (SD) of 10-15 points. We defined a minimum clinically important difference as 5 points of the PCS element of the SF-36 at 90 days (smaller differences are of unlikely importance to patients)[41]. This represents an effect size of 0.42. Assuming the mean (SD) PCS will be 38 (SD 12) with restrictive (usual) care, to detect an improvement from RBC transfusion to a mean PCS of 43 at 90% power (two-sided P value 0.05) would require 244 patients.

In this population there is a risk of loss to follow-up (other than death), which in most previous trials has been between 10% and 30%. We originally proposed to inflate the sample size allowing for a 20% loss to follow-up at 90 days. This required a sample size of 305 (randomised 1:1 between the two groups). Adjusting for pre-specified baseline covariates is expected to further increase study power and/or protect against extra variability.

In May 2024, follow-up completion for the primary outcome was 75% despite active attempts to maximise this. As part of the strategy to ensure internal validity and adequate study power it was agreed to increase the sample size to ensure complete follow-up for at least 244 surviving patients. Rates of deaths during follow-up were

12/182 (7%). A conservative approach was agreed, assuming loss to follow-up might be as high as 30%. This required an inflation in sample size from 305 to 346 patients to ensure at least 90% power for a difference in the SF-36 PCS of 5 points.

9.2 PROPOSED ANALYSES

All details of the statistical approaches will be specified in a comprehensive Statistical Analysis Plan (SAP), authored by the study statistician and approved by the independent oversight committees (TSC and DMC).

General considerations: will use the Intention-To-Treat (ITT) principle for all outcomes, to estimate treatment effectiveness. However, safety data will be analysed according to treatment actually received instead of treatment allocated.

Principle analysis of PCS SF-36 score: The primary endpoint (change from baseline PCS SF-36 score) at 90 days post randomisation will be compared between randomised groups using a mixed effects linear model, with site as a random effect, and adjustment for any strongly prognostic baseline parameters (which may include age, comorbidity score, pre-ICU recalled HRQoL, length of ICU stay, ICU mobility scale, and baseline inflammation (assessed by CRP concentration)). The expectation is that around 20-30% of those randomised will have some missing data on the primary endpoint. We will address these missing data using an appropriate model for the missing data-generating mechanisms and conduct sensitivity type analyses to investigate the robustness of the findings to the assumptions behind this model.

In addition to the full ITT approach for the primary endpoint, (i.e. the real-world effect of the intervention amongst all those offered the intervention) we will also estimate the treatment efficacy (the idealised effect achieved by those fully compliant with their randomised treatment and all aspects of the protocol).

Moderation analyses of PCS SF-36 Score: We will conduct pre-specified moderation analyses on the primary endpoint. These moderation analyses will fit interaction terms for the baseline parameters and treatment group. There are 4 baseline potential moderators of interest – (a) Co-morbidity score (0-18; functional comorbidity index; a count of morbidities); (b) Recalled SF-36 score pre ICU admission; (c) ICU mobility scale (ordinal scale); and (d) Baseline level of systemic inflammation (CRP concentration; continuous measure ranging upwards from zero with normal values being <5mg/L). These analyses will explore how important these baseline parameters are in moderating how effective the intervention is for the main outcomes. We will first explore the nature of the potential interaction by fitting each baseline parameter as a continuous interaction with treatment, and if warranted, look at suitable categorisation (e.g. above vs. below the median) for ease of clinical interpretation.

Mediation analysis of PCS SF-36 score: We are also interested in understanding the mechanisms behind any treatment effect. To this end, in the main trial analysis we will conduct mediation analyses on the model described under "Principal analysis of PCS SF-36 score." The first mediation analysis will examine the role of haemoglobin concentration (anaemia severity) using blood measurements taken at baseline and 30 days post-randomisation, to determine whether this mediates the intervention's effect. Specifically, we want to assess whether the degree of anaemia correction at

30 days, according to group allocation, relates to the endpoint. The second mediation analysis will focus on systemic inflammation. Here, we will explore whether persistent inflammation mediates the impact of the number of blood transfusions on the endpoint. We will consider other potential mediators, and include these in the final SAP prior to locking the trial database.

We also plan to measure a range of biomarkers that may provide information about the mechanisms that the intervention influences the primary outcome, based on blood sampling at baseline and 30 days. These will include effects of the intervention on iron status, marrow erythrogenesis (red blood cell production), inflammation, and immune suppression. These exploratory analyses will be underpinned by a Directed Acyclic Graph (DAG) and pre-specified analysis plan.

Secondary outcomes: Secondary outcomes will be analysed using models appropriate for the type of outcome (e.g. for continuous outcomes as per the primary endpoint/principal analysis; mortality using a Cox proportional hazards model, binary outcomes with adjusted logistic regressions).

9.2.1 Health Economic Evaluation:

The cost-effectiveness of the intervention compared with 'usual care' will take the format of a within-trial cost-effectiveness analysis and use a cost-utility analysis framework. The primary health economic outcome measure will be the incremental cost per QALY at 180 days, and a further analysis will assess the cost per LYR at 180 days. In addition, the impact of the intervention on the downstream costs, health outcomes and cost effectiveness will we assessed over a 5-year time period (depending on the results of the shorter term trial main outcome analyses). The perspective for analysis will be that of the NHS budget holder, with a secondary analysis taking a wider societal perspective (e.g. including indirect costs in terms of the costs of lost productivity).

Estimation of health service costs will rely on a combination of scrutinisation of medical records by the research team, patient completed questionnaires and linkage to routinely collected administrative healthcare data (the decision on the latter approach will be determined based on the results of the main trial and any effects seen). This will include Hospital Episode Statistics (HES) in England and the Scottish Morbidity Record (SMR), Patient Level Costing and Information System (PLICS), the Prescribing Information System (PIS) and the Unscheduled care DataMart in Scotland to include, inpatient, outpatient, A&E, community prescribing and unscheduled care. This efficient strategy will limit missing data and accurately reflect real-world activity. Unit costs for all resources used will be obtained from routine published UK/national sources (e.g. NHS Reference Costs, the Personal Social Services Research Unit).

Assessment of quality of life (health-related utility) for the estimation of QALYs will rely on the SF-6D derived from the SF36. Longitudinal utility will be adjusted for baseline values.

To summarise the analysis will present the Incremental Cost-effectiveness Ratio (ICER), the Scatterplot on the Cost-effectiveness Plane and the Cost-effectiveness Acceptability Curve (to show the probability that the intervention is cost-effective for different values of willingness to pay per additional QALY). Moderation analysis will

reflect the main statistical analysis and multivariable analysis of cost outcomes will rely on generalised linear models. Uncertainty will be estimated using non-parametric bootstrapping (for calculating the confidence intervals around cost per QALY ratios, using bootstrapped estimates of the mean cost and QALY differences). Missing data will be handled as considered most appropriate at the time of analysis, likely using multiple imputation.

10 ADVERSE EVENTS

Adverse Event (AE) and Serious Adverse Event (SAE) reporting will follow the ACCORD SOP for non-CTIMP trials (CR006).

Transfusion Related Adverse Events or Reactions and Serious Transfusion Related Adverse Reactions will be recorded in accordance with the definitions of SHOT (Serious Hazards of Transfusion), revised December 2019. Imputability of any transfusion related AE, AR or SAE will also be assessed according to the definitions given within the SHOT guidance (see Appendix 1)

https://www.shotuk.org/wp-content/uploads/myimages/SHOT-Definitions-update-10.01.20-FINAL.pdf

10.1 Definitions

10.1.1 Adverse Event (AE)

Any untoward medical occurrence in a study participant, which does not necessarily have a causal relationship with the study intervention.

10.1.2 Adverse Reaction (AR)

Any untoward and unintended response that has occurred due to the intervention.

10.1.3 Transfusion Related Adverse Reaction (AR) or Event

Any untoward and unintended response to a transfused blood component.

10.1.4 Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Serious Transfusion Related Adverse Reaction

Any AE or AR or Adverse Transfusion Reaction or unexpected adverse transfusion reaction that:

- results in death of the study participant
- is life-threatening*
- requires inpatient hospitalisation^ or prolongation of existing inpatient
- hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect
- results in any other significant medical event not meeting the criteria above

* Life-threatening in the definition of an SAE or SAR refers to an event where the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

10.2 Identifying and Recording AEs and SAEs

10.2.1 AEs and SAEs that do not require reporting

Patients included in the trial will have recently experienced life-threatening illness complicated by multiple events and complications that fulfil the definition of AEs and SAEs. For many patients the risk of further complications and events continues into the post-ICU recovery period. These include, but are not restricted to, events such as new infections, worsening of the original condition causing critical illness, worsening organ failure, critical care readmission, and cardiorespiratory complications.

The judgement of the local research team and PI will determine which events should be reported as AEs and SAEs based on clinical judgement for each event.

The following complications are being collected within the trial, and do not require reporting unless the local research team consider this appropriate:

- Major Adverse Cardiovascular Events (MACE)
- Transfusion Related Adverse Reactions
- Infections
- Death

10.2.1.1 Assessment of Transfusion Reactions

As mentioned above, transfusion related reactions will be assessed in accordance with the definitions and imputability as set out by SHOT, but will also be recorded as an AE on the trial database. All Serious Transfusion Related Adverse Reactions will be recorded as part of the trial data collection process.

10.2.2 Duration of AE and SAE reporting

AE and SAE reporting will start from the time of randomisation in the trial. *AEs and SAEs will only be reported during the intervention period*, namely from enrolment until the time of hospital discharge. Important events that might constitute AEs and SAEs that may plausibly be associated with the intervention are being recorded as part of trial data collection during 180 days follow-up after hospital discharge.

10.2.3 Reporting and follow up of AEs and SAEs

AE and SAE data will be recorded by the Investigator(s) (or a member of the research team with delegated responsibility to do so) on the Case Report Forms (CRF) and/or SAE report form. Investigators will record all AEs in the AE log in a timely fashion (usually at the time of detection). AEs and SAEs will be followed up until outcome of recovered, recovered with sequelae or death of the study participant.

10.3 Assessment of AEs

Each AE must be assessed for seriousness, causality, severity and expectedness by the Principal Investigator (PI) or another suitably qualified physician in the research team who is trained in recording and reporting AEs and who has been delegated this role. During PI absences appropriately qualified, experienced and trained site staff may assess causality and report SAEs if they have been delegated this responsibility on the delegation log by the PI.

10.3.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness (as defined in section 10.1).

10.3.2 Assessment of Causality

The Investigator will make an assessment of whether the AE is likely to be related to the study intervention according to the following definitions:

- Unrelated: where an event is not considered to have occurred as a result of the study intervention.
- Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study intervention.

Where there are two assessments of causality (e.g. between PI and Chief Investigator (CI)), the causality assessment by the Investigator cannot be downgraded. In the case of a difference of opinion, both assessments are recorded and the 'worst case' assessment is used for reporting purposes.

10.3.3 Assessment of Expectedness

If the AE is judged to be related to the study intervention, the Investigator will make an assessment of expectedness.

- Expected: The type of event is expected in line with the study intervention.
- Unexpected: The type of event was not listed in the protocol or related documents/literature as an expected occurrence.

10.3.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE and this should be recorded on the CRF or SAE form according to the following categories:

- Mild: an event that is easily tolerated by the study participant, causing minimal discomfort and not interfering with every day activities.
- Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.
- Severe*: an event that prevents normal everyday activities.

*The term 'severe' used to describe the intensity of an event should not be confused with the term 'serious', as defined in section 10.1, which is a regulatory definition based on study participant/event outcome action criteria. For example, a headache may be severe but not serious, while a minor stroke may be serious but is not severe.

10.4 Reporting SAEs to the Sponsor (ACCORD)

Any AE that is assessed as an SAE is subject to expedited reporting requirements to the Sponsor. The SAEs described in 10.2.1 do not require expedited reporting to the sponsor

The Investigator is responsible for reporting SAEs to ACCORD within 24 hours of becoming aware of the event.

SAE reports will either be emailed as a .pdf file to Safety@ACCORD.scot; or delivered in person using the Serious Adverse Event Report Form. SAE reports will be complete as far as possible and will be signed and dated by the Investigator. The SAE does not require to maintain blinding as this is an unblinded trial. The Research Governance Coordinator, or designee, will complete and return the Cover Sheet and Return Receipt or send an email to confirm receipt of the SAE report within 1 working day. If this email/fax is not received within 1 working day of sending the report to ACCORD, the Investigator must telephone ACCORD on +44 (0)131 242 3330 to check that the report has been received by ACCORD.

All copies of SAE reports emailed or faxed to ACCORD and any follow-up information and correspondence will be kept by the Investigator in the Investigator Site File (ISF) and by the Sponsor in the Sponsor File or Trial Master File (TMF).

ACCORD will report SAEs, as required, to the Chief Investigator/Trial Manager within agreed timelines.

11 SUB-STUDY TO EXPLORE REASONS THAT PATIENTS DECLINE CONSENT TO PARTICIPATE (STUDY WITHIN A TRIAL (SWAT))

11.1 Context

The optimum methodology for post-ICU intervention trials such as ABC is uncertain, but enrolment and inclusion bias are a concern given the wide variation in patient demographics, critical illness aetiology, and critical illness type/severity/duration. In previous trials, rates of consent among patients approached have been relatively low at around 30-50%. This seems surprising given the trials are generally framed

around comparing usual care to an intervention designed to test a hypothesis for improved recovery.

The reasons for low agreement to participate from a patient and participant perspective have not been explored in a UK setting. It is likely that there are various decision-making processes involved when patients are approached to participate in a post-ICU intervention trial such as this. These may relate to the organisation, for example, resource allocation and the provision of trial-related documentation. The chain of determining eligibility, inviting patients to participate, and gaining consent may also be influenced by participant-related factors. These may include staff and patients' attitudes towards the study, professional role and style, and the perceived and actual health status of the patient. Considerations of equality, diversity, and inclusion (EDI) are also important, to ensure that all people can potentially take part in research. Ensuring EDI are maximised will also increase the generalisability and relevance of the research. Understanding these issues in more detail is important for future research into ICU recovery, to avoid inclusion bias, and ensure patients with a wide range of socio-economic, health, and other characteristics are included.

11.2 Research Questions

Our overarching research question is: *'Among patients who are screened as being eligible for the trial and are approached for consent by the research team, what are the reasons that patients decline participation?'*

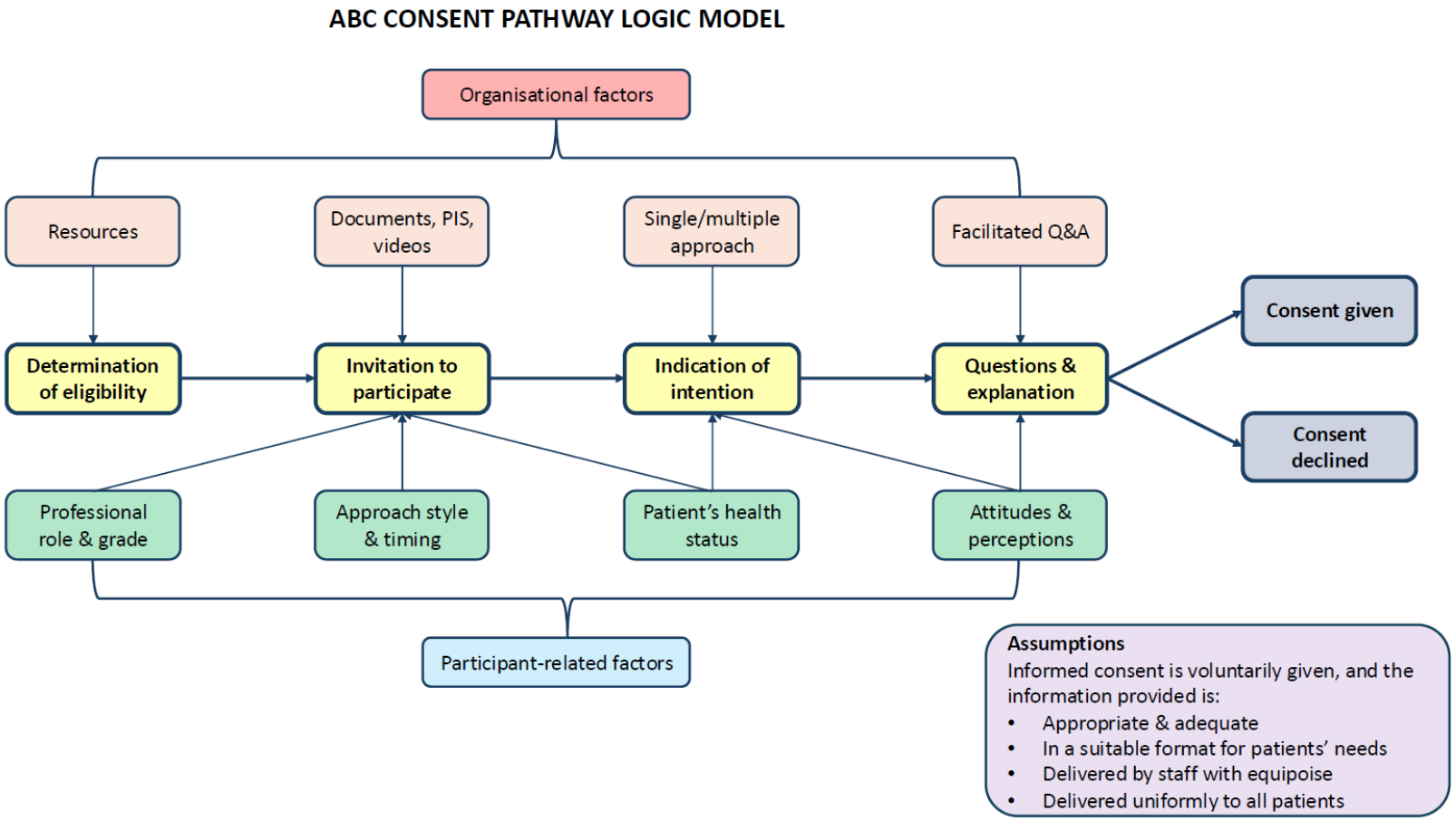
We will aim to answer the following specific research questions:

1. What are the reasons that eligible patients are not approached for consent to the trial?
2. What are organisational factors that contribute to declining participation in the trial (e.g. local resources, professional role/grade of person seeking consent, experience of researcher)?
3. What are the patient/participant related factors that contribute to declining participation in the trial (e.g., demographic, ICU illness type or severity, cognitive status/capacity, fatigue)?
4. How does the information provided (written, visual, verbal) impact on the consent process?
5. Are there other contextual factors that impact on the consent process (e.g., family involvement, timing of approach during recruitment window, parent clinical teams, local research culture/practices)?

11.3 Logic Model

A proposed logic model underpinning the reasons that eligible patients may not consent to participate in the trial is shown in figure 2. This model will underpin the proposed surveys, interviews, and focus groups and will be modified according to emerging data.

Figure 2: Preliminary logic model for reasons that eligible patients do not participate in the ABC post-ICU trial



11.4 Methodology

This mixed methods SWAT will comprise 5 parts:

1. PPI focus groups will be conducted with a group of previous ICU patients and their relatives to seek their views on why people may decline participation at this period of their recovery. These will seek to include people representing relevant issues and characteristics highlighted in the NIHR EDI toolkit. This work will be conducted with the Lothian critical care PPI volunteer group, and may inform the survey design and interview guides. No patients participating in the trial will be involved in these focus groups.
2. Recruitment data from screening logs will be summarised to aid purposive sampling of sites for part 3 and ensure a maximum variation sample.
3. A survey will be developed on the REDCap platform, that will ask research staff to rate the importance of different factors based on their experience of approaching patients in the trial. This will be developed by the research team. This will involve as many research staff as possible across all participating sites (approximately 30-40 individuals).
4. Up to 15 semi-structured interviews will be conducted at a purposive sample of sites with research staff who have been approaching patients for consent in the trial, across the participating ICUs. Additional interviews will be considered if data saturation is not achieved. We will use the 'logic model' (a simple visual plan showing resources and activities involved in the consent process) to hypothesise all the possible reasons people may decline to participate. The logic model will be used to guide the interviews which will explore the key reasons people seem to decline. This will include consideration of the aspects of inclusion highlighted in the NIHR Equality, Diversity and Inclusion Toolkit (EDI Toolkit (rssleicesterresources.org.uk)
5. We will summarise the baseline characteristics of patients who agreed to participate in the trial, and seek published or otherwise available comparator populations of anaemic ICU survivors to explore whether these are representative of all ICU patients, or whether important differences exist.

The demographics, job role and experience of participants will be recorded, together with information about their involvement in the ABC Post ICU trial (duration, patients approached and recruited etc). The PPI group discussions will be captured using note-taking and examining materials produced such as charts and 'post-it' notes (part 1, above). The semi-structured interviews with research staff (part 4, above) will be audio-recorded and transcribed verbatim. Interviews will be digitally recorded using an approved device, and transcribed verbatim by an approved transcribing service for the University of Edinburgh. Audio files will be saved within the secure project folder prior to being downloaded for transcription. Once the transcript is checked, the audio file will be deleted. The interview transcripts will then be analysed using an inductive framework analysis approach. This approach is ideal for analysing text and leaves a clear audit trail from the raw data to the final themes (including illustrative quotes). The framework method is the most suitable approach for this analysis as the aim is to use the data to explore participants' experiences and describe and interpret what happens in a particular setting systematically and transparently. The findings from all 5 parts will then be integrated to summarise and explain the main reasons and issues that mean ICU survivors declined to participate in the trial. A specific

focus of interest will be factors that are specific to this trial versus factors that may be more generic in relation to participation in ICU recovery trials.

11.5 Outputs

The results of the sub-study will be reported separately in presentations and a publication.

12 OVERSIGHT ARRANGEMENTS

12.1 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

12.2 STUDY MONITORING AND AUDIT

The ACCORD Sponsor Representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and, if so, at what frequency.

Risk assessment, if required, will determine if audit by the ACCORD QA group is required. Should audit be required, details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

12.3 PUBLIC ENGAGEMENT

A patient Personal and Public Involvement (PPI) representative will act as co-investigator throughout the trial to ensure the views and opinions of service users, carers and the public are represented. In addition, a wider PPI group will be consulted on the protocol prior to submission for ethical approval, and specifically will be asked to review patient and patient-representative materials including the Patient (or representative) Information Leaflet and consent forms.

The views of PPI representatives will be sought during interpretation of the study results as appropriate.

12.4 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Project Management Group, consisting of selected grant holders, a trial manager and trial nurse.

The Trial Manager will oversee the study and will be accountable to the Chief Investigator. The Trial Manager will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

12.5 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial and advise the investigators as required. The TSC will include an independent Chair, at least one independent clinician, at least one independent methodologist, and at least one independent PPI representative. The terms of reference of the Trial Steering Committee, the draft template for reporting, and the names and contact details are detailed in CR015 DMC & TSC Charters.

12.6 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the trial. The DMC will comprise three individuals, and include at least one statistician and one clinical content expert. The terms of reference of the Data Monitoring Committee and the names and contact details are detailed in CR0015 DMC & TSC Charters.

The DMC Charter will be signed by the appropriate individuals prior to the trial commencing.

13 GOOD CLINICAL PRACTICE

13.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

13.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

13.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

The investigator is responsible for ensuring that the procedures set out in section 5.2 are followed.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral

explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s).

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes.

13.2.2 Study Site Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

13.2.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

13.2.4 Investigator Documentation

The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs.

13.2.5 GCP Training

For non-CTIMP (i.e. non-drug) studies all researchers are encouraged to undertake GCP training in order to understand the principles of GCP. However, this is not a mandatory requirement unless deemed so by the sponsor. GCP training status for all investigators should be indicated in their respective CVs.

13.2.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study.. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

13.2.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) with regard to the collection, storage, processing and disclosure of personal information.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data and be of a form where individuals are not identified and re-identification is not likely to take place.

STUDY CONDUCT RESPONSIBILITIES

13.3 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

13.4 MANAGEMENT OF PROTOCOL NON COMPLIANCE

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, and local R&D for review and approval if appropriate.

13.4.1 Protocol deviations and violations

13.4.1.1 Definitions

A protocol **deviation** is any change, divergence, or departure from the study design, procedures defined in the protocol or GCP that does not significantly affect a subject's rights, safety, or well-being, or study outcomes.

A protocol **violation** is a deviation that may potentially significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

For the purpose of the trial, any non-compliance with the allocated RBC transfusion intervention, such as failure to transfuse in response to a trigger Hb and/or administering transfusion when the Hb concentration does not indicate transfusion, should be reported as a protocol deviation. See also section 6.1.3.

The following should be reported as deviations in the trial:

- Failure to re-check Hb concentration within 48 hours of a transfusion
- Failure to administer a blood transfusion within 48 hours of the stated trigger in the allocated group (<70g/L or <100g/L)

- In the usual care group, administration of a blood transfusion at a trigger Hb ≥70g/L without the responsible clinician providing a reason for modifying the transfusion trigger.

13.4.1.2 Patients randomised in error

Any patient who is randomised in error because they did not meet inclusion criteria and/or had an exclusion criterion will be reported as a protocol violation. If this is recognised within 24 hours of randomisation they should be withdrawn from the trial. These patients should be reported as a protocol violation. Patients withdrawn for this reason will not be included in the analysis, but will be accounted for in the trial CONSORT diagram.

If a patient is randomised in error and more than 24 hours has passed before this is recognised, they should remain in the trial and receive the allocated treatment as per protocol. These patients will be included in the analysis. However, a violation report should be submitted to ACCORD.

13.4.1.3 Recording and reporting protocol deviations and violations

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 2 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to QA@accord.scot

13.5 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (seriousbreach@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

13.6 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 3 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

13.7 END OF STUDY

The end of study is defined as the last participant's last visit.

The Investigators or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R+D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the

appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot

A summary report of the study will be provided to the REC within 1 year of the end of the study.

13.8 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

14 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

Ownership of the data arising from this study will reside with the study team.

14.1 Reporting and publication

Results of the trial will be posted on the registered clinical trial website. The trial Chief Investigator and co-investigators will oversee decisions around presentation of results to scientific and clinical meetings, public/press releases, and social media notifications. The trial data will be published in peer-reviewed journals. The decisions surrounding publication will be made by the Chief Investigator and co-investigator.

14.2 Data Sharing

Consent will be sought from participants to permit sharing of anonymised data with funders and collaborators or published on publically available resources as appropriate.

Co-investigators will have the right to access the final data set for the purpose of additional analyses that are consistent with the consent provided by participants.

Following publication of the primary paper, a de-identified individual participant data set will be submitted to a data archive for sharing purposes. Access to this data set will be under a controlled access model in line with ECTU policies at that time.

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APPENDIX 1 – Expected Transfusion Reactions as defined by SHOT

CATEGORY	TERM	
ADVERSE REACTIONS	IBCT–WCT	*Incorrect blood component transfused – Wrong Component Transfused*
	IBCT-SRNM	*Incorrect blood component transfused – Specific Requirements Not Met*
	ADU	*Avoidable transfusion, Delayed transfusion or Under- or Over-transfusion*
	HSE	*Handling and storage errors*
	RBRP	*Right blood Right Patient*
	Near Miss	
SERIOUS ADVERSE REACTIONS	FAHR	*Febrile, allergic and hypotensive reactions (formerly known as acute transfusion reactions)*
	HTR Acute	*Haemolytic Transfusion Reaction*
	HTR Delayed	
	PTP	*Post-transfusion purpura*
	TA-GvHD	*Transfusion Associated graft versus host disease*
	TACO	*Transfusion associated circulatory overload*
	TAD	*Transfusion associated dyspnoea*
	TRALI	*Transfusion related acute lung injury*
	TTI	*Transfusion transmitted infection*
OTHER REPORTING CATEGORIES	Anti-D	
	Cell Salvage	

Full definitions of terms can be found at:

https://www.shotuk.org/wp-content/uploads/myimages/SHOT-Definitions-update-10.01.20-FINAL.pdf

APPENDIX 2 - SHOT definition of Imputability

IMPUTABILITY		
N/A	Not assessable	When there is insufficient data for imputability assessment.
0	Excluded or Unlikely	When there is conclusive evidence beyond reasonable doubt for attributing the adverse reaction to causes other than the blood or blood components or where the evidence is clearly in favour of alternative causes.
1	Possible	When the evidence is indeterminate for attributing the adverse reaction either to the blood or blood component or where there may be alternative causes.
2	Likely/Probable	When the evidence is clearly in favour of attributing the adverse reaction to the blood or blood component.
3	Certain	When there is conclusive evidence beyond reasonable doubt.

Taken from:

https://www.shotuk.org/wp-content/uploads/myimages/SHOT-Definitions-update-10.01.20-FINAL.pdf

APPENDIX 3 – Sample Processing

SAMPLING PROCESSING – RESEARCH SAMPLE (Baseline and 30 days)

BLOOD TUBE	SAMPLING INSTRUCTIONS	CENTRIFUGE	ALIQUOTING	STORAGE
Serum Tube (for example – **Vacutainer SST II** (gold top) tube **Approx. 4ml tube** (3ml - 5ml)	• **Collect sample** Ideally, take baseline sample in the morning. Where baseline sample **not** collected in the morning, aim to take the 30 day sample at approximately **the same time of day as baseline was collected**. • **Allow sample to sit for 30 mins at room temperature** (for samples collected in the community processing **must be undertaken within 2 hours** of sample collection). *Hepcidin adheres to laboratory plastics at room temperature, lowering the level is left out too long.*	**1300G** **Room Temperature** **10mins**	Collect all available serum 5x 200µl aliquots & the remainder as one big aliquot	**Transfer aliquots to -80°C** (they can be stored short term at -20°C for up to 4 weeks) • Samples should be transferred to freezer immediately following processing. • If this is not possible samples can be stored at 4°C for up to a **maximum of 30 mins** (only if absolutely necessary)

It is also worth noting that ingestion of iron will cause a transient significant increase in hepcidin. If oral iron supplements taken by patient then this should be noted. ***Ideally, patients should not take an iron supplement on the day of giving a research sample at baseline and day 30, prior to the blood sample being taken.***

Minimise freeze-thaw cycles – for transfer of samples, dry ice should be used when couriered.