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INtravenous Iron to Treat Anaemia following CriTical care (INTACT): A protocol for a feasibility randomised controlled trial

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Trial registration: ISRCTN13721808 – Prospectively registered on 17 July 2018

ABSTRACT

Background: Anaemia is common in patients who survive critical illness and is associated with high levels of fatigue and poor quality of life. In non-critically ill patients, treating anaemia with intravenous iron has resulted in meaningful improvements in quality of life, but uncertainties regarding the benefits, risks, timing and optimal route of iron therapy in survivors of critical illness remain.

Methods / Design: INtravenous Iron to Treat Anaemia following CriTical care (INTACT) is an open-label, feasibility, parallel group, randomised controlled trial (RCT) with 1:1 randomisation to either intravenous iron (1000mg ferric carboxymaltose) or usual medical care. The primary objective is to assess the feasibility of a future, multicentre RCT. Participants will be followed up for up to 90 days post-randomisation. The primary outcome measures, which will be used to determine feasibility, are recruitment and randomisation rates, protocol adherence and completeness of follow-up. Secondary outcome measures include collecting clinical, laboratory, health-related quality of life and safety data to inform the power calculations of a future definitive trial.

Conclusion: Improving recovery from critical illness is a recognised research priority. Whether or not correcting anaemia, with intravenous iron, improves health-related quality of life and recovery requires further investigation. If so, it has the potential to become a rapidly translatable intervention. Prior to embarking on a phase III multicentre trial, a carefully designed and implemented feasibility trial is essential.

Key words: Anaemia; Intravenous Iron; Intensive Care; Clinical Trial; Quality of life

INTRODUCTION

Background

Anaemia is a very common problem in intensive care units (ICUs) affecting 60-80% of patients and is associated with adverse outcomes.^{1,2} Anaemia persists until hospital discharge and in some studies up to 6 months following ICU discharge, and is associated with fatigue and poor health-related quality of life (HRQoL).³⁻⁵

Iron-restricted erythropoiesis resulting from anaemia of inflammation is extremely common in ICU patients and may occur through absolute iron deficiency, functional iron deficiency or iron sequestration. Dysregulated iron homeostasis is associated with adverse outcomes in ICU patients.⁶ Our understanding of iron homeostasis has been improved by the discovery of hepcidin – the master regulator of body iron status. Hepcidin is a small peptide produced by the liver and acts by inhibiting the function of ferroportin, the sole cellular exporter of iron. Hepcidin blocks duodenal iron absorption and results in iron trapping within macrophages and hepatocytes subsequently decreasing the availability of iron for erythropoiesis.⁷ Current markers of iron status (e.g. ferritin, transferrin saturation) have limited utility in critically ill patients as the relationship between these markers and iron status is heavily confounded by inflammation. Hepcidin may be a better marker of iron status in critically ill patients, even in the presence of inflammation,^{8,9} and recent work supports the hypothesis that critically ill patients have potentially iron-responsive anaemia which may not be detectable with currently available tests. One study suggested that 35% of ICU survivors developed evidence of iron deficiency six months after ICU stay.⁴

In other contexts, intravenous (IV) iron therapy has been shown to be effective in treating anaemia with subsequent improvements in quality of life.¹⁰⁻¹³ IV iron is able to bypass hepcidin-induced restriction of iron.¹⁴ Despite this, safety concerns regarding the risk of infection caused intravenous iron infusion remain. Iron is essential for bacterial growth and exogenous iron administration has been shown to worsen shock and lung injury in canine experimental models of pneumonia.¹⁵ RCTs have not always included infection as a pre-defined end point and therefore the risk in critically ill patients remains uncertain.^{12, 16, 17}

Rationale for a trial

ICU survivors experience poor HRQoL, reduced physical function and fatigue.¹⁸⁻²⁰ Improving recovery from critical illness has been identified as a key research priority by the NIHR critical care portfolio and the James Lind Alliance. Evidence from observational studies suggests that untreated anaemia may, in part, be contributing to these symptoms.

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3 Attempts to treat anaemia during acute critical illness have so far been unsuccessful. RCTs of
4 iron supplementation in ICU patients have failed to demonstrate any evidence of benefit.^{17, 21} This
5 could partly be explained by limitations in trial design as studies were underpowered and there was
6 wide variation in patient populations and iron administration regimes.¹⁷ Biological reasons to explain
7 this lack of benefit could be due a hyporeactive bone marrow, secondary to the acute inflammatory
8 response, that may not respond to exogenous iron administration. The peak effect of iron may also
9 not be observed until 2-3 weeks after administration.^{14, 17 22, 23} This suggests that any relative risks
10 and benefits of iron probably depend on the timing of administration.
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15 We hypothesise that treating anaemia when patients are recovering from critical illness,
16 when the iron and erythropoietic profiles are more favourable, may be a more suitable time point
17 for intervention, than during the acute phase of critical illness. A large, multicentre RCT is needed to
18 answer this question but there are uncertainties regarding recruitment and follow-up rates,
19 variability in haemoglobin concentrations in the post-ICU period and choice of optimal outcome
20 measures.¹⁸ We have therefore designed the INTACT feasibility RCT, with the primary aim of
21 assessing recruitment, randomisation and follow-up rates to inform the design of a future
22 adequately powered multicentre trial.
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31 **Objectives**

32 *Primary objective*

33 To assess the feasibility of a future large multicentre RCT of intravenous iron to treat anaemia in
34 patients recovering from critical illness in intensive care.
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40 *Secondary objective*

41 To collect clinical, laboratory and health-related quality of life data to inform the power calculations
42 and health economic evaluations of any future definitive trial.
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47 **Trial design**

48 INTACT is an open-label, feasibility, parallel group, randomised controlled trial with 1:1
49 randomisation to either intervention or usual medical care. The trial is being co-ordinated by the
50 Oxford Clinical Trials Research Unit (OCTRU) and sponsored by the University of Oxford. The funding
51 is provided by the National Institute for Health Research (NIHR) as part of a Doctoral Research
52 Fellowship (DRF-2017-10-094). The trial is being conducted in accordance with the principles of the
53 Declaration of Helsinki and Good Clinical Practice.
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METHODS

Participants, interventions and outcomes

Study setting

This feasibility RCT is being undertaken in three general adult UK ICUs (John Radcliffe Hospital, Oxford; Edinburgh Royal Infirmary, Edinburgh; Royal Berkshire Hospital, Reading) which have a proven track record in ICU research.

Eligibility criteria

Written, informed consent is obtained from participants prior to any study procedures taking place.

Patients eligible for the study must comply with all of the following before randomisation:

- Requirement for ICU (Level 2 or 3 support) for ≥ 24 hours and now deemed medically stable for discharge from ICU by the attending physician
- Last measured laboratory Hb ≤ 100 g.l⁻¹

Patients are excluded if they meet any of the following criteria:

- Planned palliative care
- Planned home ventilation
- Primary neurological diagnosis with little/no rehabilitation potential
- Known hypersensitivity to iron
- Immunosuppressive therapy for organ transplant
- IV iron or erythropoietin treatment in the previous 4 weeks
- Pregnancy (breastfeeding is not an exclusion criterion)
- Personal or family history of iron overload disorders such as haemochromatosis or previously documented ferritin >1200 ng.ml⁻¹ and/or transferrin saturation $>50\%$
- History of severe asthma, eczema or atopic allergy
- Known severe chronic liver disease (e.g. Child-Pugh C or above)
- Haemodialysis dependent chronic kidney disease
- Acute uncontrolled infection – as judged by the treating clinician (e.g. ongoing bacteraemia or non-resolving sepsis) or patient expected to be on non-prophylactic antibiotics for greater than 14 days.

The inclusion and exclusion criteria are designed to include participants who reflect a general population of survivors of critical illness with moderate to severe anaemia, who may benefit from

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3 the intervention, and exclude patients who are unlikely to benefit or at increased risk of adverse
4 events from IV iron.
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8 ***Intervention***

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10 In the intervention arm, 1000mg of ferric carboxymaltose is diluted in 100 ml of 0.9% saline and
11 administered as an IV infusion over a minimum of 15 minutes. The dosing of ferric carboxymaltose is
12 based on the maximum dose that can safely be given according the Summary of Product
13 Characteristics (SmPC) within a reasonable time period. Participants are closely monitored for signs
14 of hypersensitivity during the infusion and for at least 30 minutes after the treatment. The
15 intervention can be administered at any time between ICU and hospital discharge. For participants
16 who weigh less than 50 kg, the dose would be adjusted to 20 mg.kg⁻¹.
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23 ***Usual medical care***

24 Usual medical care consists of routine ward based care including observation with monitoring and
25 transfusion when required. Current guidelines advocate adopting a restrictive transfusion policy,
26 with the exception of certain groups of patients such as those with ischaemic heart disease.²⁴ It is
27 not routine practice to administer IV iron in patients recovering from critical illness at present. Any
28 decision to commence iron therapy in this group would be at the discretion of the treating physician
29 and independent of the study and would be recorded in the Case Report Forms (CRFs).
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37 ***Participant timeline***

38 This is highlighted in Figure 1.
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42 ***Outcome measures***

43 *Primary outcome measures:*

- 44 • Recruitment and randomisation rates overall and by centre
- 45 • Protocol adherence, defined as 'number of participants allocated to the intervention who go
46 on to the receive the study drug'
- 47 • Completion rates of HRQoL questionnaires

48 *Secondary outcome measures:*

- 49 • Nosocomial infection
 - 50 • Mortality
 - 51 • Hospital length of stay
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- Changes in laboratory haematological (e.g. Hb) and iron profiles (e.g. ferritin) from baseline to 28 and 90 days post-randomisation
- Changes in Multidimensional Fatigue Inventory-20 (MFI-20), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and EuroQol-5D-5L (EQ-5D-5L) questionnaire scores from baseline to 28 and 90 days post-randomisation
- Healthcare resource use.

Sample size

As this is a feasibility study not aiming to assess treatment effects, we have not undertaken a formal power calculation. At the John Radcliffe Hospital (which will be the main recruitment centre for this trial) approximately 800 patients are admitted to the ICU each year. Of these 120 patients are elective post-operative admissions who would be expected to stay less than 48 hours and of the remaining 680 patients, assuming unit mortality of 14%, 584 would be expected to survive ICU. Based on pre-trial work and previous studies, 50% (292 patients) would leave ICU with a Hb of ≤ 100 g.l⁻¹.²⁵ Assuming 30-40% enrolment, we expect to enrol on average 100 participants per year (approximately 2 participants per week) at this site. From the three sites it is anticipated that 130 patients will be recruited over a 12month recruitment period.

Assignment of interventions

Randomisation

Eligible participants are randomised on a 1:1 ratio to receive either the intervention or usual medical care using minimisation on a secure web-based system controlled and managed by the Oxford Clinical Trials Research Unit (OCTRU), stratified on anaemia severity (Hb < 80 g.l⁻¹ versus 80-100 g.l⁻¹) and participant ICU length of stay (< 7 days versus ≥ 7 days).

Blinding

We have opted not to use a placebo study drug. This is because ferric carboxymaltose is a challenging substance to blind due to its rusty brown colour.

Data collection, management and analysis

Data collection

Data are collected using paper CRFs and then transferred to a validated electronic data entry system. Clinical data is collected at baseline (pre-randomisation) and hospital discharge. Laboratory and HRQoL data is collected at baseline, and 28 and 90-days post-randomisation. This is outlined in the

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3 study schematic in Figure 2 and detailed in Table 1. Laboratory data will include serial measurements
4 of hepcidin throughout the study period.
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6 The EQ-5D-5L is a generic preference-based measure of health that is recommended by NICE
7 for economic valuations. The MFI-20 is a 20-item self-reporting score designed and validated to
8 measure fatigue across 5 domains – general fatigue, physical fatigue, mental fatigue, reduced
9 motivation and reduced activity.²⁶ Scores can range from 4 to 20, with higher values indicative of
10 increased fatigue levels. Its use in ICU survivors has been described previously.⁴ The FACIT-F is a
11 subscale of a questionnaire developed to assess anaemia-related symptoms in patients with
12 cancer.²⁷ It consists of 13 items referring to the previous seven days. The final scores range from 0-52
13 with higher scores representing less fatigue. It has been validated to assess fatigue in ICU survivors.²⁸
14 Approximately 15-20 minutes will be required to complete all three questionnaires. Participants may
15 ask for help completing the questionnaires from relatives, bedside nurses or a member of the
16 research team. This is felt to be reasonable as problems with concentration and attention are not
17 uncommon in critically ill patients.
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28 **Retention**

29 Participation retention in ICU trials is challenging.^{28, 29, 30} To minimise loss to follow-up we will invite
30 participants to our weekly ICU follow-up clinic with full reimbursement of travel costs. If participants
31 are unable to attend, a member of the research team will undertake a home visit with appropriate
32 safe guards in place. Telephone follow-up is offered for participants who live outside a reasonable
33 geographic follow-up area to collect HRQoL data.
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40 **Data management**

41 A Data Management Plan has been produced for the study which includes references to
42 confidentiality, access and security arrangements and is available on request from the INTACT study
43 office. In brief, staff at participating centres collect data on paper CRFs, which is then be entered into
44 a password-protected online database (OpenClinica®), located on a secure University server. The
45 database has validation on data fields. Paper CRFs are stored in the Investigator Site File under
46 secure conditions. Paper copies of the consent forms will also be logged into the trial database and
47 then scanned and stored electronically in the e-Trial Master File.
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55 **Statistical analysis**

56 Results will be reported in accordance with the Consolidated Standards of Reporting Trials
57 (CONSORT) extension to randomised pilot and feasibility trials.³¹ Recruitment and follow-up rates
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3 are the main drivers for the feasibility design on the basis that unless reasonable rates can be
4 achieved no formal trial will be possible. Recruitment rate will be calculated by the number of
5 participants randomised as a proportion of total number of eligible participants. Rates will be
6 estimated based on data collected and a 95% confidence interval determined for these measures.
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10 If the estimated recruitment and follow-up rates are such that a multicentre definitive trial is
11 possible, then no formal analysis will be undertaken and data from the feasibility study will be
12 locked and carried over into the definitive trial. No formal analysis of treatment efficacy will be
13 undertaken in this case.
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16 Statistical power calculations for the definitive trial will be reviewed based on blinded data
17 collected in this feasibility trial. A 'traffic light' system shown in Table 2 will be used as a guide for
18 progression to a definitive trial.³¹ If the definitive trial is not feasible, or funding for the definitive
19 trial cannot be obtained, data analysis will be undertaken and reported in the conventional manner.
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22 Descriptive statistics will be used to describe the demographic and clinical characteristics
23 between the two groups at baseline. Clinical outcome data will be analysed depending on the type
24 of variables: for continuous variables, the difference in the means and corresponding 95%
25 confidence intervals and Analysis of Covariance, adjusting for baseline values will be used for
26 comparing the two groups. For categorical variables, the number and percentage of participants in
27 each category will be reported and Chi-squared tests will be used for comparing the two treatment
28 groups. If the variables are not normally distributed, alternative non-parametric tests will be used for
29 analysis. Analyses will be conducted on the intention-to-treat (ITT) (analysed as randomised) and
30 per-protocol (as ITT but with protocol violators excluded) populations. As this is a small study,
31 treatment effects are likely to have wide confidence intervals and consequently inferences will be
32 tentative and reported as such. Tests will be two-sided and considered to provide evidence for a
33 significant difference if p-values are less than 0.05.
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45 **Missing data**

46 Reasons for missing data, loss to follow-up and participant withdrawals will be carefully considered,
47 reported and patterns of 'missingness' will be explored. Missing data will be minimised by collecting
48 the minimum amount of data required and data queries will be resolved prior to analysis. We have
49 stated that the analysis will be on ITT basis and a per-protocol basis if the study is not considered
50 feasible. There will not be a formal statistical analysis plan and therefore deviations from it are not
51 anticipated. Any deviations from the analysis presented will be reported in the final study report.
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Monitoring and safety

Data monitoring

A trial monitoring plan has been developed and will comply with the principles of Good Clinical Practice (GCP). As this is a small study with a short duration, there is no formal Data Monitoring Committee. Instead, there is a Trial Oversight Group (TOG), which includes independent clinicians experienced in the fields of clinical trials, intensive care and haematology along with an independent statistician. The TOG will work closely with the Trial Management Group (TMG) and provide overall supervision of the study to ensure it is being conducted in accordance with GCP. A charter containing the details of the members, roles and responsibilities and planned method of functioning has been created and is available on request from the INTACT study office.

Safety

Participants surviving ICU are at a high-risk of adverse events (AEs) and serious adverse events (SAEs) secondary to their underlying disease process and/or expected complications of their critical illness. Therefore, only SAEs that might reasonably be a consequence of participation in the trial and are judged by the investigator to not be due to the underlying disease or expected complications of their critical illness will be reported. Ferric carboxymaltose is a drug with a well-known safety profile. The following rare events, if serious, must be reported on the trial specific SAE form:

- Anaphylactic / anaphylactoid reactions
- Loss of consciousness / syncope
- Bronchospasm
- Angioedema and facial oedema
- Severe anaemia (Hb <80 g.l¹) at 28 and/or 90 day follow-up

All SAEs will be submitted to the INTACT trial office within 24 hours of the investigator becoming aware.

Auditing

OCTRU will conduct a one-off audit of the study in accordance with the trial monitoring plan. Access to data will also be granted to authorised representatives from the Sponsor, host institution and the regulatory bodies to permit trial-related monitoring, audits and inspections. A trial monitoring plan is available on request from the INTACT study office.

Ethics and dissemination

Regulatory and ethics approval

This is a feasibility study of an investigational medicinal product which is broadly being used within its licensing indication. According to the Medicines and Healthcare products Regulatory Agency (MHRA), this trial has been categorised as Type A (no higher than the risk of standard care) as ferric carboxymaltose is indicated for the treatment of iron deficiency when oral preparations are likely to be ineffective or cannot be used. Clinical Trial Authorisation from the MHRA was received on 17th July 2018.

A favourable ethical opinion was obtained from South Central – Berkshire B Research Ethics Committee on 7th July 2018 (18/SC/0308). Health Research Authority approval was obtained on 20th July 2018. A favourable opinion for a substantial amendment was obtained on 18th April 2019 (see Appendix 1).

Consent

Any participants that are deemed potentially suitable will be asked by a member of the clinical team if a member of research team could come along and discuss a research study that they may be eligible for. The clinical team will also provide the participant with a Participant Information Leaflet. All eligible participants who agree verbally to be approached by the research team will be allocated a screening number and entered into the screening log, which will be kept in the Investigator Site File (ISF). The screening log will be completed and maintained by an appropriately trained member of the research team. Where a participant agrees to take part in the study, a copy of the consent form will also be filed in the medical notes. The participant must personally sign and date the latest approved version of the Informed Consent Form (ICF) before any study specific procedures are performed.

Confidentiality

The research team will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant code on all study documents and the study CRF database, with the exception of the personal identifiers database, which will be held separately to the CRF database. The personal identifiers database will be used for the sole purpose of arranging study follow-up visits. All documents will be stored securely and only accessible by study staff and authorised personnel.

Dissemination policy

The TMG will form the basis of the writing committee and advise on the nature of the publications.

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3 The study will be reported in accordance with the Consolidated Standards of Reporting Trials
4 (CONSORT) guidelines and the pilot and feasibility extension.³¹ The study findings will be presented
5 at national and international meetings and the results will be published in a high quality, peer
6 reviewed, open-access (via Pubmed) journal. Ongoing study updates will also be provided on the
7 OCTRU website (intact.octru.ox.ac.uk).
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13 **DISCUSSION**

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15 The problem of anaemia after critical illness is increasingly being recognised. With guidelines
16 advocating restrictive transfusion practices, it is likely that even more ICU survivors will be
17 discharged from hospital with anaemia. No large clinical trial has been undertaken to address the
18 correction of anaemia by the use of IV iron in ICU survivors. INTACT is an open-label, feasibility,
19 randomised controlled trial designed to answer whether a future large RCT can be undertaken.
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23 The trial design is pragmatic and aims to deliver the intervention at any point between ICU
24 and hospital discharge. The current post-ICU median (IQR) length of stay in our institution is 10 (6-
25 23) days. In order to maximise retention and minimise participant burden, we will offer
26 reimbursement of any travel expenses incurred, and conduct home visits as necessary. This
27 approach was successfully used in a recent RCT evaluating the effect of a physical rehabilitation
28 package in patients recovering from critical care where there was only a 10% loss to follow-up at 3
29 months.³³
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35 A limitation of our study is the lack of a placebo infusion. The rusty brown colour of ferric
36 carboxymaltose makes it a challenging substance to blind. This could potentially result in bias,
37 particularly for HRQoL measures. However, a recent large RCT of post-operative intravenous iron in
38 patients undergoing major elective surgery also used a usual care control group and observed no
39 differences in Short Form-36 (SF-36) scores at 12 weeks post-treatment.³⁴ As part of our study we
40 will be asking participants at the 90-day follow-up whether or not they remember which group they
41 were randomised to. We will review the decision regarding a placebo infusion for any future RCT.
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48 In conclusion, INTACT is designed to determine whether or not a large RCT of treating
49 anaemia with IV iron in patients recovering from intensive care is feasible. If so, it has the potential
50 to rapidly become a translatable intervention. The trial opened to recruitment in September 2018
51 and is anticipated to close in December 2019.
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FUNDING

This study is being funded by an NIHR Doctoral Research Fellowship (NIHR-DRF-2017-10-094) awarded to the chief investigator. There is no external industry involvement and all study drugs are being procured through local NHS commissioning arrangements. The University of Oxford is the Sponsor of the study.

COMPETING INTERESTS

The Author(s) declare that there is no conflict of interest.

AUTHORS' CONTRIBUTIONS

A.S. is the chief investigator, protocol author and grant holder. I.M. and S.J.D. participated in the statistical analysis design of the study and in drafting and revising this manuscript. All authors assisted in the design of this study. All authors have read and approved the final manuscript.

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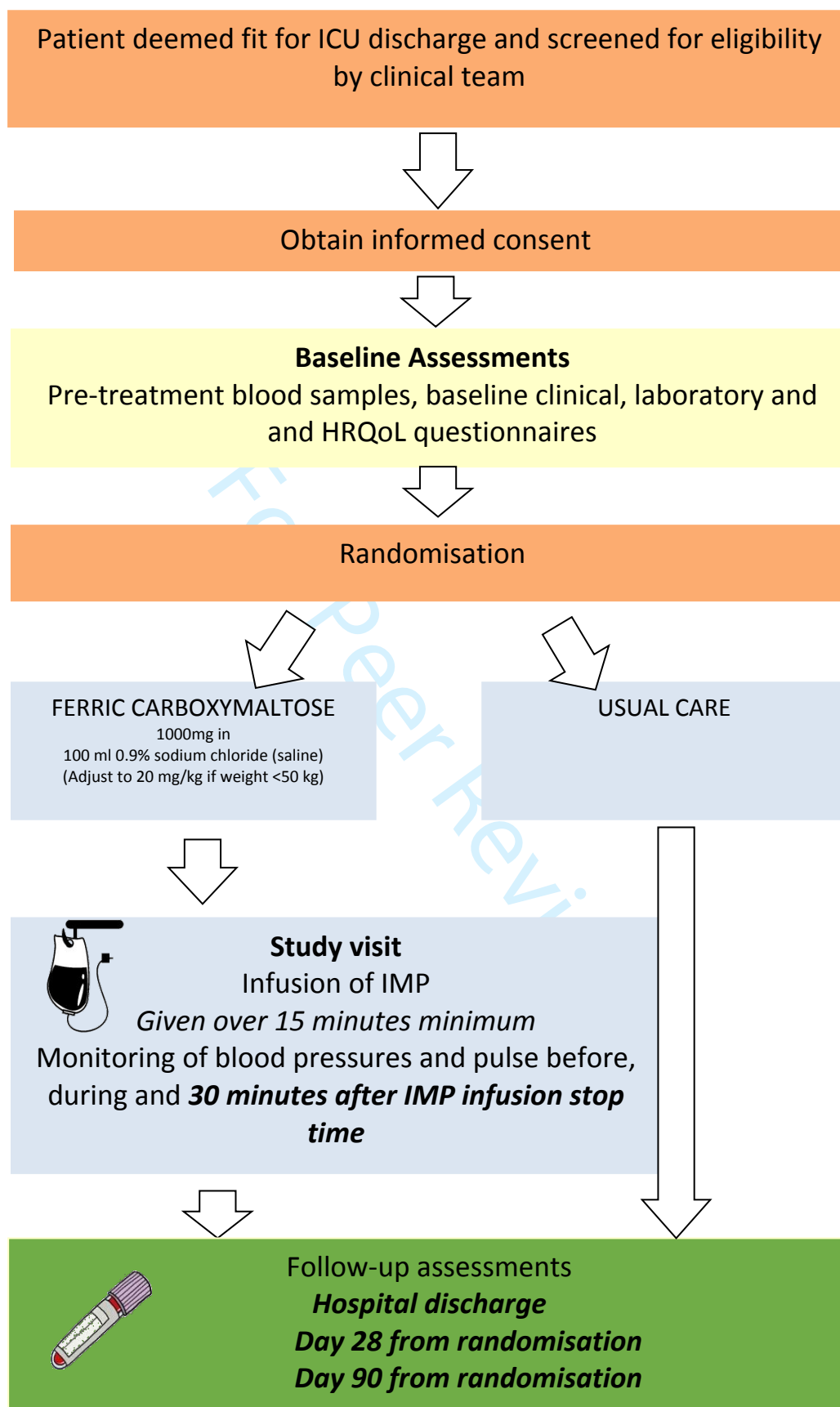
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Appendix 1: History of protocol amendments

Amendment No.	Protocol Version No.	Date issued	Details of Changes made
1	2.0	13Jul2018	Addition of pregnancy testing, specification of timeframe (24 hours) for notification of SAE to CI, and mention of heart rate and blood pressure monitoring before, during and after drug administration
2	3.0	06Mar2019	Revision of inclusion and exclusion criteria, including definition of active infection. Greater clarity on recruitment process. Dose adjustment for participants weighing less than 50 kg. Addition of telephone follow-up. Addition of Royal Berkshire Hospital as a recruitment site.

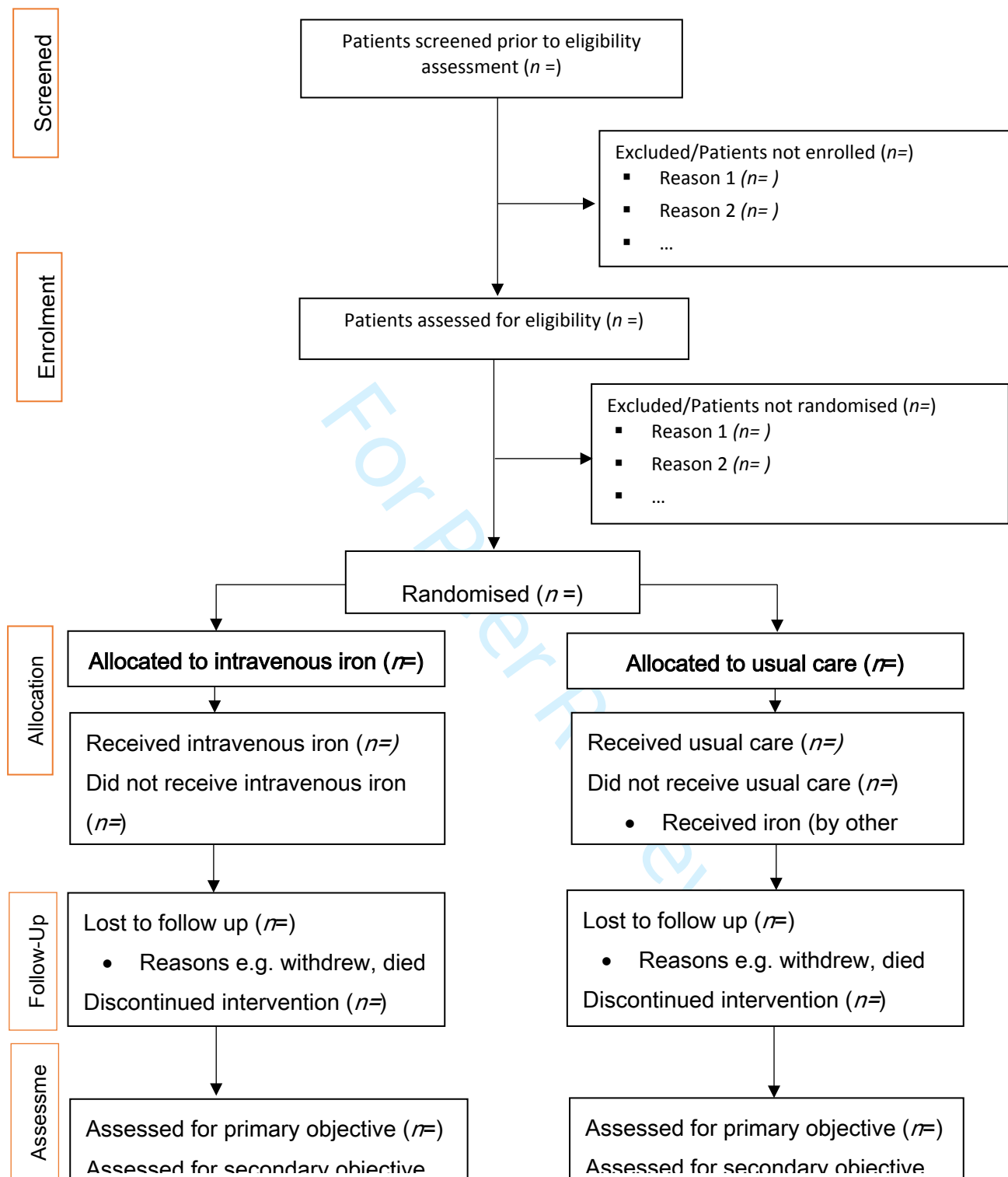
Figure 1. Study flow chart



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For Peer Review

Figure 2. CONSORT pilot and feasibility trials flow diagram schematic



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For Peer Review

Table 1. Timing of visits and data collection

Baseline (pre-randomisation)	<ul style="list-style-type: none"> • Confirmation with inclusion and exclusion criteria • Date and time of consent • Patient demographics (age, sex, weight) • Documented history of pre-existing anaemia prior to ICU admission • Charlson Co-morbidity Index • ICU admission – date and time of admission, ICU admission category, APACHE II score • ICU organ support – duration and requirement (advanced respiratory, cardiovascular and renal support using the Critical Care Minimum Dataset definitions) • Date and time of ICU discharge, ICU length of stay • Blood product administration (red cells, platelets, fresh frozen plasma, cryoprecipitate) • Hb – ICU admission and ICU discharge • Research blood samples (FBC, U&Es, LFTs, calcium, phosphate, iron profiles*, Vitamin D, EPO, hepcidin, sTfR) • Last recorded PaO₂ and SaO₂ with corresponding FiO₂ time point closest to ICU discharge • Pregnancy test result (if indicated) • HRQoL questionnaires (EQ-5D-5L, MFI-20, FACIT-F)
Hospital discharge	<ul style="list-style-type: none"> • Nosocomial infection • Survival status • ICU readmissions (if any) • Total hospital length of stay • Post-ICU blood product administration • Adverse events
Day 28	<ul style="list-style-type: none"> • Research blood samples (FBC, U&Es, LFTs, calcium, phosphate, iron profiles*, Vitamin D, EPO, hepcidin, sTfR) • HRQoL questionnaires (EQ-5D-5L, MFI-20, FACIT-F) • Bespoke questionnaires for participants use of health and social care resources • Adverse events

Day 90

- Research blood samples (FBC, U&Es, LFTs, calcium, phosphate, iron profiles*, Vitamin D, EPO, hepcidin, sTfR)
 - HRQoL questionnaires (EQ-5D-5L, MFI-20, FACIT-F)
 - Bespoke questionnaires for participants use of health and social care resources
 - Adverse events
-

*includes ferritin, serum iron, transferrin and transferrin saturation (%)

APACHEII, Acute Physiology and Chronic Health Evaluation II; EQ-5D-5L, EuroQol-5Dimension-5Level; EPO, erythropoietin; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; FBC, Full Blood Count; Hb, Haemoglobin; LFTs; HRQoL, Health-related quality of life; ICU, Intensive Care Unit, Liver Function Tests; MFI-20, Multidimensional Fatigue Inventory-20; sTfR, soluble transferrin receptor; U&Es, Urea and Electrolytes

Table 2. 'Traffic light' system to determine progression to a definitive trial

	Recruitment	Protocol adherence	Outcome Data
Green (Go)	8-11 participants per month across two centres	<5% failure to receive allocated intervention in the IV iron group	At least 80% of survivors will provide follow-up data at 90 days
Amber (Amend)	4-8 participants per month	5-10% failure to receive allocated intervention in the IV iron group	60-80% of survivors will provide follow-up data at 90 days
Red (Stop)	Less than 4 patients per month	>10% failure to receive allocated intervention in the IV iron group	50-60% of survivors will provide follow-up data at 90 days



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	13
	5b	Name and contact information for the trial sponsor	13
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10
Introduction			

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4	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	3
5	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
6				
7		6b	Explanation for choice of comparators	N/A
8				
9	Objectives	7	Specific objectives or hypotheses	4
10				
11	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	4, 5
12			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	
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17	Methods: Participants, interventions, and outcomes			
18				
19	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	5
20			be collected. Reference to where list of study sites can be obtained	
21				
22	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	5
23			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
24				
25	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	6
26			administered	
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28		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	6
29			change in response to harms, participant request, or improving/worsening disease)	
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31		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	N/A
32			(eg, drug tablet return, laboratory tests)	
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35		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
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Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6, 7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
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Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9, 10

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
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4		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
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7	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
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10	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
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14	Ethics and dissemination			
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16	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
17				
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19	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	11
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23	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
24				
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27		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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30	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
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33	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
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35	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
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38	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
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4	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
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8		31b	Authorship eligibility guidelines and any intended use of professional writers	12
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10		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
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12	Appendices			
13				
14	Informed consent	32	Model consent form and other related documentation given to participants and authorised surrogates	
15	materials			
16				
17	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	
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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.

EXECUTIVE SUMMARY

Anaemia during intensive care unit (ICU) care is very common, affecting 60-80% of patients. Furthermore, around 80-90% of ICU survivors will be discharged from hospital with some degree of anaemia and will often receive no intervention or further investigation. Up to half of these patients will have persisting anaemia three to six months later. Persisting anaemia in ICU survivors has been demonstrated to be associated with poor health related quality of life, low physical function scores and high levels of fatigue. This is important because recent evidence suggests that a significant proportion of these patients have evidence of absolute and/or relative iron deficiency, which is largely untreated.

Improving recovery from critical illness is a recognised research priority. In non-critically ill patients, treating anaemia with intravenous iron has resulted in meaningful improvements in quality of life, but uncertainties regarding the benefits, risks, timing and optimal route of iron therapy in survivors of critical illness remain. Prior to embarking on a phase III, multicentre trial, a carefully designed and implemented feasibility trial is essential.

Intravenous Iron to Treat Anaemia following Critical care (INTACT) is an open-label, feasibility, parallel group, randomised controlled trial (RCT). The overarching aim is to assess the feasibility of a future, multicentre RCT. Participants with moderate to severe anaemia (haemoglobin $< 100 \text{ g.l}^{-1}$), who have required at least 24 hours of ICU care, and are now deemed medically stable for discharge from ICU by the attending physician will be considered for inclusion. Included participants will undergo 1:1 randomisation to either a one-off dose of intravenous iron (1000mg ferric carboxymaltose) or usual medical care using minimisation and stratified on anaemia severity and ICU length of stay. Participants will be followed up at 28- and 90-days post-randomisation. We anticipate enrolling 130 participants across three intensive care units over a 52-week recruitment period.

The primary outcome measures, which will be used to determine feasibility, are recruitment and randomisation rates, protocol adherence and completeness of follow-up. Secondary outcome measures include collecting clinical, laboratory, fatigue scores (MFI-20, FACIT-F), health-related quality of life (EQ-5D-5L) and safety data to inform the power calculations of a future definitive trial. A prespecified 'traffic light' system will be used as a guide for progression to a definitive trial. The trial is being funded as part of an NIHR Doctorial Research Fellowship, sponsored by the University of Oxford and has been prospectively registered (ISRCTN 13721808).