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Original Article

Iron and erythropoietin to heal and recover after intensive care (ITHRIVE): A pilot randomised clinical trial☆

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ABSTRACT

Objective: To determine the feasibility of a pivotal randomised clinical trial of intravenous (IV) iron and erythropoietin in adult survivors of critical illness with anaemia requiring treatment in the intensive care unit.

Design: An investigator-initiated, parallel group, placebo-controlled, randomised feasibility trial.

Setting: A tertiary intensive care unit (ICU) in Perth, Western Australia.

Participants: Adults with anaemia (haemoglobin <100 g/L), requiring ICU-level care for more than 48 h, and likely to be ready for ICU discharge within 24 h.

Interventions: A single dose of IV ferric carboxymaltose and Epoetin alfa (active group) or an equal volume of 0.9% saline (placebo group).

Main outcome measures: Study feasibility was considered met if the pilot achieved a recruitment rate of ≥2 participants per site per month, ≥90% of participants received their allocated study treatment, and≥ 90% of participants were followed up for the proposed pivotal trial primary outcome - days alive and at home to day 90 (DAH_{90}).

Results: The 40-participant planned sample size included twenty in each group and was enrolled between 1/9/2021 and 2/3/2022. Participants spent a median of 3.4 days (interquartile range 2.8–5.1) in the ICU prior to enrolment and had a mean baseline haemoglobin of 83.7 g/L (standard deviation 6.7). The recruitment rate was 6.7 participants per month [95% confidence interval (CI) 4.8–9.0], DAH_{90} follow-up was 100% (95% CI 91.2%–100%), and 39 (97.5%, 95% CI 86.8%–99.9%) participants received the allocated study intervention. No serious adverse events were reported.

Conclusion: The iron and erythropoietin to heal and recover after intensive care (ITHRIVE) pilot demonstrated feasibility based on predefined participant recruitment, study drug administration, and follow-up thresholds.

1. Introduction

Anaemia is prevalent among patients requiring treatment in the intensive care unit (ICU) and is often progressive, increasing with the severity of illness and duration of organ support.[1–5] Nearly all patients discharged from the ICU with a haemoglobin of less than 100 g/L remain anaemic at hospital discharge.[6,7] Amongst ICU survivors, anaemia is an independent risk factor for prolonged hospitalisation, ICU and hospital readmission, and death.[8–11] Longer term, up to half of patients with anaemia at ICU discharge remain anaemic at six months, experiencing a markedly reduced quality of life.[12] Evaluating new treatments has been identified as a research priority.[13]

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Inflammation is a ubiquitous consequence of critical illness that drives iron deficiency and decreases circulating erythropoietin.[14,15] Iron deficiency at ICU discharge persists in up to a third of patients at six months and is an independent risk factor for death and reduced quality of life.[16,17] Preliminary evidence suggests that for patients with anaemia in the ICU, intravenous (IV) iron and erythropoietin are safe treatments that increase haemoglobin concentration.[6,18] In addition to direct effects on erythropoiesis and potential anti-inflammatory effects, recombinant human erythropoietin enhances the benefit of IV iron therapy by increasing erythroferrone and suppressing hepcidin.[19–21] However, a large, pivotal randomised clinical trial (RCT) of this combination therapy is required to evaluate patient-centred outcomes.

The primary aim of the iron and erythropoietin to heal and recover after intensive care (ITHRIVE) pilot RCT was to determine the feasibility of a pivotal clinical trial of IV iron and erythropoietin in adult survivors of critical illnesses requiring treatment in the intensive care unit. The hypothesis was that a pivotal trial would be feasible based on achieving predefined thresholds for participant recruitment, study drug administration, and follow-up.

2. Methods

2.1. Trial design

This investigator-initiated, parallel-group, placebo-controlled, randomised feasibility trial was approved by the South Metropolitan Health Service Human Research Ethics Committee (ref: RGS0000004354). Trial registration occurred prospectively (ACTRN 12621000595819), and it was conducted according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement: extension to randomised pilot and feasibility trials (checklist provided, Table 1 supplementary appendix).[22] Prior to study enrolment, prospective, written informed consent was obtained from the participant or from the legal surrogate for participants who lacked capacity. Prospectively, no between-group analyses of clinical outcomes were planned in order to include pilot participants in the pivotal trial.

2.2. Participants

The trial was conducted in the Fiona Stanley Hospital ICU, a tertiary referral centre in Perth, Western Australia. Eligible patients, identified by daily research staff screening, were adults requiring ICU-level care for more than 48 h in whom the treating clinician had determined that ICU discharge was appropriate or likely to be appropriate in the next 24 h and for whom the haemoglobin was less than 100 g/L. Key exclusion criteria were a requirement for prolonged antibiotic therapy, a contraindication to thromboembolism, chemoprophylaxis, and recent treatment for cancer. The complete eligibility criteria are provided in the supplementary appendix.

2.3. Intervention

The active intervention group received a single dose of 1 g IV ferric carboxymaltose infusion (CSL Vifor, 8152 Glattbrugg, Switzerland) over 1 h in 100 ml of 0.9% saline and a single dose of IV Epoetin alfa 40,000 IU in 1 ml (Eprex Janssen-Cilag Pty Ltd, Titusville, NJ, USA). The placebo group received 100 ml of 0.9% saline infused over 1 h and a 1 ml bolus dose of IV 0.9% saline. The study drugs were prepared and administered by a clinical staff member not directly involved in the clinical care of the participant patient. Both groups received a 50-ml flush of 0.9% saline predose and postdose of IV iron or matched placebo to reduce the risk of extravasation. There were no repeat doses.

2.4. Outcomes

The primary outcome of study feasibility was deemed to have been met if all three of the following criteria were achieved:

1. The recruitment rate is $\geq$ 2 participants per site per month
2. $\geq$ 90 % of participants receive their allocated study treatment (protocol adherence)
3. $\geq$ 90 % of participants are followed up for the proposed pivotal trial primary outcome of days at home to day 90 (DAH_{90})

Key secondary outcomes included DAH_{90}, intensive care and hospital readmission and mortality, and haemoglobin at hospital discharge. DAH_{90} is a composite outcome that counts the number of days alive and at home between randomisation and Day 90. Days spent in rehabilitation, a nursing home, or hospital readmission are

Table 1
Baseline characteristics.

Characteristic	Overall (n = 40)
Age – years	57.4 (15.6)
Male sex – no. (%)	29 (72.5)
Weight – kg	84.4 (17.6)
Frailty – no. (%)	
Not frail	20 (50)
Vulnerable	14 (35)
Frail	6 (15)
ICU admission source – no. (%)	
Emergency department	5 (12.5)
Operating theatre	28 (70.0)
Ward	1 (2.5)
Transfer from another hospital	6 (15)
Unplanned admission – no. (%)	20 (50)
Admission Type – no. (%)	
Medical	11 (27.5)
General surgical	3 (7.5)
Cardiothoracic	24 (60.0)
Trauma	1 (2.5)
Orthopaedic	1 (2.5)
APACHE II – score	16.5 (7.1)
SOFA – score	5.1 (3.1)
Organ support – no. (%)	
Mechanical ventilation	31 (77.5)
Vasoactive medication	37 (92.5)
Renal replacement therapy	7 (17.5)
Nasal High Flow Oxygen	19 (47.5)
APACHE Comorbidities – no. (%)	
Respiratory	4 (10)
Cardiovascular	0
Liver	5 (12.5)
Renal	0
Immunosuppression	0
Haemoglobin – g/L	
Hospital admission	126.4 (28.5)
ICU admission	104.5 (19.3)
On enrolment	83.7 (6.7)
Bleeding episodes – no. (%)	
Prior to ICU admission	
No bleeding	11 (27.5)
Minor bleeding	23 (57.5)
Major bleeding	6 (15.0)
In ICU prior to study enrolment	
No bleeding	11 (27.5)
Minor bleeding	24 (69.0)
Major bleeding	5 (12.5)
Red blood cell transfusion	
Median units (IQR)	2 (0–3.5)
One or more RBC units – no. (%)	27 (67.5)
Time in ICU at enrolment – median days (IQR)	3.4 (2.8–5.1)

Mean and (SD) standard deviation unless otherwise stated. APACHE: acute physiology and chronic health evaluation, ICU: intensive care unit, SOFA: sequential organ failure assessment, RBC: red blood cell.

counted as days in the hospital. Deaths prior to discharge from the index admission are counted as zero DAH_{90}. At Day 90, following randomisation, site research coordinators contacted participants by phone to check whether hospital readmission had occurred, whether there had been nonprotocol study drug administration, any adverse events had occurred, and conduct a quality-of-life survey using EuroQuol 5D-5L (EQ5D5L) and a cognitive function survey using the telephone version Montreal Cognitive Assessment (T-MOCA).[23] As part of the process of consumer input into the pivotal trial design, all pilot participants were asked to consider the minimum number of additional days at home until day 90 that would be of value to them. This was recorded as the participant-reported DAH_{90} minimum clinically important difference. Follow-up uncertainty with respect to any study outcome was resolved by contact with the participant's general practitioner and additional hospital records as required. For bleeding outcomes (none, minor, or major), standardised definitions of the Bleeding Academic Research Consortium were used.[24] A full list of outcomes is provided in the supplementary appendix.

2.5. Randomisation

A permuted block randomisation schedule with variable block size was developed by the site pharmacy department. Allocation concealment was maintained by using sequentially numbered, sealed, opaque envelopes containing the study allocation and instructions for study drug (active or placebo) administration.

2.6. Blinding

Participants, treating clinicians, and outcome adjudicators were all blinded using processes similar to past successful RCT blinding of IV iron and Erythropoietin (EPO).[6,25] Study drug administration was blinded by using opaque delivery sets, administered by a clinician not directly involved in the care of the participant. The outcome assessment was conducted by blinded adjudicators. A site start-up meeting was conducted, which included training for key study personnel on administration procedures to ensure blinding consistency and quality.

2.7. Statistical methods

Other than the feasibility endpoints identified as the primary outcome, trial registration prespecified for all outcome data to be presented in aggregate so that group-specific data could be included in the pivotal trial. All analyses were conducted on an intention-to-treat basis. No imputation was made for missing data. The coprimary outcomes were described as the number of participants enrolled per month, the number and percentage that received the study drug, and the number and percentage that were followed up to ascertain the proposed pivotal trial primary outcome of DAH_{90}. The calculation of the 95% confidence interval (CI) for the recruitment rate assumed Poisson arrivals, and the 95% CIs for the proportions were calculated using the Clopper–Pearson method. To calculate 95% CIs for the observed median DAH_{90}, a binomial method that makes no distribution assumptions was used. Secondary outcomes were reported as number and percentage for count data and mean and standard deviation (SD) or median and interquartile range (IQR) for continuous valued variables as appropriate. All adverse events considered potentially causally related to the study intervention or that were otherwise of concern in the investigator's judgement were reported, consistent with established ICU RCT practice.[26] Serious Adverse Events (SAEs) were reported according to the Good Clinical Practice Guidelines, and all deep vein thromboses and pulmonary embolisms were reported as SAEs. An independent data monitoring committee was formed to review SAEs. There was no planned interim analysis.

2.8. Sample size

The sample size was based on achieving a lower limit of the 95% confidence interval for follow-up and delivery of study treatment of >80%, considered a reasonable feasibility threshold, assuming a point estimate of 90%. This required a trial of 40 participants to achieve a lower limit for the 95% confidence interval of 80.7%.

3. Results

Between 1/9/2021 and 2/3/2022, 104 patients who met the inclusion criteria were assessed for eligibility, and 40 underwent randomisation (Fig. 1). The mean age was 57.4 (SD 15.6) years; 29 (72.5%) were male, and 20 (50%) were unplanned ICU admissions. Participants had spent a median of 3.4 days (IQR 2.8–5.1) in ICU prior to enrolment and had a mean haemoglobin of 83.7 g/L (SD6.7) at the time of randomisation. A majority had received mechanical ventilation (n = 31, 77.5%) and vasoactive medication (n = 37, 92.5%) (Table 1).

3.1. Primary outcome

The recruitment rate was 6.7 participants per month (95% CI 4.8–9.0). Of the enrolled patients, all 40 (100%, 95% CI 91.2%–100%) were followed up to ascertain DAH_{90}, and one participant allocated to receive placebo instead received open label EPO and IV iron, so that 39 (97.5%, 95% CI 86.8%–99.9%) received the allocated study intervention (Table 2 and Fig. 1).

3.2. Secondary outcomes

The median DAH_{90} was 82.0 (95% CI 76.3–83.7, mean 74.5 SD 18.6), and 10 (25%) were discharged from their index hospitalisation to a rehabilitation facility. To Day 90, there were no deaths, and 9 (22.5%) participants were readmitted to the hospital. The median EQ5D5L Visual Analogue Scale, available for 34 (85%) participants, was 88 (IQR 80–94, mean 85.7, SD 13.8). Individual domains of the EQ5D5L and the MOCA score are reported in the supplementary appendix, Table S2. The mean minimum clinically important difference in DAH_{90} reported by 33 (82.5%) trial participants was 3 (SD 0.7). There were no adverse events or SAEs reported.

4. Discussion

This single-centre pilot RCT was conducted to assess the feasibility of a large, pivotal trial of IV iron and EPO for patients with anaemia in the ICU. The trial enrolled its planned sample size of 40 participants, exceeding thresholds for the primary feasibility outcomes of recruitment rate, protocol adherence, and follow-up thresholds. The recruitment rate was 6.7 participants per month, adherence to the allocated study treatment was achieved by 39 (97.5%) and complete follow-up was achieved by all 40 trial participants. The single occurrence of open-label study drug administration was addressed through further bedside education. Minor protocol changes proposed for the pivotal trial, along with their rationale, are provided in the supplementary appendix.

The ITHRIVE pilot builds on previous study findings with the aim of conducting a pivotal trial that will evaluate the optimal clinical outcomes, intervention timing, and study drug combination for

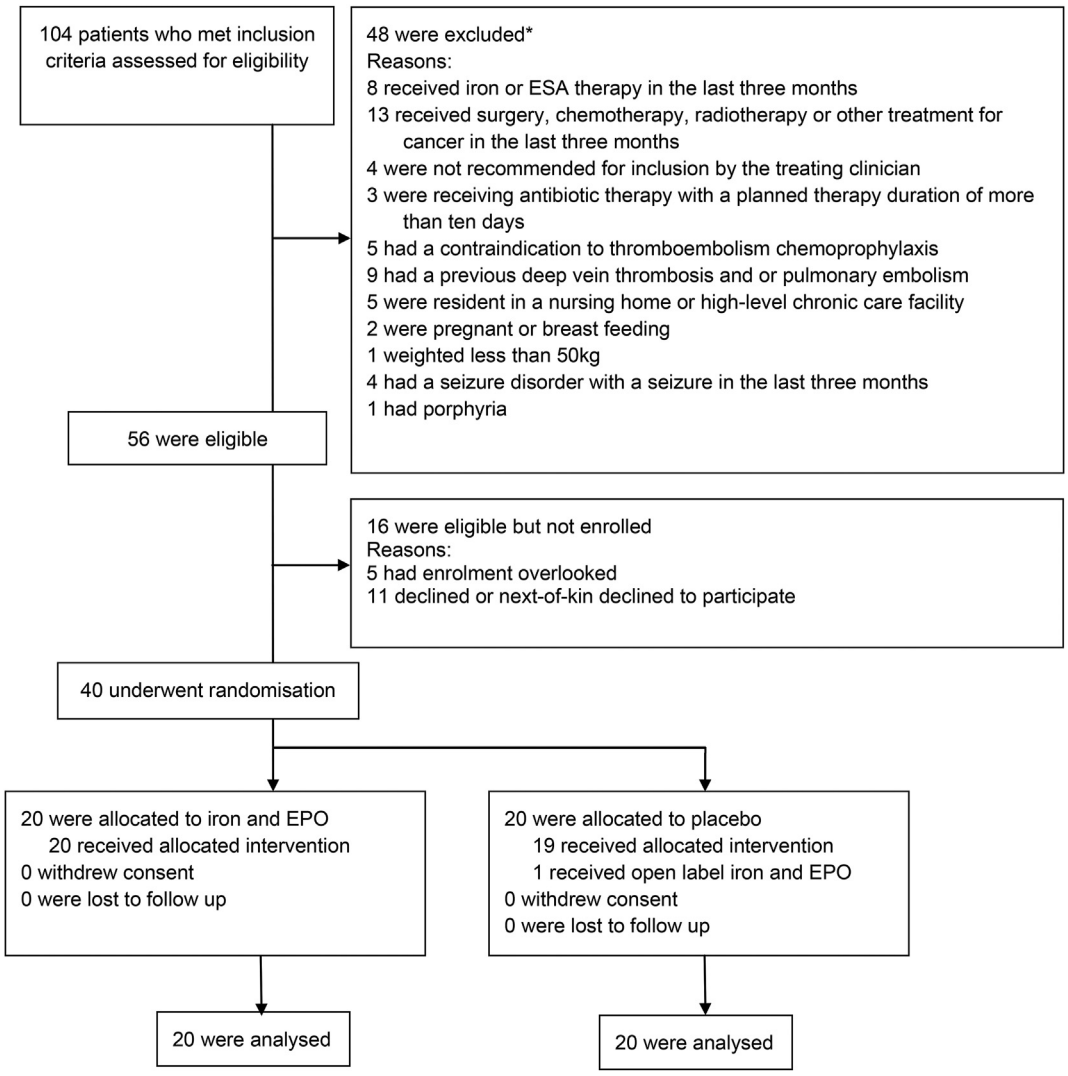

Fig. 1. *41 patients with one exclusion, seven patients with two exclusions.

patients with anaemia in the ICU. In addition to the direct adverse effects of anaemia, iron-restricted metabolism may contribute to common symptoms of functional impairment experienced by ICU survivors including weakness, fatigue, and cognitive impairment.[27] A previous study demonstrated an independent association between increasingly severe anaemia at ICU discharge and fewer days at home until Day 90.[9] An RCT of IV iron within 48 h of ICU admission found that haemoglobin was increased at hospital discharge, but the trial was not powered to evaluate clinical significance.[6] Later IV iron administration at ICU discharge in patients who have required substantial organ support may be preferable. This approach enriches the cohort for ICU survivors at risk of prolonged recovery and functional impairment and has been trialled in a previous pilot RCT in which IV iron at ICU discharge was associated with a significant haemoglobin increase, but the recruitment rate was lower than anticipated.[28] The addition of EPO to IV iron is supported by evidence of their synergistic effects and a systematic review in which ICU EPO therapy was associated with a significant lower in-hospital mortality (relative risk 0.82, 95% CI 0.71–0.94, P = 0.006, I^2 0 %).[29,30]

Although not powered to detect between-group differences, pooled analysis of the clinical outcomes suggests that the study eligibility criteria identified a cohort of ICU survivors with a high care burden following critical illness including a substantial proportion requiring discharge to a rehabilitation facility and hospital readmission within 90 days. For this group of patients, an intervention that improves recovery would be of major benefit. These data are supported by the participants' own views that the minimum clinically important difference in DAH_{90} would be three days, a finding that will help inform the sample size calculation for the pivotal trial.

This pilot RCT has limitations. The feasibility outcomes chosen are necessary but insufficient predictors of pivotal trial success. Other factors such as screening volume, study procedure requirements and complexity, and data documentation burden, will also influence trial success. However, the screened-to-enrolled ratio of 2.6:1 (104 assessed for eligibility, 40 enrolled) is relatively low, and the exclusion criteria and study processes will be refined further based on pilot experience. A larger pilot RCT with a sufficient sample size is needed to evaluate between-group differences in surrogate outcome measures such as separation in haemoglobin concentration. However, biological plausibility has been established, and a 40 participant pilot was sufficient to resolve the primary feasibility questions. Additional study sites were planned, but participation was limited to a single centre by the COVID-19 pandemic. This may have contributed to the relatively high observed recruitment rate and will be accounted for in the pivotal trial. Furthermore, protocol adherence and follow-up were also

Table 2
Outcomes.

Characteristic[a]	Outcome (n = 40)
Primary outcome	
Recruitment rate – no./month (95 % CI)	6.7 (4.8–9.0)
Follow up – no. (%, 95 % CI)	40 (100, 91.2–100)
Received allocated treatment – no. (%, 95 % CI)	39 (97.5, 86.8–99.9)
Secondary outcomes	
DAH_{90}	
Median, [95 % CI, IQR]	82.0 [76.3–83.7, 70.5–86.5]
Mean (SD)	74.5 (18.6)
Mortality – no. (%)	
Hospital	0
Day 90	0
Readmission – no. (%)	
ICU^{+}	3 (7.5)
Hospital^	9 (22.5)
Discharge destination – no. (%)	
Home	30 (75)
Other acute care facility	0
Rehabilitation facility	10 (25)
Nursing home	0
Haemoglobin – g/L	
Hospital discharge	98.4 (12.8)
Bleeding episodes – no. (%)	
No bleeding	39 (97.5)
Minor bleeding	0
Major bleeding	1 (2.5)
Red Blood Cell Transfusion – no. (%)	
Hospital discharge	4 (10.0)
Day 90	6 (15.0)
Patient reported outcome measures	
EQ5D5L VAS – median (IQR)	88 (80–94)
T-MOCA	18 (16–19)
Serious adverse events	
Deep vein thrombosis	0
Pulmonary embolism	0
Anaphylaxis	0
Other	0
Adverse events	0

[a] Mean and (SD) standard deviation unless otherwise stated. DAH_{90}: Days at Home to Day90, CI: confidence interval, IQR: interquartile range, APACHE: acute physiology and chronic health evaluation, EQ5D5L VAS EuroQol 5D5L: Visual Analogue Scale, T-MOCA: telephone version Montreal Cognitive Assessment, score range 0–22 with a score less than 19 indicating cognitive impairment, $^{+}$During index hospitalisation, ^To Day 90.

high, and feasibility measures were less sensitive to the number of sites. Eligibility based on the duration of organ failure is a pragmatic but imperfect surrogate for the likelihood of functional impairment and prolonged recovery caused by a critical illness. Although the trial included a substantial number of cardiothoracic participants, the study eligibility criteria and feasibility outcomes are generalisable to ICUs that care for a wide variety of patient cohorts. Finally, although this pilot considered one specific treatment regime, other regimes are possible including one used in a recent French pilot RCT of EPO administered to anaemic patients between three and seven days after ICU admission.[31]

5. Conclusion

The ITHRIVE pilot RCT demonstrated the feasibility of a pivotal clinical trial based on achieving predefined thresholds for participant recruitment, protocol adherence, and follow-up. The trial protocol identified and safely treated a cohort of ICU survivors for whom there is an urgent need to improve outcomes.

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Credit authorship contribution statement

All authors contributed equally to this article.

Conflict of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: EL is a Critical Care and Resuscitation Editor. David Griffith received fees for speaking from Fresenius Kabi (2021) and for BD advisory board participation (2020). In both bases, fees were paid directly to DGs group at the University of Edinburgh. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ccrj.2023.10.007.

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