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Reviews and Meta-Analysis

Safety and efficacy of iron therapy on reducing red blood cell transfusion requirements and treating anaemia in critically ill adults: A systematic review with meta-analysis and trial sequential analysis☆

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ABSTRACT

Purpose: To evaluate the safety (risk of infection) and efficacy (transfusion requirements, changes in haemoglobin (Hb)) of iron therapy in adult intensive care unit (ICU) patients.
Materials and methods: We systematically searched seven databases for all relevant studies until January 2018 and included randomized (RCT) studies comparing iron, by any route, with placebo/no iron.
Results: 805 participants from 6 RCTs were included. Iron therapy, by any route, did not decrease the risk of requirement for a red blood cell (RBC) transfusion (Risk ratio (RR) 0.91, 95% CI 0.80 to 1.04, $p = 0.15$) or mean number of RBCs transfused per participant (mean difference (MD) -0.30, 95% CI -0.68 to 0.07, $p = 0.15$). Iron therapy did increase mean Hb concentration (MD 0.31 g/dL, 95% CI 0.04 to 0.59, $p = 0.03$). There was no difference in infection (RR 0.95, 95% CI 0.79 to 1.19, $p = 0.44$). Trial Sequential Analysis suggests that the required participant numbers to detect or reject a clinically important effect of iron therapy on transfusion requirements or infection in ICU patients has not yet been reached.
Conclusion: Iron therapy results in a modest increase in Hb. The current evidence is inadequate to exclude an important effect on transfusion requirements or infection.

1. Introduction

Anaemia is highly prevalent in intensive care unit (ICU) patients; approximately 60% have a haemoglobin (Hb) concentration < 12 g/L on ICU admission and after 7 days, 80% of patients will have an Hb <90 g/L [1,2]. At present, allogeneic red blood cell (RBC) transfusion is the mainstay for treatment for anaemia in ICU patients. Depending on the case mix, approximately 30–50% of ICU patients receive an RBC transfusion and ICU patients can account for up to 20% of all hospital transfusions [1,3,4]. The majority of transfusions are used to treat anaemia with only 10–20% being used to treat haemorrhage [5]. This resource burden combined with the well recognized risks of allogeneic RBC transfusion means that there is an unmet need for safe and effective alternative interventions that will treat anaemia and also reduce transfusion requirements.

Iron therapy has been shown to improve Hb and decrease RBC transfusion requirements in a variety of clinical settings with varying effect sizes [6-8]. On the basis of this evidence, recent consensus statements and patient blood management initiatives (as part of optimising erythropoiesis) advocate the use of iron. In particular, intravenous (i.v.) iron, has been recommended as being safe and efficacious even in the settings of co-existing inflammation such as functional iron deficiency (FID) and/or iron sequestration (defined as ferritin >100 μg/L, transferrin saturation index (TSAT) <20% and/or CRP >5 mg/L) [9-11]. It is highly plausible that both the benefits and risks, particularly the risk of infection, associated with i.v. iron is dependent on the clinical context and baseline risk. Specifically, the erythropoetic response may be blunted due to co-existing inflammation and the potential for adverse events such as developing infection may be increased in the context of iron

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oversaturation, such as may occur in iron sequestration [12]. This is of concern in ICU patients who display the hallmarks of anaemia of inflammation with iron parameters in keeping with those of FID/iron sequestration mentioned above and are also at a higher baseline risk of developing infection. Therefore a better understanding of the benefits and risks of iron therapy in this cohort is needed.

A previous systematic review of iron supplementation in critically ill patients found no evidence of an effect of iron therapy, by any route, on efficacy and safety outcomes [13]. Current consensus recommends updating systematic reviews when new evidence is available and when newer, relevant synthesis methods can be applied [14]. With the publication of a recent multicenter trial [15], we conducted an update of our previous systematic review to investigate if this would alter the findings our previous review on clinically important efficacy (risk of transfusion, differences in Hb concentration and safety (mortality, risk of infection) outcomes. In addition, we also applied Trial Sequential Analysis (TSA) and assessed the quality of evidence using the grading of recommendations assessment, development, and evaluation (GRADE) guidelines to improve the quality of our analysis and clarity of our findings.

2. Methods

This systematic review was conducting according to a predefined study protocol registered on PROSPERO (CRD42015016627). We followed the recommendation by the Cochrane Collaboration [16], the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [17] and the GRADE guidelines [18].

2.1. Eligibility criteria

To be included in this meta-analysis, the following criteria had to be met: (i) randomized controlled trials (RCT); (ii) patients admitted to any adult ICU or high-dependency unit (HDU); (iii) iron supplementation by any route (oral, intravenous, intramuscular) versus placebo or no iron therapy. Co-interventions were only included if they were present in both/all arms.

2.2. Study identification

The last search date was 15th January 2018. One review contributor (CD) searched the following databases: CENTRAL (Cochrane Central Register of Controlled Trials) in *The Cochrane Library*, MEDLINE, Embase, CINAHL, PubMed (e-publications ahead of print only), Web of Science (1990 onwards) and the Transfusion Evidence Library (1950 onwards). Ongoing trials were sought from trial registration websites. The full search strategy is available in Appendix 1 (Supplemental digital content, Appendix 1).

2.3. Study selection and data extraction

Two review authors (AS, HW) independently screened citations from the systematic search. All trials that fulfilled the inclusion criteria were investigated in full text. Data were extracted by the same two review authors (AS, HW) onto a pre-piloted data collection form that was used for the previous version of this review. Disagreements were solved through discussion and if no resolution was found, a third author (SJS) adjudicated. We sought unclear or missing data by contacting the authors of the individual trials.

2.4. Outcomes

The pre-defined co-primary efficacy outcomes were: (i) requirement for allogeneic RBC transfusion; (ii) mean number of RBCs transfused; and (iii) mean haemoglobin (Hb) concentration. Secondary safety outcomes were: (i) all-cause mortality; (ii) in-hospital infection (as defined by the study authors); (iii) ICU length of stay (LOS); (iv) hospital LOS; (v) morbidity scales (e.g. organ dysfunction scores such as Multiple Organ Dysfunction Score (MODS)); (vi) health-related quality of life (HrQoL); and (vii) adverse events. We defined two time points: (i) short-term (≤10 days) (ii) medium-term (>10 days, the last measured time point in hospital or end of the trial).

2.5. Risk of bias assessment

Study quality was judged using the Cochrane Collaboration tool for assessing risk of bias [19]. A three-point scale was used to determine low, high, or unclear risk of bias. Three review authors (AS, NBR, HW) assessed risk of bias independently both for this updated review (AS, HW) and for the previous version (AS, NBR).

2.6. Quality of evidence

In accordance with the GRADE approach [18], we assessed the overall quality of evidence for all co-primary outcomes and a secondary outcome of in-hospital infection. We evaluated the quality of evidence and our confidence in the effect estimates on the basis of trial quality, consistency and directness as well as conclusions drawn from TSA and rated the overall quality of evidence as “high”, “moderate”, “low” or “very low”.

2.7. Data synthesis

Statistical analyses were performed using Review Manager (RevMan, version 5.3) [20] and TSA program version 0.9 beta (www.ctu.dk/tsa) [21]. We used random effects models throughout. Where possible, continuous variables were reported as mean difference (MD) with 95% confidence interval (CI). For outcomes that were deemed likely to be skewed in distribution, namely number of RBC transfusions, reported mean and standard deviation (SD) were transformed to a natural logarithmic scale using the methods of Higgins et al. [22]. Dichotomous variables were reported as relative risk (RR) with corresponding 95% CI. Heterogeneity was assessed using the I^2 statistic [23].

2.8. Subgroup and sensitivity analyses

We planned to perform subgroup analyses if there were at least two RCTs with comparable subgroups reporting the primary outcomes: (i) different iron preparation (enteral vs. intravenous) and (ii) use of co-interventions e.g. erythropoietin. We intended to perform sensitivity analysis by only including trials at low risk of bias (defined as trials with no high risk of bias domains and at least half of the remaining domains considered to be at low risk of bias).

2.9. Trial sequential analysis

Cumulative meta-analysis may result in type 1 errors due to repeated testing of accumulating data [24]. We applied trial sequential analysis (TSA) to assess this risk. TSA calculates a required information size (IS) (overall sample size to obtain the required level of statistical power) based on the available data by taking into the consideration the event rate in the control group, a plausible relative risk reduction/increase and the anticipated heterogeneity variance (D^2) of the meta-analysis.[17] We applied TSA to the following dichotomous outcomes: (i) requirement for RBC transfusion (efficacy); (ii) in-hospital infection (safety).

We estimated a baseline risk of 50% of requiring an allogeneic RBC transfusion based approximately on the proportion of participants receiving a transfusion in the control group on the trials included in this systematic review. We considered a 12% relative risk reduction (RRR) as clinically meaningful. We estimated a baseline risk of developing an

infection of 30%. This was based on the results of a large observational study [25]. We considered a 17% relative risk increase (RRI) of developing an infection from receiving iron therapy as clinically relevant. These estimates are from a meta-analysis assessing the safety and efficacy of intravenous iron across a range of patient populations [6].

We produced futility boundaries such that if the cumulative *Z*-curve crossed the futility threshold, evidence showed that the treatment effect did not differ more than the anticipated effect size. We used the O'Brien Fleming alpha-spending function with an overall type I error rate of 5% and with 80% statistical power to derive two-sided sequential monitoring and futility boundaries.

3. Results

3.1. Characteristics of included studies

Our search identified 1123 records and we assessed 33 full-text articles after exclusion by screening of titles, duplicates and abstracts (Supplemental digital content, Fig. S1). We included 6 RCTs [15,26-30]. One ongoing trial was identified [31]. Details of the included RCTs are shown in Table 1. The six RCTs included a total of 805 participants of which 438 received iron and 367 received no iron/placebo. Four RCTs were single-center trials. Four trials were carried out in surgical ICUs (trauma, cardiothoracic, neurosurgical, burns, and general surgical) and two trials were carried out in mixed ICUs that included medical, surgical and trauma participants.

Three trials compared intravenous iron to intravenous placebo [15,26,29], one trial compared intravenous iron to no iron (control) [30], one trial compared oral iron to oral placebo [28] and one trial included three arms [27]: (i) intravenous iron and oral placebo, (ii) oral iron and intravenous placebo, and (iii) oral and intravenous placebo. Two trials included groups that received erythropoietin and data from these groups was excluded for this analysis [27,30]. Two trials administered co-interventions: ascorbic acid, cyanocobalamin and folic acid [29] or folic acid only [30].

3.2. Risk of bias assessments

Two trials [15,28] were judged as having low risk of bias across all domains (Supplemental digital content, Fig. S2). Four trials reported to have achieved adequate participant and personnel blinding [15,26-28]. Four trials were judged as having unclear risk of detection bias [26,27,29,30]. Three trials reported high levels of attrition of randomized participants [26,27,29]. Detailed risk of bias assessment for each trial is provided in Appendix 2 (Supplemental Digital Content, Appendix 2).

3.3. Quality of evidence

The GRADE quality of evidence ranged from very low to moderate. We predominantly downgraded studies for risk of bias (mainly attrition bias) and for imprecision due to the optimal sample size not being reached and for the wide variation in confidence intervals.

3.4. Co-primary outcomes

All six trials reported on the number of participants who received an RBC transfusion. Meta-analysis showed no evidence of an effect of iron supplementation on the number of participants requiring an RBC transfusion (RR 0.91, 95% CI 0.80 to 1.04, $p = 0.15$, $I^2 = 22\%$) (Fig. 1). Subgroup analysis by route of administration showed no evidence of a difference in the effect of iron therapy by either intravenous or oral routes (Fig. 2). The TSA adjusted CI was 0.69 to 1.20 with available data showing that only 27% of the required IS to detect or reject a RRR of 12% has been reached (Fig. 3). In TSA adjusted for the two trials with overall low risk of bias, the TSA adjusted CI was 0.76 to 1.09 with the available data showing that only 60% of the required IS had been reached (Supplemental digital content, Fig. S3). The GRADE quality was judged to be *low* (Table 2).

Three trials reported the mean number of RBC units received per participant in both groups [15,26,29]. After transforming to a log scale, meta-analysis of these three trials showed no evidence that iron supplementation reduced the mean number of allogeneic RBC units transfused (MD -0.30, 95% CI -0.68 to 0.07, $p = 0.15$, $I^2 = 60\%$) (Fig. 1). The GRADE quality was judged to be *low* (Table 2).

Mean (SD) differences in Hb concentration were reported at short-term follow-up in three trials [26,27,30] and at mid-term follow-up in four trials [15,26,27,29] (Fig. 1). Mean Hb at medium-term follow-up was higher in participants that received iron (MD 0.31 g/dL, 95% CI to 0.04 to 0.59, $p = 0.03$, $I^2 = 0\%$) (*moderate* quality of evidence). There was no significant difference in the mean Hb concentration between both groups at short-term follow-up (MD −0.25 g/dL, 95% CI -0.79 to 0.28, $p = 0.35$, $I^2 = 57\%$) (*very low* quality of evidence) (Fig. 1).

3.5. Secondary outcomes

Five trials reported in-hospital mortality [15,27-30]. There was no evidence of an effect of iron supplementation on mortality (RR 1.09, 95% CI 0.60 to 1.98, $p = 0.77$, $I^2 = 34\%$) (Fig. 4). Causes of death were not reported in any trial. Three trials reported on infection with varying definitions [15,28,29]. In meta-analysis, there was no evidence of a difference in the risk of infection in participants who received iron compared to those who did not (RR 0.95, 95% CI 0.79 to 1.19, $p = 0.44$, $I^2 = 27\%$) (Fig. 4). The TSA adjusted CI was 0.39 to 2.33 with the cumulative *Z*-curve showing that only 12% of the required IS for to detect or reject a RRI of 17% had been reached (Supplemental digital content, Fig. S4). The GRADE quality was judged to be *low*. Trials that reported antibiotic use did not find a significant difference in mean number of antibiotic days between the intervention and control groups (14 vs. 16 days, $p = 0.45$ [28]; 14 vs. 16 days, $p = 0.64$ [29]).

Three trials reported ICU and hospital LOS [15,28,29] whereas one only reported ICU LOS [30]. We did not perform meta-analysis as LOS is often reported as median (with interquartile range) due to non-parametric distribution. One trial did however report mean (SD) data and found a significantly longer ICU LOS in the control group compared to the intervention group (58 (31) vs. 29 (18) days, $p < 0.05$) [30]. Of the remaining three trials, there was no difference in median ICU LOS (6 vs. 6 days, $p = 0.70$ [15]; 14 vs. 16 days, $p = 0.69$ [28], 10 vs. 11 days, $p = 0.53$ [29]) and in median hospital LOS (15 vs. 18 days, $p = 0.75$ [15]; 14 vs. 16 days, $p = 0.24$ [28]; 14 vs. 16 days, $p = 0.50$ [29]). Only one trial reported on median ICU organ failure support-free days [15] and found no difference between the intervention and control group (2 vs. 2 days, $p = 0.89$). No trials reported on health related quality of life.

One trial reported serious adverse events (SAE) and found no difference between the intravenous iron (pulmonary embolus (PE) = 2, deep vein thrombosis (DVT) = 2) and placebo (PE = 3, DVT = 1) (RR 1.0, 95% CI 0.26 to 3.84, $p = 1.0$) groups [15]. One trial of oral iron versus oral placebo found no differences in adverse events between groups (12.4% vs. 8.7%, $p = 0.62$) [28]. Adverse events in this trial were gastrointestinal side effects. Sensitivity analyses for risk of bias were intended but were not carried out due to the limited number of included studies.

4. Discussion

4.1. Key findings

Our updated systematic review identified one additional RCT, which was incorporated into the meta-analyses. The main findings from this systematic review are: First, we found no evidence of an effect of iron on transfusion requirements, mortality or risk of infection in ICU patients. Secondly, the route of iron administration, in particular i.v., did

Table 1
Characteristics of the included studies.

Study	Garrido-Martin et al. [26]		Madi-Jebara et al. [27]		Pierraci et al. [28]		Pierraci et al. [29]		van Iperen et al. [30]		Litton et al. [15]	
	Iron	No iron	Iron	No iron	Iron	No iron	Iron	No iron	Iron	No iron	Iron	No iron
No. randomized	IV 71, Oral 73	66	40	40	97	103	75	76	12	12	70	70
No. analysed	IV 54, Oral 53	52	40	40	97	103	75	75	12	12	70	70
Age (mean, SD/range)	IV 65 (11) Oral 65 (10)	65 (12)	59.1 (9.1)	55.3 (9.5)	55.7 (1.9)	58.2 (1.7)	41.6 (18–83)	40.4 (18–87)	67 (49–89)	69 (45–80)	58.5 (18.8)	56.0 (21.1)
Male %	IV 70.3% Oral 71.7%	76.9%	90%	90%	50.5%	46.6%	77.3%	60.5%	66.6%	66.6%	63%	74%
ICU setting	Cardiothoracic		Cardiothoracic		General surgical, burns, neurosurgical		Trauma		Mixed (surgical, medical, neurological, trauma)		Mixed (general surgical, cardiothoracic, neurosurgical, medical, trauma)	
Number of centers	One		One		One		Four		One		Four	
Inclusion criteria	>18 years old, elective cardiac surgery under extracorporeal circulation, no previous anaemia, susceptible to treatment, no preoperative blood transfusion, able to complete all study visits are per protocol, able to provide written consent.		Elective cardiac surgery with CPB, Post-pump Hb 7–10 g/dL.		General surgical, burn, neurosurgical ICUs, Age > 18 years, Hb < 13 g/dL prior to enrollment, <72 h from hospital admission, current tolerance of enteral medication, expected ICU LOS > 5 days.		Admitted to ICU with trauma, Hb < 12 g/dL, Age > 18 years, <72 h from ICU admission, expected ICU LOS > 5 days.		Hb < 11.2 g/dL, <12.1 g/dL if cardiac disease, age > 18 years, expected ICU LOS > 7 days, informed consent from patient or relative.		Admitted to an ICU for <48 h, Anticipated to require ICU care beyond the next calendar day, Hb <100 g/L at any time during the preceding 24 h, age 18 years or greater	
Exclusion criteria	Elective cardiac surgery without exclusion criteria, fibrinolytic therapy 48 h prior to CPB, impaired renal function (CrCl<50 mls.min^{-1}), previous surgery for IE, re-do surgery, pregnant or lactating, active gastrointestinal bleeding, B12 deficit, ferropenic anaemia, asthma or allergy, active infection, included in another study, hepatic disease, history of allergy to iron, unlikely to adhere to protocol follow-up.		Intra-operative blood transfusion, post-operative hemodynamic instability, ejection fraction <40%, chronic kidney disease, hypothermic bypass, hypersensitivity to iron.		Active bleeding, chronic inflammatory conditions, end-stage renal disease, hematologic disorders, macrocytic anaemia, current use of EPO, pregnancy, prohibition of RBC transfusion, imminent death, co-enrollment in another trial.		Active hemorrhage, iron overload (serum ferritin>1000 ng.mL^{-1}), conditions associated with iron overload e.g. haemachromatosis, active infection, chronic inflammatory conditions, pre-existing haematological disorders, macrocytic anaemia, current/recent (within 30 days) use of immunosuppression, use of EPO within 30 days, pregnancy or lactation, prohibition of RBCs, imminent death, history of allergy to iron.		Pregnancy, iron deficiency anaemia (ferritin<50 μg.L^{-1}), vitamin B12 deficiency (<160 pmol.L^{-1}), recent use of cytostatics or recent radiotherapy, life expectancy <7 days, chronic renal failure, prior use of EPO.		Suspected or confirmed sepsis, serum ferritin >1200 ng/mL or Tsat >50%, history of haemochromatosis, known administration if IV iron in the preceding 3 months, Jehovah's witness or other documented exclusion to receiving blood products, receiving ESA in the 3 months prior to ICU admission, known hypersensitivity to intravenous iron, pregnancy, palliative treatment intent, death is deemed imminent and inevitable, weight <40 kg, participant in competing study	
Intervention(s)	i) IV iron-hydroxide sucrose complex (Venofer; Uriach Lab) 3 doses of 100 mg/24 h during pre- and post-hospitalization, and 1 pill/24 h of oral placebo during the same period and during 1 month after discharge. ii) Ferrous fumarate (105 mg of iron) 1 pill/24 h orally pre- and postoperatively and during 1 month after discharge, and intravenous placebo while hospitalised.		i) IV iron (Venofer; Luitpold Pharmaceuticals) 200 mg/day to reach total iron deficit + s/c placebo [a]		Enteral ferrous sulphate 325 mg (oral solution or capsule) (Rockwell Compounding Inc.) thrice daily until hospital discharge. Co-intervention: Ascorbic acid 500 mg thrice daily, Cyanocobalamin 1 mg, Folic acid 1 mg.		IV Iron sucrose (Venofer; Luitpold Pharmaceuticals) 100 mg thrice weekly for up to 6 doses or until ICU discharge.		IV iron saccharate (Venofer; Vifor) 20 mg and IV folic acid 1 mg daily from D1–14 [b] Co-intervention: Folic acid 1 mg daily		IV iron (ferric carboxymaltose) 500 mg. Assessed for repeat dosing after 4 days if still in ICU and fulfilling all other eligibility criteria.	
Comparator	Oral and intravenous placebo pre- and postoperatively following same protocol.		Placebo – s/c and i.v. (0.9% Saline).		Oral placebo, same schedule as intervention protocol. Co-intervention: Ascorbic acid 500 mg thrice daily, Cyanocobalamin 1 mg, Folic acid 1 mg.		IV placebo (100 mls of 0.9% saline) similar dosing schedule to intervention.		No iron Co-intervention: Folic acid 1 mg daily.		IV placebo (100mls of 0.9% saline) similar dosing schedule to intervention	

(continued on next page)

Table 1 (*continued*)

Study	Garrido-Martin et al. [26]		Madi-Jebara et al. [27]		Pierraci et al. [28]		Pierraci et al. [29]		van Iperen et al. [30]		Litton et al. [15]	
	Iron	No iron	Iron	No iron	Iron	No iron	Iron	No iron	Iron	No iron	Iron	No iron
Reported outcomes (follow-up time points, days)	• Hb concentration (Baseline, operating room entry (D7), exit operating room, ICU admission, ICU discharge, postoperative D10 and D30 post-hospital hospital discharge) • Immature reticulocyte fraction, reticulocyte count, serum ferritin (D1, postoperative D10 and D30 post-hospital discharge) • RBC transfusion (no. patients transfused, location of transfusion, mean number of units)		• Hb concentration (D0, D1–5, D15, D30) • Reticulocyte counts (D1, D5, D15, D30) • Serum ferritin (D0, D5, D15) • RBC transfusion • Mortality		• Difference in Hct (Baseline, D7, D14, D21, D28) (primary outcome) • Serum iron, serum ferritin, eZPP (Baseline, D7, D14, D21, D28) • RBC transfusion • Estimated blood loss per study day • Nosocomial infection • Antibiotic days • Adverse outcomes – gastrointestinal upset • ICU & Hospital LOS • Mortality	• Number of total doses of study drug received • Hb concentration (daily) • Serum iron, serum ferritin, serum Tsat, eZPP (Baseline, D7, D14) • RBC transfusions • Transfusion-free days • Nosocomial infection & type • Antibiotic exposure • ICU & Hospital LOS • Mortality	• Hb concentration (D0, D7, D14, D21) • Reticulocyte count, sTfR (D0, D7, D14, D21) • Serum EPO (D0, D2, D6, D10, D21) • Serum iron, transferrin, Tsat, ferritin, eZPP, CRP (D0, D10, D21) • Mean blood loss (D0-D21) • RBC transfusion (mean number of units) (D0-D21) • ICU LOS • Mortality		• RBC transfusion (mean number of units) (Randomisation to hospital discharge) • Hb at hospital discharge • Proportion of patients receiving RBC transfusion • ICU and hospital LOS • Nosocomial infection • Mortality	

ICU = intensive care unit; Hb = haemoglobin; Hct = Haematocrit; Tsat = transferrin saturation; sTfR = soluble transferrin receptor; eZPP = erythrocyte zinc protoporphyrin; LOS = length of stay; CBP = cardiopulmonary bypass; RBC = red blood cell; EPO = erythropoietin; CrCl = creatinine clearance; IE = Infective endocarditis

[a] In a second intervention arm, patients received intravenous iron and recombinant-human EPO(300 IU/kg) subcutaneously on day 1; this treatment arm was not included in this review because the co-intervention was not matched in the control group.

[b] In a second intervention arm, patients received intravenous iron and EPO alfa (300 IU/kg) subcutaneously on days 1,3,5,7,9; this treatment arm was not included in this review because the co-intervention was not matched in the control group.

not appear to influence the risk of requiring a blood transfusion. Thirdly, iron therapy, when given to acute, critically ill patients results in a modest improvement in Hb at longer follow-up time points.

Although the point estimate for our outcome of transfusion requirements favoured iron therapy, the difference was not statistically significant. A plausible reason for the early ineffectiveness of iron could be because the erythropoietic response is blunted due to high levels of inflammation associated with the acute phase of critical illness. Pro-inflammatory cytokines such as interleukin-6 (IL-6) have been shown to inhibit the EPO gene which could potentially explain the inappropriately low circulating EPO levels observed in critically ill patients [32-34]. Furthermore, hepcidin – the key hormonal regulator of iron status, is upregulated by IL-6 which subsequently inhibits iron mobilization through internalization of ferroportin, a key iron export protein [35]. As a result iron is trapped within macrophages thereby limiting its availability for erythropoiesis. This contributes to states of FID and/or iron sequestration often observed in patients with anaemia and co-existing inflammation. Hepcidin also blocks absorption of iron from the gastrointestinal tract, which may explain the ineffectiveness of oral iron in treating such patients [35,36].

In contrast, i.v. iron can bypass this 'hepcidin block' [37] and therefore has been proposed as a safe and *effective* treatment option in perioperative patients with anaemia and co-existing inflammation [9]. However, our subgroup analysis by route of administration found no evidence of an effect of i.v. iron on reducing risk of RBC transfusion. This is in agreement with the findings of a recent systematic review of postoperative iron following elective surgery that also found that i.v. iron did not decrease the risk of RBC transfusion [38]. Although we did not specifically seek out to investigate surgical patients, the majority of the included participants in our systematic review were from surgical ICUs. In the most recent IRONMAN trial, the iron profile of participants randomized to the intervention group was characterised by iron sequestration with a mean (SD) ferritin of 317 (218) ng ml^{-1}, mean (SD) TSAT of 13 (10)% and mean (SD) CRP of 111(83) mg l^{-1} [15]. This was similar to the iron profiles of post-operative surgical participants from a recent large RCT of post-operative intravenous iron in patients undergoing major elective surgery [39]. Therefore, our findings could, in part, be externally generalizable to perioperative surgical patients with anaemia and co-existing inflammation.

Our TSA findings suggest that the required sample size to definitively answer the question of 'does iron reduce transfusion requirements in ICU patients?' has not been met. The authors of the IRONMAN trial, in the supplementary material, provided a power calculation suggesting that 1572 participants would be required to detect a 0.5 unit decrease in RBC transfusion requirements [15]. Putting it all together, until high-quality, adequately powered studies are carried out we suggest caution in using iron therapy, by any route, in anaemic ICU patients and perhaps even perioperative patients with co-existing inflammation.

We found that the use of iron is associated with an increase in Hb at longer follow-up periods. Unfortunately, the data do not allow for the potentially important (and beneficial) clinical consequences of a rise in Hb to be addressed. Persistence of anaemia beyond ICU discharge and its possible association with long-term morbidity is now increasingly being recognized [40,41,42]. This is important, because any therapeutic effect for iron, in particular i.v. iron preparations, may not occur for 2–4 weeks and efficacy may therefore be missed in studies focusing on short-term outcomes. Recent work has shown that hepcidin levels are markedly increased on ICU admission but decrease significantly over time and that this reduction is associated with resolution of inflammation as defined by decreased IL-6 and CRP concentrations [43]. Therefore, it is biologically attractive to consider administered iron during the latter/recovery phases of critical illness, when inflammation and hepcidin levels are regressing, and therefore the response to iron may even be larger. Stratifying patients according to hepcidin levels to guide iron therapy has shown promise in other clinical settings

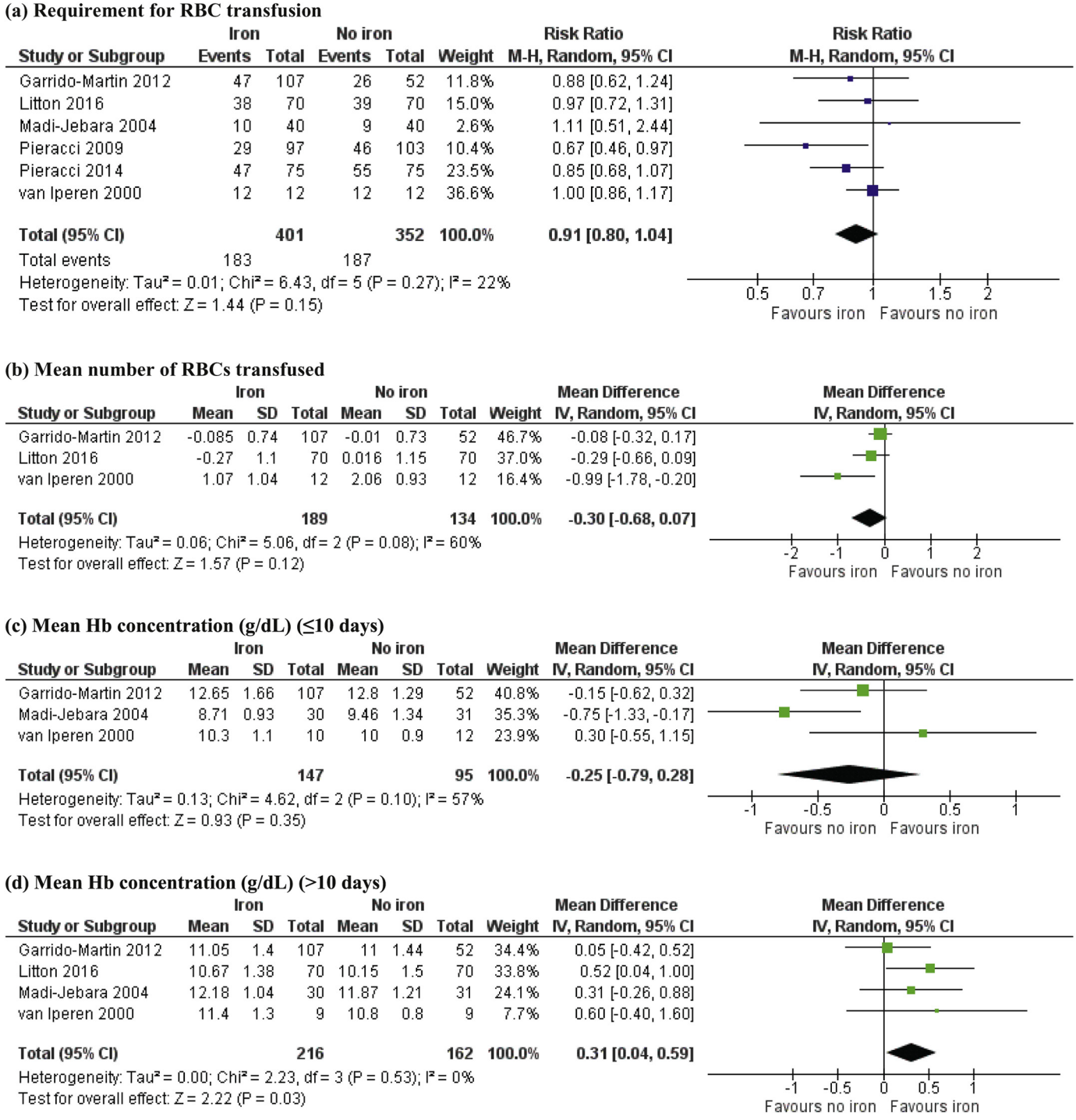

Fig. 1. Forest plots of the effect of iron supplementation, by any route, on co-primary outcomes. RBC = red blood cell, Hb = hemoglobin, CI = confidence interval, M-H = Mantel-Haenszel, IV = Inverse Variance.

[44,45]. Outside the critical care setting, improvements in Hb have translated into meaningful improvements fatigue and overall well-being [46]. No studies in this systematic review provided data on functional outcomes or on fatigue – a cardinal symptom of anaemia and one which is increasingly becoming recognized as being the most distressing to ICU survivors [47], but one study is currently ongoing [31].

The risk of infection associated with iron therapy remains a potential concern amongst clinicians. I.v. iron administration can lead to increased levels of circulating free iron, which has been associated with impaired T-cell and neutrophil function and promotion of pathogen growth in in vitro and in vivo studies involving animals and humans [48]. Recent work in an animal model of bacterial pneumonia demonstrated worsening of shock, lung injury and mortality following administration of i.v. iron [49]. One systematic review reported a significantly increased risk of infection (RR 1.34, 95% CI 1.10 to 1.64; 24 RCTs, 4400 participants) when intravenous iron was compared to oral iron or no iron [6]. A more recent systematic review which pooled data from 32 RCTs showed a point estimate which again favoured infection, although this was statistically non-significant (RR 1.17; 95% CI 0.83 to 1.65) [7]. We found no evidence of an increased risk of infection but, this should be interpreted with caution due to small sample sizes of included studies, and infection not being a predefined or consistently collected using

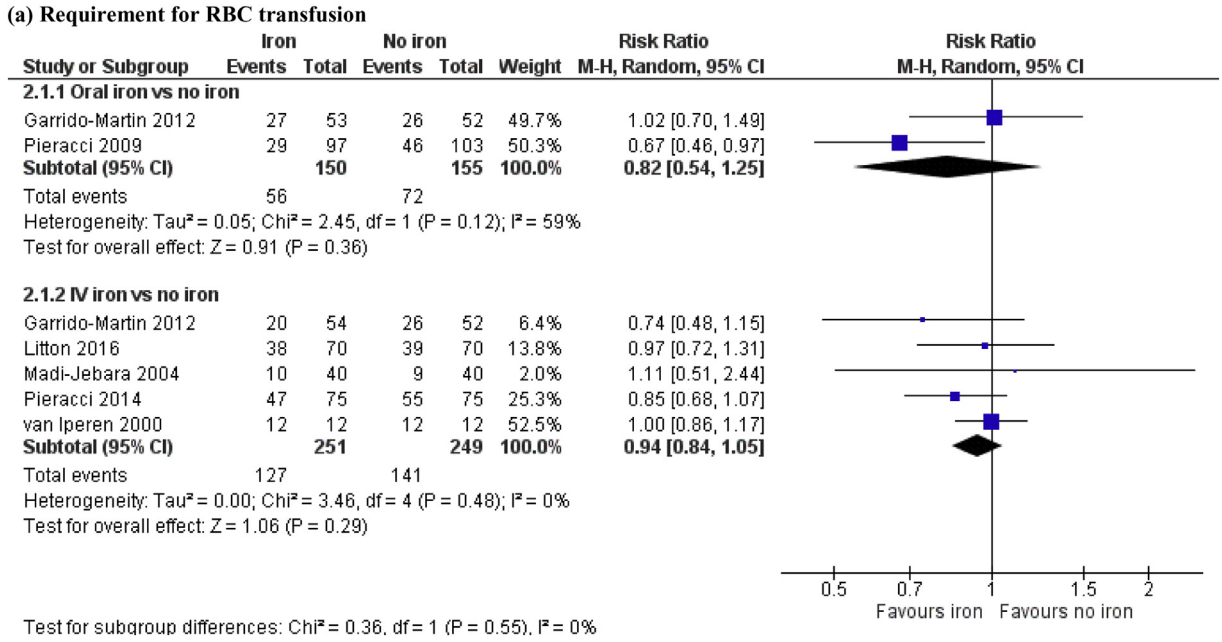

Fig. 2. Subgroup analysis: Forest plots of the effect of iron supplementation by either intravenous or oral iron administration on red blood cell transfusion requirement. RBC = red blood cell, Hb = hemoglobin, CI = confidence interval, M-H = Mantel-Haenszel, IV = Inverse Variance.

standardized definitions [50], Our TSA findings suggested a projected sample size of approximately 8 times the number participants included in this review was required to answer this question definitively.

4.2. Strengths and limitations

The strength of the review is the strict methodological process; we followed Cochrane Collaboration and PRISMA recommendations, performed a comprehensive search and carried out duplicate data extraction and risk of bias assessments. Compared to the previous review, we used TSA to increase the reliability of our meta-analysis and provide required sample sizes A potential caveat to this would be our estimation of a 30% baseline risk of developing infection. This was based on a study published 12 years ago and it is reasonable to assume that this risk will have reduced over time. A reduction in the baseline risk, assuming a 17% RRI remains clinically relevant, would influence the sample sizes calculated. We also performed GRADE evaluations on the quality of evidence for important efficacy and safety outcomes. The limitations to the conclusions of this systematic review can be attributed to the clinical and methodological differences between the trials. Outcomes and follow-up time points for certain outcomes e.g. haemoglobin measurements, were not standardized across trials

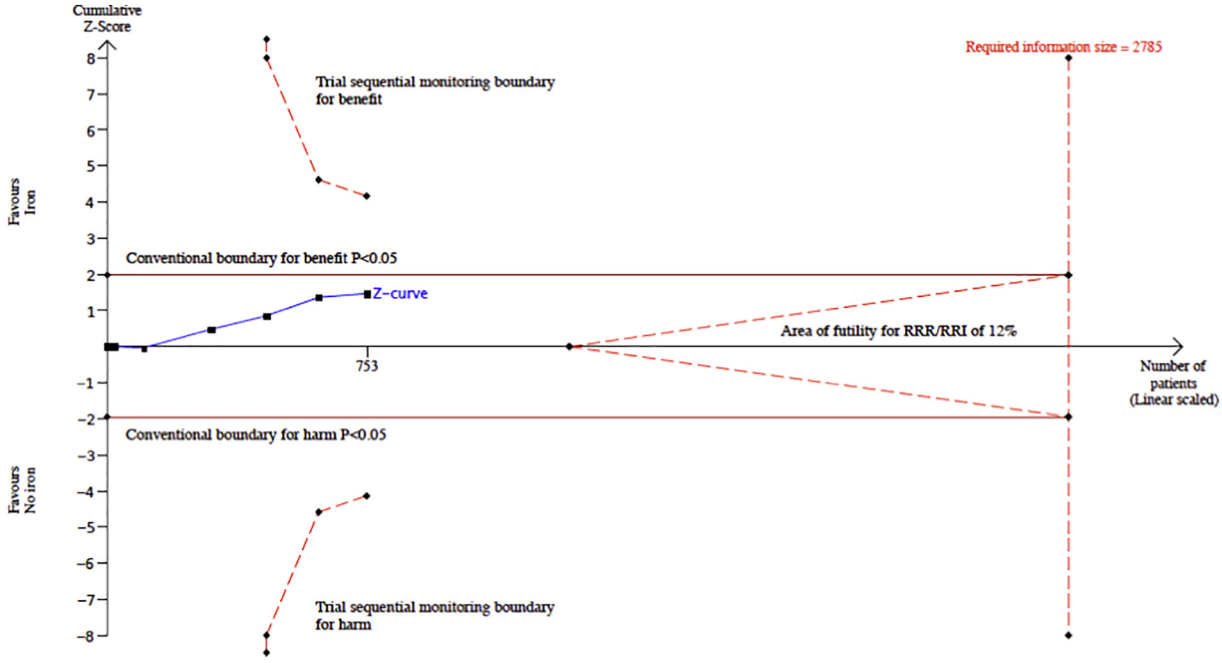

Fig. 3. Trial sequential analysis (TSA) of all trials of the effect of iron (by any route) on requiring a blood transfusion. Control event proportion of 50%, diversity (D^2) of 35%, alpha of 5%, power of 80% and relative risk reduction (RRR) of 12%. The relative risk (RR) was 0.91 with a naïve 95% CI 0.80 to 1.04 in a random-effect model and TSA-adjusted CI 0.69 to 1.20. As the cumulative Z-curve has not reached the futility area or the required information size (IS), we are unable to exclude a RRR of 12%.

Table 2
Summary of findings including GRADE quality assessment of evidence.

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no iron	With Iron (by any route)		Risk with no iron	Risk difference with Iron (by any route)
Blood transfusion 753 (6 RCTs)	serious [a]	not serious	not serious	serious [b]	none	⊕⊕◯◯ Low	187/352 (53.1%)	183/401 (45.6%)	RR 0.91 (0.80 to 1.04)	531 per 1000	48 fewer per 1000 (106 fewer to 21 more)
Mean number of RBC units received 323 (3 RCTs)	serious [c]	not serious	not serious	serious [b]	none	⊕⊕◯◯ Low	134	189	–	The mean number of RBC units received ranged from −0.01 to 2.06 mean (log no. of RBC units)	MD 0.3 mean (log no. of RBC units) lower (0.67 lower to 0.08 higher)
Mean Hb (g/dL) at short-term follow-up 242 (3 RCTs)	serious [c]	serious [d]	not serious	serious [b]	none	⊕◯◯◯ Very low	95	147	–	The mean Hb (g/dL) at short-term follow-up ranged from 9.46–12.8 g/dL	MD 0.25 g/dL lower (0.79 lower to 0.28 higher)
Mean Hb (g/dL) at mid-term follow-up 378 (4 RCTs)	serious [c]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	162	216	–	The mean Hb (g/dL) at mid-term follow-up ranged from 10.15–11.87 g/dL	MD 0.31 g/dL higher (0.04 higher to 0.59 higher)
In-hospital infection 487 (3 RCTs)	not serious	not serious	serious [e]	serious [d]	none	⊕⊕◯◯ Low	116/245 (47.3%)	111/242 (45.9%)	RR 0.95 (0.76 to 1.19)	473 per 1000	24 fewer per 1000 (114 fewer to 90 more)

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference; **RBC:** Red blood cell; **Hb**: Haemoglobin; **RCT**: Randomized controlled trial.
[a] Downgraded one level as 3 studies were at high risk of incomplete reporting.
[b] Rated down for imprecision as optimal information size not reached.
[c] Downgraded one level was 1 study was at high risk of reporting bias and 1 study was at unclear risk across multiple domains.
[d] Downgrade by one level due to wide variation in confidence intervals.
[e] Downgraded by one due to differences in outcome reporting.

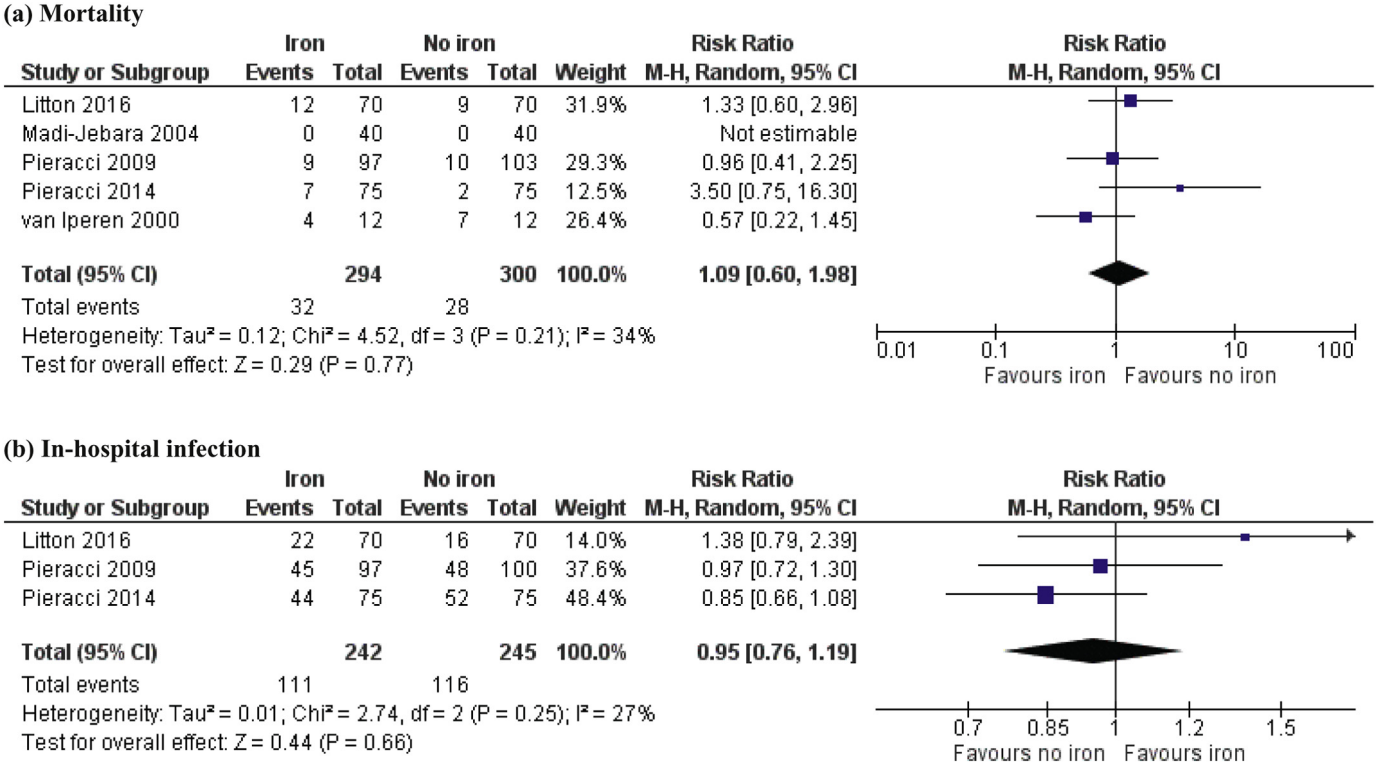

Fig. 4. Forest plots of the effect of iron supplementation, by any route, on secondary outcomes. RBC = red blood cell, Hb = hemoglobin, CI = confidence interval, M-H = Mantel-Haenszel, IV = Inverse Variance.

thereby limiting our meta-analysis. Our a priori anticipated intervention effects could be considered as being too conservative and therefore lead to larger than required information sizes – a recognized limitation of TSA [21].

5. Conclusion

The potential impact on iron therapy on transfusion requirements and the risk of infection remains inconclusive. The finding of an improvement in Hb at follow-up periods of >10 days warrants further research, as there may be clinical benefits of improved functional recovery in a cohort that have a substantial burden of poor quality of life after intensive care. The overall quality of evidence ranged from very low to moderate. Any further trials should be adequately powered to patient centered outcomes with adequate long-term follow-up and safety end points (e.g. infection), focus on the timing and route of iron administration and attempt to identify patients likely to mount an erythropoietic response to iron.

Statement of contribution

A.S, S.F. and S.J.S contributed substantially to study design, data analysis and interpretation. C.D carried out the searches. A.S. and H.W. performed data extraction for this review. A.S and S.F. carried out the data analysis and interpretation. A.S. drafted the manuscript and S.F., H.W., N.B.R., S.M., E.L., and S.J.S. revised it critically. All authors have read and approved the final version of the manuscript.

Conflict of interest

This report is independent research supported by the National Institute for Health Research (NIHR Doctoral Research Fellowship, Dr. Akshay Shah, DRF-2017-10-094). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research of the Department of Health.

On behalf of all other authors, the corresponding author states that there is no conflict of interest.

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Ethics

No ethical approval required.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2018.11.005.

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