BMJ Open

Risk of infection associated with intravenous iron preparations: a protocol for updating a systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-024618
Article Type:	Protocol
Date Submitted by the Author:	05-Jun-2018
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Keywords:	Systematic review, Intravenous Iron, Infection, Mortality, Meta-analysis

Risk of infection associated with intravenous iron preparations: a protocol for updating a systematic review

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Total word count: 2086 (including Abstract)

Key words: Intravenous Iron; Infection; Mortality; Systematic review; Meta-analysis

ABSTRACT

Introduction

The benefits and risk of intravenous iron have been documented in previous systematic reviews and continue to be the subject of randomised controlled trials (RCTs). An ongoing issue that continues to be raised is the relationship between administering iron and developing infection. This is supported by biological plausibility from animal models. We propose an update of a previously published systematic review and meta-analysis with the primary focus being infection.

Methods and analysis

We will include randomised controlled trials (RCTs) and non-randomised studies (NRS) in this review update. We will search the relevant electronic databases. Two reviewers will independently extract data. Risk of bias for RCTs and NRS will be assessed using the relevant tools recommended by The Cochrane Collaboration. Data extracted from RCTs and NRS will be analysed and reported separately. Pooled data from RCTs will be analysed using a random effects model. We will also conduct subgroup analyses to identify any patient populations that may be at increased risk of developing infection. We will provide a narrative synthesis on the definitions, sources, and responsible pathogens for infection in the included studies. Overall quality of evidence on the safety outcomes of mortality and infection will be assessed using the GRADE approach.

Ethics and dissemination

This systematic review will only investigate published studies and therefore ethical approval is not required. The results will be broadly distributed through conference presentations and peer-reviewed publications.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Systematic review protocol primarily focusing on a safety outcome (risk of infection) with intravenous preparations.
- Comprehensive review that will include data from randomized controlled trials and non-randomised studies.
- Infection is not often a predefined endpoint in published studies and definitions of infection will vary across studies.
- There will be considerable heterogeneity in participant populations, doses and types of intravenous iron used and follow-up time points

INTRODUCTION

Treating anaemia is a key pillar of Patient Blood Management and a recent James Lind prioritisation exercise ranked the timely identification of anaemia and treatment as a Top 10 priority for research into blood transfusion and blood donation. Systematic reviews have shown the efficacy of intravenous iron with regards to treating anaemia and reducing blood transfusion requirements (1, 2), although with varying degrees of effect size and the primary outcomes in majority of trials were haematological (change in haemoglobin concentration, transfusion requirements) instead of clinical outcomes (eg Quality of Life (QoL).

Despite the widespread use of intravenous iron (1, 2), uncertainty persists as to whether intravenous iron is associated with an increased risk of infection. The uncertain relationship between iron and infection has long been pustulated and remains atopic of interest in on-going trials of oral iron, for example in the setting of malaria and other tropical infections in low-resource country settings (REF). Iron is essential for extracellular pathogens as it an ideal redox catalyst for important cellular processes such as respiration and DNA replication (3). Humans are able to withhold free (non-transferrin-bound) iron from invading pathogens through a process termed nutritional immunity in an effort to limit infection (3, 4). Intravenous iron administration can lead to increased levels of circulating free iron, which can be detrimental to the host and promote pathogen growth. Such an interaction is supported by biological plausibility in recent animal models where administration of intravenous iron worsening shock, lung injury and mortality (5).

Litton et al (2) have previously performed a systematic review investigating the efficacy and safety of intravenous iron therapy. This review identified 72randomized controlled trials (RCTs) that included 10,605 participants. The authors reported a reduced risk of requirement for red blood cell (RBC) transfusion (Risk Ratio (RR) 0.74, 95% CI 0.62 to 0.88; 22 RCTs, 3321 participants). Of note, this potential benefit was counterbalanced 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. 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) ((6). Interpreting data on infection from these meta-analyses is challenging because infection is not always defined as a pre-specified, standardised outcome measure in RCTs but rather reported as safety outcome. A recent editorial highlighted the need for an adequately powered trial of intravenous iron with infection as a primary outcome (4).

Given the on-going uncertainty regarding the risk of infection, the primary objective of this systematic review update of the review by Litton et al. (2) is to identify and incorporate more recent trial data to evaluate the safety data for intravenous iron on the risk of infection across all clinical settings. A better understanding of the characterization of infection in patients receiving iron therapy will help inform the design of subsequent trials in particular groups of patients (e.g. critically ill, emergency surgery) in whom the risk of infection is of clinical concern. Our secondary objective is to continue to collect efficacy data to focusing primarily on changes in haemoglobin concentration, transfusion requirements and functional outcomes.

METHODS

We used the PRISMA-P reporting guidelines(7). Studies will be selected according to the criteria outlined below. The study protocol has been registered on PROSPERO (CRD42018096023)

Eligibility criteria

We will include randomized controlled trials (RCTs) from 1st January 2013 onwards as the last search date for the previous review was June 2013 (2). We will also include non-randomized studies (NRS) in this updated review as infection may not always be reported in RCTs and the findings of infection outcomes reported in NRS may be useful to inform the design of a future RCT. We will only include NRS that meet the following criteria:

- Published since 1st January 2007 as this is the year from which newer intravenous iron preparations (Ferinject®, Monofer®, Venofer®) received and/or renewed their marketing authorization. Therefore any data extracted is likely to be reflective of current practice.
- At least two comparable groups [including controlled before-and-after, and prospective/retrospective cohort studies].
- Quasi-RCTs
- Provide data on our primary outcome of infection

We will exclude any studies that provide no outcome data of interest, NRS published before 1st January 2007 and NRS that do not have an intravenous iron comparison arm. We will include studies examining all participant populations (including paediatrics, pregnancy) but excluding healthy volunteers. Included studies would compare intravenous iron to no iron/placebo or oral iron.

Our primary outcome of interest is the number of patients who develop an infection as defined by the study authors. Secondary safety and efficacy outcomes include:

- Mortality – short-term (≤30 days), long-term (>30 days)
- Hospital length of stay
- Change in haemoglobin concentration from baseline/pre-treatment levels to end of study period
- Transfusion requirements during study period (% transfused, mean number of RBC units transfused)

Information sources and Search strategy

We will search the following databases for RCTs (from 1st January 2013), systematic reviews and NRS (from 1st January 2007) – Cochrane Central Register for Controlled Trials; MEDLINE (Ovid interface); Ovid Interface; CINAHL; Transfusion Evidence Library; Web of Science Conference Proceedings Citation Index-Science. This will be supplemented by searching ongoing trial databases such as ClinicalTrials.gov and WHO International Clinical Trials Search Registry Platform. Citation lists of included studies and relevant reviews

will also be scanned to identify any studies missed by the search. A draft MEDLINE search strategy is included in Appendix 1.

Study selection

Literature search results will be uploaded to Covidence, a web-based software platform, to facilitate citation screening between reviewers. Review authors will independently screen the titles and abstracts yielded by the search against the prespecified inclusion criteria. Two review authors will then independently screen the full text reports and decide whether these meet the inclusion criteria. Disagreements will be resolved through discussion, and if necessary, referred to a third reviewer. The study selection process will be reported in a PRISMA flow diagram.

Data extraction

For RCTs, two reviewers will use the data extraction form used for the original review to extract data independently. We will standardize and pilot a data extraction form for NRS and items for extraction from NRS will include:

- Data on confounding factors
- Comparability of groups based on consideration of confounding factors
- Methods used to control for confounding
- Effect estimates – both adjusted and unadjusted if available

For both sets of studies we will extract the following additional data, if reported, on the outcome of infection:

- Definition of infection used (i.e. guideline based, laboratory based, clinical discretion)
- Site of infection (e.g. lung, wound, gastrointestinal)
- Reporting of identified pathogens
- Antibiotic usage

Disagreements will be resolved through discussion, and if necessary, referred to a third reviewer. We will contact study authors to resolve any uncertainties.

Risk of bias assessment

Risk of bias for the RCTs will be reported using the Cochrane Risk of Bias tool (8). For the non-RCT data, risk of bias will be reported using the ROBINS-I developed by the Cochrane Bias Methods Group (9). Two reviewers will make these judgements independently.

Data synthesis

Data from RCTs and NRS will be analysed and reported separately.

RCTs

The primary end-point will be the proportion of participants who developed an infection. Dichotomous outcomes (infection, mortality, requirement for blood transfusion) will be reported as risk ratios with corresponding 95% Confidence Intervals (CI). Continuous outcomes will be reported as weighted mean (with 95% CI) or standardized mean differences (95% CI) as appropriate. For continuous measures, the mean difference in change from baseline values between groups will be used preferentially; if change from baseline values are not reported then the mean difference in measures at follow up will be used. The unit of analysis will be per individual randomized. Data from included studies will be pooled for meta-analysis using a random effects model. Statistical heterogeneity will be tested using the I^2 statistic and I^2>50% will be considered as substantial heterogeneity. If substantial heterogeneity is present among the trials, the study characteristics of the included studies will be analysed and we will attempt to explain the heterogeneity by subgroup analysis or sensitivity analysis. If sufficient data is available we will undertake meta-regression to examine the effect of intravenous iron dose and baseline iron status on the association between intravenous iron and infection. Statistical analysis will be conducted on RevMan 5.1. and STATA (Version 14, StataCorp LP, College Station, TX, USA).

NRS

For NRS, we will only report results descriptively on the primary outcome of infection instead of pooling results due to heterogeneity in clinical conditions, study designs and variations in statistical adjustment. If possible, results will be displayed in a forest plot, with studies sorted according to study design features, and the pooled estimate will be suppressed as recommended by the Cochrane Collaboration (6).

Analysis of subgroups

Subgroup analysis of the primary safety outcome (infection) will be performed on the following clinical settings:

- In-patient medical (any)
- Outpatient (any)
- Elective surgical
- Non-elective (urgent/emergency) surgical
- Obstetrics
- Paediatrics
- Critically ill

We will carry out a sensitivity analysis on infection and mortality outcomes by excluding studies with a high risk of bias. We will assess for publication bias on the primary outcome with a funnel plot if ≥10 studies are available, plotting the odds ratio for proportion that develop infection against the standard error of the log odds ratio.

A systematic narrative synthesis will be provided with information presented in the text and tables to summarise data on infection provided in the include studies. This narrative synthesis will explore the definitions of infection used, reporting of infection source and pathogens and antibiotic use.

Confidence in cumulative evidence

According to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, we will assess the overall quality of evidence for the main safety outcomes of infection and mortality (10). In line with current GRADE guidance, if the certainty of evidence differs between RCTs and NRS, we will present Summary of Findings (SoF) tables for the higher certainty of evidence. If the certainty ratings are the same, results from both bodies will be presented separately (11).

DISCUSSION

Recent patient blood management efforts have attempted to reduce blood transfusion by using alternative therapies such as intravenous iron. Safety concerns surrounding older preparations, mainly anaphylaxis, have been allayed by the development of newer, stable preparations which has led to intravenous iron being used more frequently in multiple settings (12). Despite its widespread use, concerns surrounding infection remain both from systematic reviews and animal models.

Our review will provide an up to date and comprehensive estimate of the risk of infection associated with intravenous iron preparations across multiple patient groups. In addition, we will also provide on the characterization of infection as step towards standardizing infection as an outcome measure for future trials of intravenous iron.

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Author statement: AAS, AS, SJS and EL conceived the idea for the review update. AS prepared the initial protocol draft with input from SB and SJS and contributed to the revision of the manuscript. CD will perform the search and AS, JR, AJP, and ED will screen and extract data. All listed authors contributed to the development of the idea and drafting and revision of the manuscript.

Funding: AAS is funded by an NIHR Doctoral Research Fellowship (DRF-2017-10-094). This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflicts of interest: RB has received educational grants / honorarium from Pharmacosmos UK and Vifor Pharma. AGA's research department has received grant support from Syner-Med, UK, Pharmacosmos, Denmark and Vifor Pharma, Switzerland. Honoraria or travel support received for lecturing from the following companies: Ethicon Endosurgery, Johnson and Johnson Ltd, UK, Olympus, Essex, UK., Vifor Pharma Ltd, Glattbrugg, Switzerland and Pharmacosmos, Denmark.

Appendix 1: Draft MEDLINE Search Strategy

MEDLINE (OvidSP)

1. exp Ferric Compounds/
2. exp Ferrous Compounds/
3. exp Iron/
4. (alvofer or colliron or faremio or ferion or feriv or fermed or ferri saccharate or ferric hydroxide sucrose or ferric oxide saccharate or ferric saccharate or ferrinemia or ferrisaccharate or ferrivenin or ferrologic or ferrous saccharate or ferrovin or fesin or hemafer s or hemafer-s or idafer or (iron adj2 hydroxide sucrose complex) or iron saccharate or iron sucrose or ironcrose or iviron or nefro-fer or nefrofer or neo ferrum or nephroferol or proferrin or referen or reoxyl or saccharate ferric or saccharate iron or saccharated ferric oxide or saccharated iron oxide or sucro fer or sucrofer or sucroven or veniron or venofer or venotrix).tw,kf.
5. (anaemex or cosmofer or dexferrum or dexiron or dextrafer or dextran fe or dextran ferrous or dextran iron or driken or fenate or fer dextran or ferric dextran or ferridex or tranferrisat or ferrodex or ferrodextran or ferrous dextran or ferrum lek or fervetag or hibiron or imferdex or imferon or impheron or imposil or infed or infufer or iron dextran complex or ironate or monofar or proferdex or uniferon or uniferon or uniferron).tw,kf.
6. or/1-5
7. exp Administration, Intravenous/
8. (intravenous* or IV or "I.V." or infus* or inject* or parenteral*).tw,kf.
9. 7 or 8
10. 6 and 9
11. (ferric carboxymaltose or Ferinject or Injectafer or Iroprem).tw,kf.
12. (ferlecit or ferlixit or ferric gluconate or ferrigluconate or ferrlecit or gluconate ferric sodium or (iron adj2 gluconate) or sodium ferrigluconate or intravenous iron sucrose or iron sucrose injection* or venofer).tw,kf.
13. (diafer or ferric derisomaltose or iron isomaltoside or monofer or monafer or monoferro or monover or ferumoxytol or feraheme or rienso).tw,kf.
14. (IV iron or "I.V. iron" or iron therapy or ((intravenous* or inject* or infus* or parenteral) adj3 iron)).tw,kf.
15. or/10-14
16. RANDOMIZED CONTROLLED TRIAL.pt.
17. CONTROLLED CLINICAL TRIAL.pt.
18. (randomi* or trial*).tw,kf.
19. (placebo* or randomly or groups).ab.
20. CLINICAL TRIALS AS TOPIC.sh.
21. or/16-20
22. 15 and 21
23. limit 22 to yr="2013 -Current"
24. exp COHORT STUDIES/
25. (cohort* or controlled trial* or controlled stud* or comparative trial* or comparative stud* or comparison group* or comparator group* or control group* or safety stud*).tw,kf.
26. ((follow up or observational) adj (study or studies)).tw,kf.
27. (longitudinal* or retrospective* or prospective* or cross sectional*).mp.
28. CROSS-SECTIONAL STUDIES/
29. CONTROLLED BEFORE-AFTER STUDIES/
30. OBSERVATIONAL STUDY/
31. HISTORICALLY CONTROLLED STUDY/
32. INTERRUPTED TIME SERIES ANALYSIS/
33. (nonrandom* or non random*).tw,kf.
34. ((before adj15 (after or during)) or "before-after" or time series or time point* or repeated measur*).tw,kf.
35. (pre-post or pre-test* or pretest* or posttest* or post-test* or (pre adj5 post)).tw,kf.
36. or/24-35
37. Meta-Analysis.pt.
38. (meta analy* or metaanaly*).ab.
39. META-ANALYSIS/
40. or/37-39
41. (studies or trials).ab.
42. 40 and 41
43. (meta analy$ or metaanaly$).ti.
44. (systematic* adj2 (review* or overview*)).tw,kf.
45. (evidence synthes* or cochrane or medline or pubmed or embase or cinahl or cinhal or lilacs or "web of science" or science citation index or search terms or literature search or published articles or search strateg* or reference list* or bibliograph* or handsearch* or hand search* or manual* search*).ab.
46. (additional adj (papers or articles or sources)).ab.

47. ((electronic or online) adj (sources or resources or databases)).ab.
48. (relevant adj (journals or articles)).ab.
49. "REVIEW LITERATURE AS TOPIC"/
50. META-ANALYSIS AS TOPIC/
51. or/42-50
52. Review.pt.
53. exp CLINICAL TRIALS AS TOPIC/
54. (selection criteria or inclusion criteria).ab. or critical appraisal.ti.
55. (data adj (extraction or analys*)).ab.
56. RANDOMIZED CONTROLLED TRIALS/
57. OBSERVATIONAL STUDY/
58. ((cohort* or observational or retrospective* or safety) adj1 (trial* or stud*)).tw,kf.
59. or/53-57
60. 52 and 59
61. 51 or 60
62. (Comment or Editorial).pt.
63. 61 not 62
64. 36 or 63
65. exp animals/ not humans/
66. 64 not 65
67. 15 and 66
68. limit 67 to yr="2007 -Current"
69. 23 or 68

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	1, 4
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	5
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1, 2
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	12
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important	n/a

		protocol amendments	
Sources	#5a	Indicate sources of financial or other support for the review	12
Sponsor	#5b	Provide name for the review funder and / or sponsor	12
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	12
Rationale	#6	Describe the rationale for the review in the context of what is already known	4, 5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5, 6
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	6, 7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7, 8
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	8, 9
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	8, 9
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

BMJ Open

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Manuscript ID	bmjopen-2018-024618.R1
Article Type:	Protocol
Date Submitted by the Author:	11-Feb-2019
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Primary Subject Heading:	Haematology (incl blood transfusion)
Secondary Subject Heading:	Evidence based practice
Keywords:	Systematic review, Intravenous Iron, Infection, Mortality, Meta-analysis

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Total word count: 2227 (including Abstract)

Key words: Intravenous Iron; Infection; Mortality; Systematic review; Meta-analysis

ABSTRACT

Introduction

The benefits and risk of intravenous iron have been documented in previous systematic reviews and continue to be the subject of randomised controlled trials (RCTs). An ongoing issue that continues to be raised is the relationship between administering iron and developing infection. This is supported by biological plausibility from animal models. We propose an update of a previously published systematic review and meta-analysis with the primary focus being infection.

Methods and analysis

We will include randomised controlled trials (RCTs) and non-randomised studies (NRS) in this review update. We will search the relevant electronic databases. Two reviewers will independently extract data. Risk of bias for RCTs and NRS will be assessed using the relevant tools recommended by The Cochrane Collaboration. Data extracted from RCTs and NRS will be analysed and reported separately. Pooled data from RCTs will be analysed using a random effects model. We will also conduct subgroup analyses to identify any patient populations that may be at increased risk of developing infection. We will provide a narrative synthesis on the definitions, sources, and responsible pathogens for infection in the included studies. Overall quality of

evidence on the safety outcomes of mortality and infection will be assessed using the GRADE approach.

Ethics and dissemination

This systematic review will only investigate published studies and therefore ethical approval is not required. The results will be broadly distributed through conference presentations and peer-reviewed publications.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Systematic review protocol primarily focusing on a safety outcome (risk of infection) with intravenous preparations.
- Comprehensive review that will include data from randomised controlled trials and non-randomised studies.

- Infection is not often a predefined endpoint in published studies and definitions of infection will vary across studies.
- There will be considerable heterogeneity in participant populations, doses and types of intravenous iron used and follow-up time points

INTRODUCTION

Treating anaemia is a key pillar of Patient Blood Management and a recent James Lind prioritisation exercise ranked the timely identification of anaemia and treatment as a Top 10 priority for research into blood transfusion and blood donation (1). Systematic reviews have shown the efficacy of intravenous iron with regards to treating anaemia and reducing blood transfusion requirements (2, 3), although with varying degrees of effect size and the primary outcomes in majority of trials were haematological (change in haemoglobin concentration, transfusion requirements) instead of clinical outcomes (eg Quality of Life (QoL).

Despite the widespread use of intravenous iron (1, 2), uncertainty persists as to whether intravenous iron is associated with an increased risk of infection. The uncertain relationship between iron and infection has long been postulated and remains a topic of interest in on-going trials of oral iron, for example in the setting of malaria and other tropical infections in low-resource country settings (4). Iron is essential for extracellular pathogens as it an ideal redox catalyst for

important cellular processes such as respiration and DNA replication (5). Humans are able to withhold free (non-transferrin-bound) iron from invading pathogens through a process termed nutritional immunity in an effort to limit infection (5, 6). Intravenous iron administration can lead to increased levels of circulating free iron, which can be detrimental to the host and promote pathogen growth. Such an interaction is supported by biological plausibility in recent animal models where administration of intravenous iron worsening shock, lung injury and mortality (7).

Two recent systematic reviews have investigated the efficacy and safety of intravenous iron therapy (2, 7). The first systematic review identified 72 randomized controlled trials (RCTs) that included 10,605 participants. The authors reported a reduced risk of requirement for red blood cell (RBC) transfusion (Risk Ratio (RR) 0.74, 95% CI 0.62 to 0.88; 22 RCTs, 3321 participants). Of note, this potential benefit was counterbalanced 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 (2). The second systematic review pooled data from 32 RCTs and showed a point estimate which again favoured infection, although this was statistically non-significant (RR 1.17; 95% CI 0.83 to 1.65) ((8). Interpreting data on infection from these meta-analyses is challenging because infection is not always defined as a pre-specified, standardised outcome measure in RCTs but rather reported as safety outcome. A recent editorial highlighted the need for an adequately powered trial of intravenous iron with infection as a primary outcome (6).

Given the on-going uncertainty regarding the risk of infection, the primary objective of this systematic review was to update the previous review by Litton et al (2) by identifying and incorporating recent trial data to evaluate the safety data for intravenous iron on the risk of infection across all clinical settings. A better understanding of the characterization of infection in patients receiving iron therapy will help inform the design of subsequent trials in particular groups of patients (e.g. critically ill, emergency surgery) in whom the risk of infection is of clinical concern. Our secondary objective is to continue to collect efficacy data to focusing primarily on changes in haemoglobin concentration, transfusion requirements and functional outcomes.

METHODS

We used the PRISMA-P reporting guidelines(9). Studies will be selected according to the criteria outlined below. The study protocol has been registered on PROSPERO (CRD42018096023).

Eligibility criteria

We will include randomized controlled trials (RCTs) from 1st January 2013 onwards as the last search date for the previous review was June 2013 (2). We will also include non-randomized studies (NRS) in this updated review as infection may not always be reported in RCTs and the

findings of infection outcomes reported in NRS may be useful to inform the design of a future RCT.

We will only include NRS that meet the following criteria:

- Published since 1st January 2007 as this is the year from which newer intravenous iron preparations (Ferinject®, Monofer®, Venofer®, Injectofer®) received and/or renewed their marketing authorization. Therefore any data extracted is likely to be reflective of current practice. Studies evaluating low molecular weight dextran (INFed®, Cosmofer®), ferumoxytol, ferric pyrophosphate citrate (TriFeric®) and iron polymaltose will also be included.
- At least two comparable groups [including controlled before-and-after, and prospective/retrospective cohort studies].
- Quasi-RCTs
- Provide data on our primary outcome of infection

We will exclude any studies that provide no outcome data of interest, NRS published before 1st January 2007 and NRS that do not have an intravenous iron comparison arm. We will include studies examining all participant populations (including paediatrics, pregnancy) but excluding healthy volunteers. Included studies would compare intravenous iron to no iron/placebo or oral iron.

Our primary outcome of interest is the number of patients who develop an infection as defined by the study authors. Secondary safety and efficacy outcomes include:

- Mortality – short-term (≤30 days), long-term (>30 days)
- Hospital length of stay
- Change in haemoglobin concentration from baseline/pre-treatment levels to end of study period
- Transfusion requirements during study period (% transfused, mean number of RBC units transfused)

Information sources and Search strategy

We will search the following databases for RCTs (from 1st January 2013), systematic reviews and NRS (from 1st January 2007) – Cochrane Central Register for Controlled Trials; MEDLINE (Ovid interface); Ovid Interface; CINAHL; Transfusion Evidence Library; Web of Science Conference Proceedings Citation Index-Science. This will be supplemented by searching ongoing trial databases such as ClinicalTrials.gov and WHO International Clinical Trials Search Registry Platform. Citation lists of included studies and relevant reviews will also be scanned to identify any studies missed by the search. A draft MEDLINE search strategy is included in Appendix 1.

Study selection

Literature search results will be uploaded to Covidence, a web-based software platform, to facilitate citation screening between reviewers. Review authors will independently screen the titles and abstracts yielded by the search against the prespecified inclusion criteria. Two review authors will then independently screen the full text reports and decide whether these meet the inclusion criteria. Disagreements will be resolved through discussion, and if necessary, referred to a third reviewer. The study selection process will be reported in a PRISMA flow diagram.

Data extraction

For RCTs, two reviewers will use the data extraction form used for the original review to extract data independently. We will standardize and pilot a data extraction form for NRS and items for extraction from NRS will include:

- Data on confounding factors
- Comparability of groups based on consideration of confounding factors
- Methods used to control for confounding
- Effect estimates – both adjusted and unadjusted if available

For both sets of studies we will extract the following additional data, if reported, on the outcome of infection:

- Definition of infection used (i.e. guideline based, laboratory based, clinical discretion)
- Site of infection (e.g. lung, wound, gastrointestinal)
- Reporting of identified pathogens
- Antibiotic usage

Disagreements will be resolved through discussion, and if necessary, referred to a third reviewer.

We will contact study authors to resolve any uncertainties.

Risk of bias assessment

Risk of bias for the RCTs will be reported using the Cochrane Risk of Bias tool (10). For the non-RCT data, risk of bias will be reported using the ROBINS-I developed by the Cochrane Bias Methods Group (11). Two reviewers will make these judgements independently.

Data synthesis

Data from RCTs and NRS will be analysed and reported separately.

RCTs

The primary end-point will be the proportion of participants who developed an infection.

Dichotomous outcomes (infection, mortality, requirement for blood transfusion) will be reported as risk ratios with corresponding 95% Confidence Intervals (CI). Continuous outcomes will be reported as weighted mean (with 95% CI) or standardized mean differences (95% CI) as appropriate. For continuous measures, the mean difference in change from baseline values between groups will be used preferentially; if change from baseline values are not reported then the mean difference in measures at follow up will be used. The unit of analysis will be per individual randomized. Data from included studies will be pooled for meta-analysis using a random effects model. Statistical heterogeneity will be tested using the I^2 statistic and I^2>50% will be considered as substantial heterogeneity. If substantial heterogeneity is present among the trials, the study characteristics of the included studies will be analysed and we will attempt to explain the heterogeneity by subgroup analysis or sensitivity analysis. If sufficient data are available we will undertake meta-regression to examine the effect of cumulative intravenous iron dose and the incidence of infection in the control group (as a surrogate for background/endemic burden of infection) on our primary outcome. Statistical analysis will be conducted on RevMan 5.1. and STATA (Version 14, StataCorp LP, College Station, TX, USA).

NRS

For NRS, we will only report results descriptively on the primary outcome of infection instead of pooling results due to heterogeneity in clinical conditions, study designs and variations in statistical adjustment. If possible, results will be displayed in a forest plot, with studies sorted according to study design features, and the pooled estimate will be suppressed as recommended by the Cochrane Collaboration (6).

Analysis of subgroups

Subgroup analysis of the primary safety outcome (infection) will be performed on the following:

- Clinical settings (in-patient medical (any), outpatient (any), elective surgical, non-elective (urgent/emergency) surgical, obstetrics, paediatrics, critically ill)
- Different iron profiles at enrolment as defined by the study authors (true iron deficiency, functional iron deficiency, iron restricted erythropoiesis)
- Mode of administration (e.g. single dose, continuous infusion, multiple boluses)
- Cumulative dose of intravenous iron
- Incidence of infection in the control group

We will carry out a sensitivity analysis on infection and mortality outcomes by excluding studies with a high risk of bias. We will assess for publication bias on the primary outcome with a funnel plot if ≥10 studies are available, plotting the odds ratio for proportion that develop infection against the standard error of the log odds ratio.

A systematic narrative synthesis will be provided with information presented in the text and tables to summarise data on infection provided in the include studies. This narrative synthesis will explore the definitions of infection used, reporting of infection source and pathogens and antibiotic use.

Confidence in cumulative evidence

According to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, we will assess the overall quality of evidence for the main safety outcomes of infection and mortality (12). In line with current GRADE guidance, if the certainty of evidence differs between RCTs and NRS, we will present Summary of Findings (SoF) tables for the higher certainty of evidence. If the certainty ratings are the same, results from both bodies will be presented separately (13).

Patient and public involvement

Patients and members of the public were not directly involved in the design of this study. However, appropriate management of anaemia, through interventions such as iron therapy, has been identified as a key research priority in a recent James Lind Priority Setting Partnership exercise (1).

DISCUSSION

Recent patient blood management efforts have attempted to reduce blood transfusion by using alternative therapies such as intravenous iron. Safety concerns surrounding older preparations, mainly anaphylaxis, have been allayed by the development of newer, stable preparations which has led to intravenous iron being used more frequently in multiple settings (14). Despite its widespread use, concerns surrounding infection remain both from systematic reviews and animal models.

Our review will provide an up to date and comprehensive estimate of the risk of infection associated with intravenous iron preparations across multiple patient groups. In addition, we will also provide data on the characterisation of infection as a step towards standardizing infection as an outcome measure for future trials of intravenous iron.

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Author statement: AAS, AS, SJS and EL conceived the idea for the review update. AS prepared the initial protocol draft with input from SB and SJS who contributed to the revision of the manuscript. CD will perform the search and AS, JR, AJP, and ED will screen and extract data. All

listed authors, including MO, AGA, RB and SB contributed to the development of the idea and drafting and revisions of the manuscript.

Funding: AAS is funded by an NIHR Doctoral Research Fellowship (DRF-2017-10-094). This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflicts of interest: RB has received educational grants / honorarium from Pharmacosmos UK and Vifor Pharma. AGA's research department has received grant support from Syner-Med, UK, Pharmacosmos, Denmark and Vifor Pharma, Switzerland. Honoraria or travel support received for lecturing from the following companies: Ethicon Endosurgery, Johnson and Johnson Ltd, UK, Olympus, Essex, UK., Vifor Pharma Ltd, Glattbrugg, Switzerland and Pharmacosmos, Denmark.

Appendix 1: Draft MEDLINE Search Strategy

MEDLINE (OvidSP)

1. exp Ferric Compounds/
2. exp Ferrous Compounds/
3. exp Iron/
4. (alvofer or colliron or faremio or ferion or feriv or fermed or ferri saccharate or ferric hydroxide sucrose or ferric oxide saccharate or ferric saccharate or ferrinemia or ferrisaccharate or ferrivenin or ferrologic or ferrous saccharate or ferrovin or fesin or hemafer s or hemafer-s or idafer or (iron adj2 hydroxide sucrose complex) or iron saccharate or iron sucrose or ironcrose or iviron or nefro-fer or nefrofer or neo ferrum or nephroferol or proferrin or referen or reoxyl or saccharate ferric or saccharate iron or saccharated ferric oxide or saccharated iron oxide or sucro fer or sucrofer or sucroven or veniron or venofer or venotrix).tw,kf.
5. (anaemex or cosmofer or dexferrum or dexiron or dextrafer or dextran fe or dextran ferrous or dextran iron or driken or fenate or fer dextran or ferric dextran or ferridex or tranferrisat or ferrodex or ferrodextran or ferrous dextran or ferrum lek or fervetag or hibiron or imferdex or imferon or impheron or imposil or infed or infufer or iron dextran complex or ironate or monofar or proferdex or uniferon or uniferon or uniferron).tw,kf.
6. or/1-5
7. exp Administration, Intravenous/
8. (intravenous* or IV or "I.V." or infus* or inject* or parenteral*).tw,kf.
9. 7 or 8
10. 6 and 9
11. (ferric carboxymaltose or Ferinject or Injectafer or Iroprem).tw,kf.
12. (ferlecit or ferlixit or ferric gluconate or ferrigluconate or ferrlecit or gluconate ferric sodium or (iron adj2 gluconate) or sodium ferrigluconate or intravenous iron sucrose or iron sucrose injection* or venofer).tw,kf.
13. (diafer or ferric derisomaltose or iron isomaltoside or monofer or monafer or monoferro or monover or ferumoxytol or feraheme or rienso).tw,kf.
14. (IV iron or "I.V. iron" or iron therapy or ((intravenous* or inject* or infus* or parenteral) adj3 iron)).tw,kf.
15. or/10-14
16. RANDOMIZED CONTROLLED TRIAL.pt.
17. CONTROLLED CLINICAL TRIAL.pt.
18. (randomi* or trial*).tw,kf.
19. (placebo* or randomly or groups).ab.
20. CLINICAL TRIALS AS TOPIC.sh.
21. or/16-20
22. 15 and 21
23. limit 22 to yr="2013 -Current"
24. exp COHORT STUDIES/
25. (cohort* or controlled trial* or controlled stud* or comparative trial* or comparative stud* or comparison group* or comparator group* or control group* or safety stud*).tw,kf.
26. ((follow up or observational) adj (study or studies)).tw,kf.
27. (longitudinal* or retrospective* or prospective* or cross sectional*).mp.
28. CROSS-SECTIONAL STUDIES/
29. CONTROLLED BEFORE-AFTER STUDIES/
30. OBSERVATIONAL STUDY/
31. HISTORICALLY CONTROLLED STUDY/
32. INTERRUPTED TIME SERIES ANALYSIS/
33. (nonrandom* or non random*).tw,kf.
34. ((before adj15 (after or during)) or "before-after" or time series or time point* or repeated measur*).tw,kf.
35. (pre-post or pre-test* or pretest* or posttest* or post-test* or (pre adj5 post)).tw,kf.
36. or/24-35
37. Meta-Analysis.pt.
38. (meta analy* or metaanaly*).ab.
39. META-ANALYSIS/
40. or/37-39
41. (studies or trials).ab.
42. 40 and 41
43. (meta analy$ or metaanaly$).ti.
44. (systematic* adj2 (review* or overview*)).tw,kf.
45. (evidence synthes* or cochrane or medline or pubmed or embase or cinahl or cinhal or lilacs or "web of science" or science citation index or search terms or literature search or published articles or search strateg* or reference list* or bibliograph* or handsearch* or hand search* or manual* search*).ab.
46. (additional adj (papers or articles or sources)).ab.

47. ((electronic or online) adj (sources or resources or databases)).ab.
48. (relevant adj (journals or articles)).ab.
49. "REVIEW LITERATURE AS TOPIC"/
50. META-ANALYSIS AS TOPIC/
51. or/42-50
52. Review.pt.
53. exp CLINICAL TRIALS AS TOPIC/
54. (selection criteria or inclusion criteria).ab. or critical appraisal.ti.
55. (data adj (extraction or analys*)).ab.
56. RANDOMIZED CONTROLLED TRIALS/
57. OBSERVATIONAL STUDY/
58. ((cohort* or observational or retrospective* or safety) adj1 (trial* or stud*)).tw,kf.
59. or/53-57
60. 52 and 59
61. 51 or 60
62. (Comment or Editorial).pt.
63. 61 not 62
64. 36 or 63
65. exp animals/ not humans/
66. 64 not 65
67. 15 and 66
68. limit 67 to yr="2007 -Current"
69. 23 or 68

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	1, 4

	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	5
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1, 2
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	12, 13
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Sources	#5a	Indicate sources of financial or other support for the review	13
Sponsor	#5b	Provide name for the review funder and / or sponsor	13
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	N/A
Rationale	#6	Describe the rationale for the review in the context of what is already known	4, 5
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such	5, 6

		as years considered, language, publication status) to be used as criteria for eligibility for the review	
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7, 8
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7, 8
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7, 8
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	8, 9
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	8, 9
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10