Supplementary Online Content

Shah AA, Donovan K, Seeley C, et al. Risk of infection associated with administration of intravenous iron: a systematic review and meta-analysis. *JAMA Netw Open*. 2021;4(11):e2133935. doi:10.1001/jamanetworkopen.2021.33935

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Search strategy

The following databases were searched for randomised controlled trials (from 2013 to present), systematic reviews and non-randomised trials with a comparator group (from 2007 to present) on 28.9.20:

Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*) & CDSR 2020, Issue 9 MEDLINE (OvidSP, 1946 to present) Embase (OvidSP, 1974 to present) CINAHL (EBSCOHost) (1937 to present) PubMed (e-publications ahead of print only) Transfusion Evidence Library (1950 to present) LILACS (1982 to present) Web of Science Conference Proceedings Citation Index-Science (CPCI-S) (Thomson Reuters, 1990 to present)

Ongoing trial databases: CENTRAL ClinicalTrials.gov (clinicaltrials.gov) WHO International Clinical Trials Registry Search Platform (ICTRP)

SEARCH STRATEGIES

CENTRAL (The Cochrane Library)

- #1 MeSH descriptor: [Ferric Compounds] explode all trees
- #2 MeSH descriptor: [Ferrous Compounds] explode all trees
- #3 MeSH descriptor: [Iron] explode all trees

#4 (alvofer or colliron or faremio or ferion or feriv or fermed or ferri saccharate or ferric hydroxide sucrose or ferric oxide saccharate or saccharated ferric oxide 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 near/2 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 sucroven or veniron or venofer or venotrix)

- #5 #1 or #2 or #3 or #4
- #6 MeSH descriptor: [Administration, Intravenous] explode all trees
- #7 (intravenous* or IV or "IV" or infus* or inject* or parenteral*)
- #8 #6 or #7
- #9 #5 and #8

#10 (ferric carboxymaltose or Ferinject or Injectafer or Iroprem or ferlecit or ferlixit or ferric gluconate or ferrigluconate or ferric or gluconate ferric sodium or (iron near/2 gluconate) or iron isomaltoside or intravenous iron sucrose or iron sucrose injection* or sodium ferrigluconate or diafer or ferric derisomaltose or venofer or monofer or monofer or monoferro or monover or ferumoxytol or feraheme or rienso or "IV iron" or "IV iron" or "iron therapy" or ((intravenous* or inject* or infus* or parenteral) near/3 iron))

#11 (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 or ironate or monofar or proferdex or uniferon or uniferon or uniferron)

#12 ferumoxytol or injectafer or infed or cosmofer or iron polymaltose or triferic or ferric pyrophosphate citrate

#13 #4 or #9 or #10 or #11 or #12 with Publication Year from 2013 to 2020, in Trials

#14 #4 or #9 or #10 or #11 or #12 with Cochrane Library publication date Between Jan 2007 and Dec 2020, in Cochrane Reviews, Cochrane Protocols

#15 #13 or #14

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 oxide, saccharated 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 nefro-fer 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 sucrofer or venotrix).tw,kf.

5. or/1-3

6. exp Administration, Intravenous/

7. (intravenous* or IV or "IV" or infus* or inject* or parenteral*).tw,kf.

8.6 or 7

9.5 and 8

10. (ferric carboxymaltose or Ferinject or Injectafer or Iroprem).tw,kf.

11. (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.

12. (diafer or ferric derisomaltose or iron isomaltoside or monofer or monofer or monoferro or monover or ferumoxytol or feraheme or rienso).tw,kf.

13. (IV iron or "IV iron" or iron therapy or ((intravenous* or inject* or infus* or parenteral) adj3 iron)).tw,kf.

14. (ferumoxytol or injectafer or infed or cosmofer or iron polymaltose or triferic or ferric pyrophosphate citrate).mp.

15. (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 transferrisat 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 uniferon).mp.

16. 4 or 9 or 10 or 11 or 12 or 13 or 14 or 15

17. RANDOMIZED CONTROLLED TRIAL.pt.

18. CONTROLLED CLINICAL TRIAL.pt.

19. (randomi* or trial*).tw,kf.

20. (placebo* or randomly or groups).ab.

21. CLINICAL TRIALS AS TOPIC.sh.

22. or/17-21

23. exp animals/ not humans/

24. 22 not 23

25. 16 and 24

26. limit 25 to yr="2013 -Current"

27. exp COHORT STUDIES/

28. (cohort* or controlled trial* or controlled stud* or comparative trial* or comparative stud* or comparison group* or comparator group* or control group*).tw,kf.

29. ((follow up or observational) adj (study or studies)).tw,kf.

30. (longitudinal* or retrospective* or prospective* or cross sectional*).mp.

31. CROSS-SECTIONAL STUDIES/

32. CONTROLLED BEFORE-AFTER STUDIES/

33. OBSERVATIONAL STUDY/

34. HISTORICALLY CONTROLLED STUDY/

35. INTERRUPTED TIME SERIES ANALYSIS/

36. (nonrandom* or non random*).tw,kf.

37. ((before adj15 (after or during)) or "before-after" or time series or time point* or repeated measur*).tw,kf.

38. (pre-post or pre-test* or pretest* or posttest* or post-test* or (pre adj5 post)).tw,kf.

39. or/27-38

40. Meta-Analysis.pt.

41. Systematic Review.pt.

42. (meta analy\$ or metaanaly\$).ti.

43. (systematic* adj2 (review* or overview*)).tw,kf.

44. (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.

45. (additional adj (papers or articles or sources)).ab.

46. ((electronic or online) adj (sources or resources or databases)).ab.

47. (relevant adj (journals or articles)).ab.

48. "REVIEW LITERATURE AS TOPIC"/

49. "Systematic Reviews as Topic"/

50. META-ANALYSIS AS TOPIC/

51. or/40-50

52. Review.pt.

53. exp CLINICAL TRIALS AS TOPIC/

- 54. selection 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*) adj1 (trial* or stud*)).tw,kf.
- 59. or/53-58
- 60. 52 and 59
- 61. 51 or 60
- 62. (Comment or Letter or Editorial).pt.
- 63. 61 not 62
- 64. 39 or 63
- 65. exp animals/ not humans/
- 66. 64 not 65
- 67.16 and 66
- 68. limit 67 to yr="2007 -Current"
- 69. 26 or 68

EMBASE (OvidSP)

1. ferric carboxymaltose/ or ferric gluconate/ or iron dextran/ or iron isomaltose/ or iron saccharate/

2. (alvofer or colliron or faremio or ferion or feriv or fermed or ferri saccharate or ferric hydroxide sucrose or ferric oxide saccharate or ferric oxide, saccharated 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 saccharate ferric oxide or sucro fer or sucrofer or venotrix).tw.

3. (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 uniferon).tw.

4. (Ferric carboxymaltose or Ferinject or Injectafer or Iroprem).tw.

5. (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.

6. (diafer or ferric derisomaltose or iron isomaltoside or monofer or monofer or monoferro or monover or ferumoxytol or feraheme or rienso).tw,kf.

7. ferumoxytol/

8. (IV iron or "IV iron" or iron therapy or ((intravenous* or inject* or infus* or parenteral) adj3 iron)).tw.

9. (ferumoxytol or injectafer or infed or cosmofer or iron polymaltose or triferic or ferric pyrophosphate citrate or feraheme or rienso).mp.

10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

- 11. Meta Analysis/
- 12. Systematic Review/
- 13. (meta analy* or metaanalys*).tw.
- 14. ((systematic* or literature) adj2 (review* or overview* or search*)).tw.

15. (cochrane or embase or cinahl or cinhal or lilacs or BIDS or science citation index or psyclit or psychit or psychifo or psychia.

- 16. ((electronic* or online) adj (sources or resources or databases)).ab.
- 17. (additional adj (articles or papers or sources)).ab.
- 18. (reference lists or bibliograph* or handsearch* or hand search* or manual* search*).ab.
- 19. (relevant adj (journals or articles)).ab.
- $20. \ (search \ term^* \ or \ published \ articles \ or \ search \ strateg^*).ab.$
- 21. or/11-20
- 22. (data extraction or selection criteria or inclusion criteria).ab.
- 23. review.pt.
- 24. 21 or (22 and 23)
- 25. editorial.pt.
- 26. 24 not 25

27. crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/

28. (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or doubl* blind* or singl* blind* or assign* or allocat* or volunteer*).mp.

29. 27 or 28

30. MAJOR CLINICAL STUDY/

- 31. LONGITUDINAL STUDY/
- 32. RETROSPECTIVE STUDY/
- 33. OBSERVATIONAL STUDY/
- 34. INTERVENTION STUDY/

35. PROSPECTIVE STUDY/ not RANDOMIZED CONTROLLED TRIAL/

- 36. COHORT ANALYSIS/
- 37. COMPARATIVE STUDY/

38. (cohort* or controlled trial* or controlled stud* or comparative trial* or comparative stud* or comparison group* or comparator group* or control group*).tw.

- 39. ((follow up or observational) adj (study or studies)).tw.
- 40. (longitudinal* or retrospective* or prospective* or cross sectional*).mp.
- 41. (nonrandom* or non random*).tw.
- 42. ((before adj15 (after or during)) or "before-after" or time series or time point* or repeated measur*).tw.
- 43. (pre-post or pre-test* or pretest* or posttest* or post-test* or (pre adj5 post)).tw.
- 44. or/30-43
- 45. 26 or 44
- 46. 10 and 29
- 47. limit 46 to yr="2013 -Current"
- $48.\ 10\ and\ 45$
- 49. limit 48 to yr="2007 -Current"
- 50. 47 or 49

CINAHL (EBSCOHoST)

- S1 (MH "Ferric Compounds+")
- S2 (MH "Ferrous Compounds")
- S3 (MH "Iron")
- S4 S1 OR S2 OR S3
- S5 (MH "Administration, Intravenous+")
- S6 TX (intravenous* or IV or "IV" or infus* or inject* or parenteral)
- S7 S5 OR S6
- S8 S4 AND S7
- S9 TX (alvofer or colliron or faremio or ferion or feriv or fermed or ferri saccharate or ferric hydroxide sucrose or ferric oxide saccharate or ferric oxide, saccharated 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 N2 hydroxide sucrose complex) or iron saccharate or iron sucrose or ironcrose or iviron or nefro-fer or neo ferrum or nephroferol or proferrin or referen or reoxyl or saccharate ferric or saccharate iron or saccharate ferric oxide or saccharated iron oxide or sucro fer or sucroven or veniron or venotrix)
- S10 TX (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 transferrisat 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)
- S11 TX (ferric carboxymaltose or Ferinject or Injectafer or Iroprem or venofer or ferlecit or ferlixit or ferric gluconate or ferrigluconate or ferricit or gluconate ferric sodium or (iron N2 gluconate) or sodium ferrigluconate or diafer or ferric derisomaltose or iron isomaltoside or monofer or monofer or monoferro or monover or ferumoxytol or feraheme or rienso or "IV iron" or "IV iron" or "iron therapy" or ((intravenous* or inject* or infus* or parenteral) N3 iron))
- S12 S8 OR S9 OR S10 OR S11
- S13 (MH "Prospective Studies+")
- S14 (MH "Case Control Studies+")
- S15 (MH "Correlational Studies") OR (MH "Cross Sectional Studies")
- S16 TI ((cohort study or cohort studies)) OR AB ((cohort study or cohort studies))
- S17 TI ((observational stud* or retrospective stud*)) OR AB ((observational stud* or retrospective stud*))
- S18 S13 OR S14 OR S15 OR S16 OR S17
- S19 (MH Clinical Trials+)
- S20 PT Clinical Trial
- S21 TI ((controlled trial*)) or (clinical trial*)) OR AB ((controlled trial*) or (clinical trial*))
- S22 TI ((singl* blind*) OR (doubl* blind*) OR (trebl* blind*) OR (tripl* blind*) OR (singl* mask*) OR (doubl*

mask*) OR (tripl* mask*)) OR AB ((singl* blind*) OR (doubl* blind*) OR (trebl* blind*) OR (tripl* blind*) OR (singl* mask*) OR (doubl* mask*) OR (tripl* mask*))

- S23 TI randomi* OR AB randomi*
- S24 MH RANDOM ASSIGNMENT
- S25 TI ((phase three) or (phase III) or (phase three)) or AB ((phase three) or (phase III) or (phase three))
- S26 (TI (random* N2 (assign* or allocat*))) OR (AB (random* N2 (assign* or allocat*)))
- S27 MH PLACEBOS OR (TI placebo* OR AB placebo*)
- S28 S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27
- S29 MH META ANALYSIS
- S30 MH SYSTEMATIC REVIEW
- S31 TI ("meta analys*" OR metaanalys* OR "systematic review" OR "systematic overview" OR "systematic

search*") OR AB ("meta analys*" OR metaanalys* OR "systematic review" OR "systematic overview" OR "systematic search*")

S32 TI ("literature review" OR "literature overview" OR "literature search*") OR AB ("literature review" OR "literature overview" OR "literature search*")

S33 TI (cochrane OR embase OR cinahl OR cinhal OR lilacs OR BIDS OR science AND citation AND index OR cancerlit) OR AB (cochrane OR embase OR cinahl OR cinhal OR lilacs OR BIDS OR science AND citation AND index OR cancerlit)

S34 MH QUANTITATIVE STUDIES

S35 (MH "Controlled Before-After Studies") OR (MH "Historically Controlled Study") OR (MH "Interrupted Time Series Analysis") OR (MH "Nonrandomized Trials") OR (MH "Pretest-Posttest Design+") OR (MH "Static Group Comparison") OR (MH "Solomon Four-Group Design")

S36 TX nonrandom* or non random*

S37 TX ((before N15 (after or during)) or "before-after" or time series or time point* or repeated measur*)

- S38 TX (pre-post or pre-test* or pretest* or posttest* or post-test* or (pre N5 post))
- S39 TX TI ((controlled stud*) or (clinical stud*)) OR AB ((controlled stud*) or (clinical stud*))
- S40 S18 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39
- S41 S12 AND S28
- S42 S12 AND S28 Limiters Published Date: 20130101-20201231
- S43 S12 AND S40
- S44 S12 AND S40 Limiters Published Date: 20070101-20201231
- S45 S42 OR S44

PubMed

- #1 (alvofer[TIAB] OR colliron[TIAB] OR faremio[TIAB] OR ferion[TIAB] OR feriv[TIAB] OR fermed[TIAB] OR "ferri saccharate" [TIAB] OR "ferric hydroxide sucrose" [TIAB] OR "ferric oxide saccharate" [TIAB] OR "ferric saccharate"[TIAB] OR ferrinemia[TIAB] OR ferrisaccharate[TIAB] OR ferrivenin[TIAB] OR ferrologic[TIAB] OR "ferrous saccharate"[TIAB] OR ferrovin[TIAB] OR fesin[TIAB] OR "hemafer-s"[TIAB] OR "hemafer-s"[TIAB] OR idafer[TIAB] OR "iron hydroxide sucrose complex"[TIAB] OR "iron saccharate"[TIAB] OR "iron sucrose"[TIAB] OR ironcrose[TIAB] OR iviron[TIAB] OR "nefro-fer"[TIAB] OR nefrofer[TIAB] OR "neo ferrum"[TIAB] OR nephroferol[TIAB] OR proferrin[TIAB] OR referen[TIAB] OR reoxyl[TIAB] OR "saccharate ferric"[TIAB] OR "saccharate iron"[TIAB] OR "saccharated ferric oxide"[TIAB] OR "saccharated iron oxide" [TIAB] OR "sucro fer" [TIAB] OR sucrofer [TIAB] OR sucroven [TIAB] OR veniron[TIAB] OR venofer[TIAB] OR venotrix[TIAB] OR anaemex[TIAB] OR cosmofer[TIAB] OR dexferrum[TIAB] OR dexiron[TIAB] OR dextrafer[TIAB] OR "dextran fe"[TIAB] OR "dextran ferrous"[TIAB] OR "dextran iron"[TIAB] OR driken[TIAB] OR fenate[TIAB] OR "fer dextran"[TIAB] OR "ferric dextran"[TIAB] OR ferridex[TIAB] OR tranferrisat[TIAB] OR ferrodex[TIAB] OR ferrodextran[TIAB] OR "ferrous dextran" [TIAB] OR "ferrum lek" [TIAB] OR fervetag [TIAB] OR hibiron [TIAB] OR imferdex[TIAB] OR imferon[TIAB] OR impheron[TIAB] OR imposil[TIAB] OR infed[TIAB] OR infufer[TIAB] OR "iron dextran"[TIAB] OR ironate[TIAB] OR monofar[TIAB] OR proferdex[TIAB])
- #2 (intravenous*[TIAB] OR IV[TIAB] OR "IV"[TIAB] OR infus*[TIAB] OR inject*[TIAB] OR parenteral*[TIAB])
- #3 #1 AND #2
- #4 ("ferric carboxymaltose"[TIAB] OR Ferinject[TIAB] OR Injectafer[TIAB] OR Iroprem[TIAB] OR venofer[TIAB] OR ferlecit[TIAB] OR ferlixit[TIAB] OR "ferric gluconate"[TIAB] OR ferrigluconate[TIAB] OR ferrigluconate[TIAB] OR "gluconate ferric sodium"[TIAB] OR "iron gluconate"[TIAB] OR "sodium ferrigluconate"[TIAB] OR diafer[TIAB] OR "ferric derisomaltose"[TIAB] OR "iron isomaltoside"[TIAB] OR monofer[TIAB] OR "iron injection"[TIAB] OR "iron "iron injection"[TIAB] OR "iron injectable iron"[TIAB] OR "iron infusion"[TIAB] OR "iron infusions"[TIAB] OR "iron infusions"[TIAB
- #5 #3 OR #4

- #6 (random* OR blind* OR "control group" OR placebo* OR controlled OR groups OR trial* OR "systematic review" OR "meta-analysis" OR metaanalysis OR "literature search" OR medline OR pubmed OR cochrane OR embase OR case control* OR "case series" OR cohort* OR comparative OR comparison OR comparator OR "follow-up study" OR "follow-up studies" OR observational* OR retrospective* or non-random* OR pre-post or pre-test* or posttest* or post-test* OR before-after) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])
- #7 #5 AND #6

TRANSFUSION EVIDENCE LIBRARY

Subject Area: Clinical Practice – Management of Anaemia Date Limit: 2013-2020

LILACS

tw:((ferric carboxymaltose OR ferinject OR injectafer OR iroprem OR iron sucrose OR venofer OR ferlecit OR ferlixit OR ferric gluconate OR ferrigluconate OR ferrlecit OR gluconate ferric sodium OR iron gluconate OR sodium ferrigluconate OR diafer OR ferric derisomaltose OR iron isomaltoside OR monofer OR monofer OR monoferro OR monover OR ferumoxytol OR feraheme OR rienso OR iv iron OR IV iron OR iron therapy OR intravenous iron OR injectable iron OR iron infusion OR iron infusions OR infused iron OR parenteral iron)) AND (instance:"regional") AND (db:("LILACS") AND year_cluster:("2007"-"2020"))

WEB OF SCIENCE

- #1 TS=(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 hydroxide sucrose 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 saccharate ferric oxide or saccharate iron or venofer or venotrix)
- #2 TS=(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 or ironate or monofar or proferdex)
- #3 #1 or #2
- #4 TS=(intravenous* or IV or "IV" or infus* or inject* or parenteral*)
- #5 #3 and #4
- #6 TS=(ferric carboxymaltose or Ferinject or Injectafer or Iroprem or venofer or ferlecit or ferlixit or ferric gluconate or ferrigluconate or ferrlecit or gluconate ferric sodium or (iron near/2 gluconate) or sodium ferrigluconate or diafer or ferric derisomaltose or iron isomaltoside or monofer or monafer or monoferro or monover or ferumoxytol or feraheme or rienso or "IV iron" or "IV iron" or "iron therapy" or ((intravenous* or inject* or infus* or parenteral) NEAR/3 iron))
- #7 #5 OR #6
- #8 TS=(random* OR blind* OR "control group" OR placebo* OR controlled OR groups OR trial* OR "systematic review" OR "meta-analysis" OR metaanalysis OR "literature search" OR medline OR pubmed OR cochrane OR embase OR case control* OR "case series" OR cohort* OR comparative OR comparison OR comparator OR "follow-up study" OR "follow-up studies" OR observational* OR retrospective* or non-random* OR pre-post or pre-test* or posttest* or post-test* OR before-after)
- #9 #7 AND #8 [Indexes=CPCI-S, BKCI-S Timespan=2007-2020]

ClinicalTrials.gov

Intervention or Title: (ferric carboxymaltose OR ferinject OR injectafer OR iroprem OR iron sucrose OR venofer OR iron isomaltoside OR monofer OR ferumoxytol OR feraheme OR ferrlecit or rienso OR IV iron OR iron th erapy OR intravenous iron OR iron infusion)

ICTRP

Single Search Box: (ferric carboxymaltose OR ferinject OR injectafer OR iroprem OR iron sucrose OR venofer OR iron isomaltoside OR monofer OR ferumoxytol OR feraheme OR ferrlecit or rienso OR IV iron OR iron therapy OR intravenous iron OR iron infusion

eAppendix 2. Descriptive summary of findings of non-randomized studies (NRS)

The number of participants in the included NRS ranged from 39 to 2547. The clinical settings included surgery (n = 5), CKD (n = 3) and digestive diseases.

Risk of bias

Overall risk of bias was moderate for seven NRS and only one study was deemed to be at overall low risk of bias. All studies were at serious or moderate risk of bias due to confounding, mainly due to the absence of or lack of controlling for important confounders. Risk of bias in measurement of outcomes was moderate across all studies due to outcome assessors either being aware of the intervention status or insufficient information was available to make a decision.

Infection

Three studies reported no statistically significant increases in the risk of infection associated with intravenous iron. One study found an increased risk and two studies reported a lowering of risk. One study, which lacked a comparator group, only reported an incidence of 25.9% of infection in patients with underlying digestive diseases receiving intravenous iron. Four studies provided no definition of infection. Of the remaining four studies, three studies used recognised classification systems (CDC, MedDRA, ICD-9 classification) and one study used an investigator-led definition.

eAppendix 3. GRADE assessment for primary outcome

	Certainty assessment					Summary of findings					
						Overall certainty of evidence	Study event rates (%)		Relative	Anticipated absolute effects	
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		With comparator	With IV iron	effect (95% CI)	Risk with comparator	Risk difference with IV iron
Infection											
19480 (64 RCTs)	not serious ^a	serious ^b	not serious ^c	not serious ^d	none	⊕⊕⊕⊖ MODERATE	950/9391 (10.1%)	1102/10089 (10.9%)	RR 1.17 (1.04 to 1.31)	100 per 1,000	17 more per 1,000 (from 4 more to 31 more)

CI: Confidence interval; IV: Intravenous; RR: Risk ratio

Explanations

a. Most information is from studies at low or unclear risk of bias. Point estimate largely unchanged in sensitivity analyses that excludes studies at high risk of bias.

b. Downgraded for inconsistency due to moderate heterogeneity (41.4%) and variation in point estimates across studies.

c. Population, intervention and comparators are broadly representative of current practice. Iron sucrose continues to be used in low to middle-income countries. d. Large number of participants and 95% CI excludes no effect

Study ID	Methods	Participants	Interventions (IV iron)	Comparator	Primary outcome	Secondary outcomes
Abdelazim et al, ³¹ 2017	Multicenter RCT (n = 3) (Kuwait)	Pregnant women >18 years, 24- 30 weeks' gestation, Hb 8-10 g/dL due to iron deficiency anaemia n = 260	Iron sucrose 200mg doses - calculated to total iron deficit	Oral iron	Treatment efficacy - changes in hemoglobin, serum ferritin, MCV at 3-months post- treatment	-
Abhilashini et al, ³² 2014	Single center RCT (India)	Pregnant women, 30-34 weeks' gestation, with established iron deficiency anaemia with Hb 6-8 g/dL n = 100	Iron sucrose according to Ganzoni formula, given over multiple dose	Ferrous sulphate 200mg x3/day	Change in Hb up to 37 weeks' gestation	
Adhikary et al, ³³ 2011	Single center RCT (Nepal)	CKD established on EPO, Hb <11 g/dL, Tsat <25%, Ferritin <300 ng/mL n = 90	Iron sucrose (Total 1000mg over 5 weeks)	Ferrous fumarate 152mg x3/day Both groups: 4000 IU EPO weekly	Improvement in Hb 30 days after therapy	
Agarwal et al, ³⁵ 2006	Multicenter RCT (n = 26) (USA)	Age >18 years, CKD (eGFR between 10 and 59 ml/min), Hb <12 g/dL, serum ferritin <100 ng/mL, Tsat <20% n = 75	Ferric gluconate 250mg on 4 separate days	Ferrous sulfate 325mg x3/day for 6 weeks	Change in hemoglobin from baseline to end point (day 43)	(i) Changes in iron parameters; (ii) HRQoL
Agarwal et al, ³⁴ 2015	Multicenter RCT (n = 2) (USA)	CKD Stage 3, Hb <120 g/L, Serum ferritin <100 ng/mL or Tsat <25% n = 136	Iron sucrose 200mg weekly for 5 weeks	Ferrous sulfate 325mg x3/day for 8 weeks	Between group difference in slope of mGFR from baseline to two years	(i) Changes in hemoglobin; (ii) Changes in KDQOL.
Aggarwal et al, ³⁶ 2003	Single center RCT (India)	Established CKD on conservative treatment, age >15 years, Hb 5-8 g/dL	Iron dextran 200 mg	Oral iron sulphate 200mg x3/day	Not specified, but measurements included changes in Hb and iron	

		n = 40			profiles, and adverse events	
Akhtar et al, ³⁷ 2018	Single center RCT (Pakistan)	Postpartum anaemia within 24- 48 hours of delivery, Hb 7-10 g/dL and ferritin <15 mcg/L n = 60	Iron sucrose 400mg (two doses)	Ferrous sulphate 200mg x3/day for 6 weeks	Changes in Hb and ferritin from baseline until 40 days postpartum	
Al et al, ³⁸ 2005	Single center RCT (Turkey)	Pregnant women between 26-34 weeks' gestation, Hb 8 to 10.5 g/dL, ferritin <13 ng/mL n = 90	Iron sucrose calculated to target hemoglobin (divided doses)	Oral iron 100mg x3/day	Hb concentration at day 28 post-treatment and at delivery	(i) Changes in ferritin levels; (ii) adverse effects; and (iii) fetal birth weight
Al-Momen et al, ³⁹ 2006	Single center RCT (Saudi Arabia)	Pregnant women gestational age <32 weeks, Hb <9 g/dL, ferritin <20 ng/mL n = 111	Iron sucrose calculated to target Hb	Ferrous sulphate 300 mg x3/day	Not specified, but measurements included changes in Hb and iron profiles, and safety monitoring	
Allen et al, ⁴⁰ 2015	Multicenter RCT (n = 15) (USA)	Age >18 years, Restless leg syndrome with baseline IRLS score >15 n = 46	Ferric carboxymaltose 500mg given twice	0.9% saline IV placebo	Changes in IRLS scores	(i) Changes in CG1-1 and PG-1; (ii) safety
Anker et al, ⁴¹ 2009	Multicenter RCT (n = 75) (Europe)	Adults >18 years, NYHA class II or III, LVEF <45%, Hb 95 - 135 g/dL, ferritin <100 ng/mL or 100 - 299 ng/mL with Tsat <20% n = 459	Ferric carboxymaltose 200mg doses calculated to iron deficit	0.9% saline IV placebo (opaque infusion kits)	Self-reported Patient Global Assessment and NYHA functional class at week 24	(i) self-reported PGA and NYHA class at weeks 4 and 12; (ii) distance on 6-minute walk-test; (iii) EQ-5D- 5L; (iv) adverse events; (v) changes in Hb and iron profiles
Athibovonsuk et al, ⁴² 2013	Single center (Thailand)	Age 20-70 years, Gynaecological malignancy receiving first-line platinum- based chemotherapy n = 64	Iron sucrose 200mg after each cycle of chemotherapy	Ferrous fumarate 200mg x3/day throughout	Requirement for blood transfusion	(i) total number of transfusion units; (ii) number of cycles requiring blood transfusion; (iii) changes in

				course of chemotherapy		hemoglobin; (iv) serious adverse events
Auerbach et al, ⁴³ 2004	Multicenter RCT (n = 4) (USA)	Histologic diagnosis of cancer, Hb <10.5 g/dL, ferritin <450 ng/mL, Tsat <19% n = 157	Intervention 1: Iron dextran 100mg boluses Intervention 2: Iron dextran total dose infusion	Comparator 1: No iron Comparator 2: Ferrous sulphate 325mg daily	Change in Hb from baseline to end point (6 weeks)	Haematopoietic response; (ii) time to Hb response; (iii) QoL
Auerbach et al, ⁴⁴ 2010	Multicenter RCT (Europe, USA, Russia)	Age >18 years, active nonmyeloid malignancies, Hb <10 g/dL related to cancer and chemotherapy n = 243	Iron dextran 400mg	No iron All groups received darbopoeitin 300-500 mcg	Achievement of target Hb (>11 g/dL)	 (i) Time to acheive target Hb; (ii) proportion of patients with an Hb rise >2 g/dL; (iii) change in FACT-F fatigue scale; (iv) safety
Bager et al, ⁴⁵ 2014	Single center RCT (Denmark)	Age >18 years admitted with non-variceal upper GI bleeding; ~48h post stabilisation of bleeding source and endoscopy; Anaemia according WHO definitions (Hb <12 g/dL in women; <13 g/dL in men) n = 97	Ferric carboxymaltose 1000mg	Oral ferrous sulphate 100mg x2/day for 3 months	Difference in Hb between both groups at 3 months post- treatment	(i) Proportion of patients with normal Hb at end of study; (ii) proportion of patients with Hb increased >2 g/dL; (iii) restoration of iron stores
Bailie et al, ⁴⁶ 2010	Multicenter RCT (n=62) (USA), cross-over trial	Adults with anaemia (WHO definition) with evidence of iron deficiency into one of the following cohorts: (i) secondary to CKD (Tsat <25% and ferritin <300 ng/mL) (ii) secondary to IBD (Tsat <25% and ferritin <300 ng/mL)	Ferric carboxymaltose 15mg/kg	0.9% saline IV placebo	Treatment-related adverse events within first 7 days	(i) Treatment-related adverse events during first 24 hours; (ii) all adverse events

Barish et al,47	Multicenter RCT	 (iii) other conditions (Tsat <25% and ferritin <100 ng/mL) n = 559 Age 18-85 years old, Diagnosis 	Intravenous ferric	Standard	Evaluate safety of	Changes in
2012 (1)*	(n = 95) (USA)	Age 18-85 years old, Diagnosis of iron deficiency anaemia (Hb <11g/dL), Ferritin <100 ng/mL, Tsat $<30\%$ (mixed population included CKD, Postpartum, GI bleeding, other) n = 708	carboxymaltose 750mg weekly until calculated iron deficit met (Ganzoni formula)	medical care	maximal dose of ferric carboxymaltose	hemoglobin and iron status
Barish et al, ⁴⁷ 2012 (2)*	Multicenter RCT (n = 95) (USA)	Age 18-85 years, Diagnosis of iron deficiency anaemia (Hb <11g/dL), Ferritin <100 ng/ml, Tsat <30% (mixed population included CKD, Postpartum, GI bleeding, other) n = 738	Intravenous ferric carboxymaltose 750mg or 15 mg/kg, whichever was smaller, one- off dosing	Standard medical care	Evaluate safety of maximal dose of ferric carboxymaltose	Changes in hemoglobin and iron status
Bastit et al, ⁴⁸ 2008	Multicentre RCT (Europe)	Age >18 years, Hb <11 g/dL, non-myeloid malignancy n = 396	Iron sucrose 200mg at each study visit (weeks 1, 4, 7, 10, 13 and 16)	Usual care	Proportion of patients achieving Hb >12 g/dL or rise of >2 g/dL	(i)time to achieving response; (ii) transfusion requirements; (iii) HRQoL measured by FACT-F; (iv) adverse events
Batool et al, ⁴⁹ 2018	Single center RCT (Pakistan)	Postpartum anaemia (Hb <10 g/dL) n = 82	Iron sucrose 200mg weekly for six weeks	Ferrous sulphate 200mg x3/day for 6 weeks	Hb response, defined as Hb rise of >3.5 g/dL, after 6 weeks of therapy	
Bayoumeu et al, ⁵⁰ 2002	Single center RCT (France)	Age >18 years, Pregnant women at 6 months gestation, Hb 8 - 10 g/dL, ferritin <50 mcg/L n = 50	Iron sucrose calculated to target Hb given	Oral iron 80 md x3/day for 4 weeks	Primary outcome not specified, but outcome measures included changes in Hb, iron	

			over 6 slow IV injections		profiles up to day 30, neonatal iron status	
Beck-da-Silva et al, ⁵¹ 2013	Multicenter RCT (Brazil)	Age <18 years, Heart failure NYHA functional class II, LVEF <40% within previous six months, Hb 9-12 g/dL, Tsat <20%, ferritin <500 mcg/L n = 23	Iron sucrose 200mg once a week for 5 weeks + oral placebo t.d.s. for 8 weeks	Comparator 1: Ferrous sulphate 200mg t.d.s. for 8 weeks and IV placebo for 5 weeks Comparator 2: Oral and IV placebo	Changes in maximal oxygen consumption	Changes in hemoglobin and iron stores
Beguin et al, ⁵² 2013	Multicenter RCT (Belgium)	Age 16-70 years, received autologous stem cell transplant for multiple myeloma or lymphoma, ferritin >100 ng/mL n = 72	Iron sucose 200mg on days 28, 42 and 56 after stem cell transplant + EPO	Comparator 1: EPO 300 mcg given at day 28 post-stem cell transplant followed by 2- weekly intervals until day 112 post-transplant Comparator 2: no i.v or EPO	Proportion with complete correction of anaemia (Hb >13g/dL) before day 126 post- transplant	(i) Median time to increase Hb level by >2 g/dL; (ii) proportion of responders (>2 g/dL) before day 126; (iii) transfusion requirements; (iv) adverse events; (v) quality of life using FACIT-F questionnaires
Bencaiova et al, ⁵³ 2009	Single center RCT (Switzerland)	Non-anaemic pregnant women between 15 and 20 weeks' gestation n = 260	Iron sucrose (1st phase - 400mg, 2nd phase - 600mg)	Ferrous sulphate 80mg daily until delivery	Percentage of pregnant women prior to delivery with Hb <11 g/dL	(i) changes in Hb and ferritin; (ii) birth weight; (iii) gestational age at birth; (iv) transfusion requirements; (v) hospital LOS after delivery
Bernabeu- Wittel et al, ⁵⁴ 2016	Multicentre RCT (n = 13) (Spain)	Age >65 year, requiring hip fracture surgery with Hb 9-12 g/dL	Intervention 1: Ferric	s.c. placebo and 0.9% saline IV	RBC transfusion requirements within 60 days	(i) changes in Hb levels 24 and 72 hours after surgery; (ii) mortality; (iii) adverse

		n = 306	carboxymaltose 1000mg and EPO Intervention 2: Ferric carboxymaltose 1000mg + s.c placebo	placebo (opaque infusion kits)		events; (iv) HRQoL; (iv) medical complications (MI, DVT, stroke, infection, delirium)
Bhandal et al, ⁵⁵ 2006	Single center RCT (UK)	Postpartum IDA, defined as Hb <9 g/dL and ferritin <15 mcg/L at 24-48 hours post-delivery) n = 44	Iron sucrose 400mg split over 2 doses	Ferrous sulphate 200mg x2/day over 6 weeks	Primary outcome not specified but study outcomes included changes in Hb, ferritin and adverse events	
Bhavi et al, ⁵⁶ 2017	Single center RCT (India)	Pregnant women between 14 and 34 weeks' gestation, Hb 7- 11 g/dL, ferritin <15ng/ml n = 112	Iron sucrose 200mg - total administered over multiple doses as per Ganzoni formula	Ferrous fumarate 100mg daily for 4 weeks	Changes in hemoglobin and iron stores	Safety and tolerability
Biboulet et al, ⁵⁷ 2018	Single center RCT (France)	Scheduled for elective hip or knee arthroplasty with Hb between 10 and 13 g/dL n = 100	Ferric carboxymaltose 1000mg (single dose) and 40,000 IU Eprex weekly for 3 weeks prior to surgery	Ferrous sulphate 160mg x2/day until day of surgery and 40,000 IU Eprex weekly for 3 weeks prior to surgery	Hb the day before surgery	 (i) Changes in ferritin; (ii) Erythrocyte mass the day before surgery; (iii) Postoperative Hb
Bielza et al, ⁵⁸ 2020	Single center RCT (Spain)	Age >70 years scheduled to undergo hip fracture surgery n = 153	Iron sucrose 200mg on days 1, 3 and 5 of admission	0.9% saline IV placebo (opaque infusion kits)	Difference in absolute functional gain defined as Barthel's Index at discharge minus BI on admission	 (i) Functional recovery at 3 months; (ii) mortality at 3,6 and 12 months; (iii) transfusion requirements; (iv) Hb at 3 months; (v) nosocomial infection;

						(vi) Postoperative delirium
Birgegard et al, ⁶⁰ 2010	Single center RCT (Sweden)	Blood donors with at least 5 previous blood donations, n = 120	Iron sucrose 200mg after each donation	Iron sulphate 100mg once daily for 20 days after each donation	Iron status at the end of the study	(i) iron status during the study; (ii) RLS frequency and severity
Birgegard et al, ⁵⁹ 2016	Multicenter RCT (n = 47) (Asia, USA, Europe)	Age >18 years, Non-myeloid malignancies on chemotherapy, Hb <120 g/dL, Tsat <50%, ferritin <800 mcg/L n = 350	Iron isomaltoside (amount as per Ganzoni formula) single dose	Iron sulfate 100mg x2/day for 12 weeks	Change in hemoglobin from baseline to 4 weeks post-treatment	(i) Changes in hemoglobin, serum ferritin, TIBC, Tsat and iron levels; (ii) Changes in quality of life from baseline; (iii) adverse drug reactions
Bisbe et al, ⁶¹ 2014	Single center RCT (Spain)	Adults >18 years, undergoing total knee arthroplasty, postoperative Hb <12 g/dL or Tsat <20% n = 122	Ferric carboxymaltose (amount as per Ganzoni formula) single dose	Ferrous sulphate 100mg once daily for 21 days	(i) Change in hemoglobin from post- operative day 4 to day 30; (ii) percentage of patients without anaemia (Hb >12g/dL)	 (ii) Hb at day 30; (ii) changes in quality of life (EQ-5D and BI); (iii) distance in 6- MWT; (iv) percentage of transfused patients; (v) adverse events (including infection)
Boomershine et al, ⁶² 2016	Single center RCT (USA)	Age >18 years with fibromyalgia, Hb <13 g/dL n = 81	Ferric carboxymaltose (15mg/kg), given over two doses	0.9% saline IV placebo (opaque infusion kits)	Proportion of patients with >13-point improvement from baseline to day 42 in FIQR score	(i) Changes in Hb and iron stores; (ii) changes in vital signs; (iii) adverse events
Breymann et al, ⁶³ 2008	Multicenter RCT (n = 20) (Europe)	Postpartum anaemia with Hb <10.5 g/dL n = 349	Ferric carboxymaltose 1000mg	Ferrous sulfate 100mg x2/day for 12 weeks	Change from baseline Hb to week 12 post- treatment	 (i) Changes in iron profiles; (ii) transfusion requirements; (iii) proportion of patients who achieved Hb

						levels of 12-16 g/dL; (iv) safety
Breymann et al, ⁶⁴ 2017	Multicenter RCT (n = 29) (International)	Age >18 years, 2nd or 3rd trimester pregnancy with iron deficiency anaemia (Hb <11 g/dL, ferritin <20 ng/mL) n = 252	Ferric carboxymaltose 1000-1500mg	Oral ferrous sulphate	Change in Hb from baseline to 3 weeks post-treatment	 (i) Changes in Hb and iron profiles; (b) proportion of women who achieved anaemia correction; (c) time to anaemia correction; (d) changes in HRQoL (SF-36)
Burden et al, ⁶⁵ 2015	Single center RCT (UK)	Elite athletes with non-anaemic iron deficiency (ferritin <30 mcg/L for females; <40 mcg/L for men) n = 15	Ferric carboxymaltose 500mg single dose	0.9 saline IV placebo (opaque infusion kits)	Changes in hepcidin and iron profiles in response to iron treatment up to 4 weeks post-treatment	(i) Changes in Hb and t-Hb mass; (ii) changes in aerobic capacity
Burns et al, ⁶⁶ 1996	Single center RCT (USA)	Hospitalised patients requiring total parenteral nutrition, iron deficiency defined as Fe-to- TIBC ratio <10% n = 23	Iron dextran 10mg supplemented to TPN for 7 days	No iron	Not specified. Outcome measurements included changes in Hb, iron profiles, transfusion requirements and infection	
Charles- Edwards et al, ⁶⁷ 2019	Single center RCT (UK)	Age >30 years, Symptomatic chronic stable heart failure, ferritin <100 mcg/L or 100-300 mcg/L with Tsat <20% n = 40	Iron isomaltoside 1000mg	0.9% saline IV placebo (opaque infusion kits)	Change in skeletal muscle energetics two weeks post-treatment	 (i) Changes in 6MWT; (ii) peak oxygen consumption; (iii) Hb and iron profiles; (iv) NYHA symptoms; (v) LVEF
Charytan et al, ⁶⁹ 2005	Multicenter RCT (n = 16) (USA)	Age >18 years, non-dialysis dependent CKD, Hb <10.5 g/dL, Tsat <15%, ferritin <300 ng/mL n = 96	Iron sucrose 200mg on days 1, 8, 15, 22 and 29	Ferrous sulfate 325mg x3/day	Mean changes in Hb and ferritin from baseline to day 43	 (i) Changes in Tsat; (ii) number of patients achieving Hb >11 g/dL; (iii) adverse events

Charytan et al, ⁶⁸ 2012	Multicenter RCT (n = 56) (USA)	Adults aged 18-85 years, 3/12 history non-dialysis dependent CKD (Hb <11.5 g/dL) or dialysis dependent CKD (Hb <12.5 g/dL) n = 254	Ferric carboxymaltose 15mg/kg (max 1g) in non- dialysis dependent CKD; 200mg in dialysis dependent CKD	Usual medical care Both groups received EPO 2000 U	Safety of maximum administered dose	 (a) Proportion of patient receiving Hb increase of >1g/dL; (b) proportion of patients achieving an Hb >12.0 g/dL; (b) Mean changes in Hb, ferritin, Tsat
Cho et al, ⁷⁰ 2016	Single center RCT (Korea) Crossover trial	Age >18 years, Primary restless legs syndrome, no co- morbidities n = 65	Ferric carboxymaltose 1000mg	0.9% saline IV placebo (opaque infusion kits)	Change from baseline in the International RLS Severity scale at week 6 post-treatment	(i) Change in sleep (Pittsburg Sleep Quality Index) and health-related quality of life (SF-36)
Cho et al, ⁷¹ 2018	Single center RCT (Korea)	Restless leg syndrome, International RLS score >15, ferritin <300 ng/mL, Hb >12 g/dL, Tsat <45% n = 65	Ferric carboxymaltose 500mg	0.9% saline IV placebo (opaque infusion kits)	Change from baseline in IRLS score at week six post-randomisation	(i) Changes in SF-36 and sleep quality
Coyne et al, ⁷² 2007	Multicenter RCT (n = 37) (USA)	Age >18 years, CKD on HD for >90 days, ferritin <1200 ng/mL, Tsat <25%, Hb <11 g/dL, established on EPO n = 134	Ferric gluconate 1g adminstered over 8 consecutive doses of 125mg	Usual care	Change in Hb from baseline to week 6	 (i) Percentage of with Hb response >2 g/dL; (ii) changes in iron profiles; (iii) safety
Dalal et al, ⁷³ 2008	Single center RCT (India)	Pregnant women (26-34 weeks' gestation) with anaemia, Hb 7- 11 g/dL n = 150	Iron sucrose 200mg weekly - calculated to match iron deficit	Ferrous sulphate 100mg x2/day until delivery	Changes in Hb from baseline to 2 weeks, 4 weeks and delivery	(i) Safety; (ii) maternal and fetal outcomes
Damineni et al, ⁷⁴ 2016	Single center RCT (India)	Postpartum anaemia, defined as Hb 7-10 g/dL n = 90	Ferric carboxymaltose 1000mg	Ferrous ascorbate 100mg x2/day for 6 weeks	Change in Hb at 6 weeks post-treatment	(i) Proportion of patients with rise in Hb >3 g/L; (ii) tolerability and compliance

Dangsuwan et al, ⁷⁵ 2010	Single center RCT (Thailand)	Age 20-65 years, gynaecology malignancy who have undergoing surgery and receiving chemotherapy, Hb <10 g/dL n = 44	Iron sucrose 200mg one dose	Ferrous sulphate 200mg x3/day	Incidence of RBC transfusion in subsequent chemotherapy cycle	(i) Changes in Hb; (ii) no. of RBC units; (iii) adverse events; (iv) QoL scores measured by FACT-An
Darwish et al, ⁷⁶ 2019	Single center RCT (Egypt)	Pregnant women gestational >14 weeks, Hb 7-10 g/dL, ferritin <12mg/L n = 66	Iron dextran, amount as per Ganzoni formula over multiple doses	Ferrous fumarate 60mg x3/day for 4 weeks	Change in Hb from baseline to 4 weeks	(i) Changes in iron stores; (ii) adverse effects
Deeba Shafi et al, ⁸³ 2012	Single center RCT (India)	Pregnant women 28-37 weeks' gestation with established iron deficiency anaemia (Hb 6-10 g/dL and Ferritin <15ng/ml) n = 200	Iron sucrose 200mg on alternate days, calculated to achieve Hb of 12 g/dL	Ferrous ascorbate 200mg daily	Hb at 2, 4 and 6 weeks post-treatment	Ferritin at 2, 4 and 6 weeks post-treatment
Deng et al, ⁷⁷ 2017	Single center RCT (China)	CKD patients on haemodialysis with RLS, ferritin <200 ng/mL, Tsat <20% n =32	Iron sucrose 100mg x3/week until total dose of 1000mg	0.9% saline IV placebo (opaque infusion kits) Both groups received EPO	Changes in International RLS scores at two weeks post-treatment	(i) Changes in Hb and iron status; (ii) safety and adverse events
Drexler et al, ⁷⁸ 2020	Single center RCT (Austria)	Iron deficient (ferritin <30 mcg/L) blood donors n = 176	Ferric carboxymaltose 1000mg	Ferrous sulphate 100mg (x3 per week) for 10 weeks	Change in Tsat (%) at 8-12 weeks post- randomisation	 (i)Changes in other markers of iron status and Hb; (ii) adverse events; (iii) tolerance; (iv) symptoms of restless leg syndrome, HRQoL and fatigue
Dubey et al, ⁷⁹ 2016	Single center RCT (India)	Pregnant women gestation age 20-34 weeks, Hb 7-9 g/dL, Ferritin <15 ng/mL n = 200	Iron sucrose calculated to target Hb of 11 g/dL	Oral iron 100mg x3/day throughout pregnancy	Changes in Hb on day 14 and day 28 post- randomisation	(i) Changes in reticulocyte count and ferritin; (ii) side effects; (iii) proportion of women achieving Hb >11 g/dL; (iv) neonatal outcomes; (v)

						transfusion requirements
Edwards et al, ⁸⁰ 2009	Single center RCT (UK)	Adults scheduled to undergo bowel resection for colorectal cancer n =62	Iron sucrose 600mg split over 2 doses	0.9% saline IV placebo (opaque infusion kits)	Change in Hb between recruitment and day of admission	(i) RBC transfusion rate; (ii) changes in iron profiles; (iii) hospital LOS; (iv) adverse events
El Khouly et al, ⁸¹ 2017	Single center RCT (Egypt)	Postpartum iron deficiency anaemia, Hb <9 g/dL and ferritin < 15 mcg/L n = 352	Iron sucrose 200mg x3/week	Oral ferrous sulphate 150mg x2/day for 6 weeks	Changes in Hb and ferritin up to day 60 postpartum	Safety, tolerability and compliance
Evstatiev et al, ⁸² 2013	Multicenter RCT (n = 69) (Europe)	Age >18 years, Non-anaemic patients with IBD n = 206	Ferric carboxymaltose 500mg	0.9% saline IV placebo (opaque infusion kits)	Time to occurrence of anaemia (Hb <12 g/dL in females and 13 g/dL in males)	(i) Proportion of patients with anaemia at 2,4,6 and 8 months post-treatment; (ii) changes in HRQoL (SF-36); (iii) changes in Crohn's disease activity
Favrat et al, ⁸⁴ 2014	Multicenter RCT (n = 21) (Europe)	Women aged>18 years (premenopausal), symptomatic fatigue, borderline anaemia (Hb >11.5 g/dL) with evidence of iron deficiency (ferritin <15 mcg/L or ferritin <50 mcg/L and Tsat <20%) n = 290	Ferric carboxymaltose 1000mg	0.9% saline IV placebo (opaque infusion kits)	Proportion of patients who improved Piper Fatigue Score by >1 from baseline to day 56	(i) Changes in PFS total and subscale score and SF-12 QoL score; (ii) correction of anaemia and iron deficiency; (iii) adverse events
Ferrer-Barcelo et al, ⁸⁵ 2019	Single center RCT (Spain)	Age >18 years, non-variceal acute upper gastrointestinal bleed (Hb <10 g/dL on day of hospital discharge) n = 61	Ferric carboxymaltose 1500-2000mg	Ferrous sulphate 325mg x2/day for 6 weeks	Resolution of anaemia at day 42 (men, Hb >13 g/dL; women, Hb >12 g/dL)	(i) Partial response (Hb rise >2 g/dL); (ii) changes in iron profiles; (iii) adverse events

Fishbane et al, ⁸⁶ 1995	Single center RCT (USA)	Adults with CKD on haemodialysis for atleast 3 months, receiving EPO, serum ferritin >100 ng/mL, Tsat >15% n = 28	Iron dextran 200mg twice weekly	Ferrous sulphate (325mg x3/day) or iron polysaccharide (150mg x2/day)	Not specified. Outcome measurements included haematocrit, ferritin and Tsat	
Friel et al, ⁸⁷ 1995	Single center RCT (Canada)	Low birth weight newborns n = 26	Iron dextran 250 mcg/kg/day	No iron	Not specified. Outcome measurements included haematologic and biochemical parameters, infection rates, red blood cell haemolysis and iron balance	
Froessler et al, ⁸⁸ 2013	Single center RCT (Australia)	Women with iron deficiency anaemia (Hb <110 g/L and ferritin <12 mcg/L), antenatal between 28-36 weeks' gestation, or within 72 hours of birth or delivery with blood loss >500 mls. n = 271	Iron sucrose 400mg (divided into 2 doses)	Ferrous sulphate 160mg daily for 6 weeks postpartum or until delivery (if started antenatal)	Incidence of severe anaemia (Hb<8 g/dL) prior to hospital discharge	RBC transfusion requirements
Froessler et al, ⁸⁹ 2016	Single center RCT (Australia)	Age >18 years scheduled for abdominal surgery, Hb <12 g/dL (females) and <13 g/dL; (males), ferritin <300 mcg/L, Tsat <25% n = 72	Ferric carboxymaltose 15mg/kg pre- operatively, and 0.5 mg per 1mL of blood loss postoperatively	Usual medical care	Incidence of RBC transfusion	(i) Changes in Hb from randomisation to admission; (ii) ICU admission; (iii) perioperative morbidity (infection, respiratory failure, renal impairment, DVT); (iv) discharge Hb; (v) length of stay; (vi) 30-day mortality; (vii) HRQoL scores

Garrido- Martin et al, ⁹⁰ 2012	Single center RCT (Spain)	Age >18 years, elective cardiac surgical ICU (postoperative) n = 159	Iron sucrose 300mg (given over 3 separate doses) and oral placebo	Comparator 1: Ferrous fumarate 105mg daily for 1 month and IV placebo Comparator 2: IV and oral placebo	Change in Hb from baseline up to day 30 post-hospital discharge	(i)changes in iron profiles; (ii) postoperative transfusion requirements
Grote et al, ⁹¹ 2009	Multicenter RCT (n = 3) (Sweden)	Age 18-70 years, Restless leg syndrome, ferritin <45 mcg/L n = 60	Iron sucrose 200mg (x5 doses over 3 weeks)	0.9% saline IV placebo (opaque infusion kits)	Between group difference in International RLS score at the 11-week follow-up visit	(i) Treatment effectson daytime sleepiness;(ii) adverse events;(iii) changes in Hb andiron status
Gupta et al, ⁹² 2014	Single center RCT (India)	Singleton pregnancy between 24-34 weeks' gestation, Hb 7 - 9 g/dL and ferritin <15 ng/mL n = 100	Iron sucrose calculated to target Hb of 11 g/dL	Ferrous sulphate 200 mg x3/day for 4 weeks	Increase in hemoglobin and ferritin over 4 weeks post-treatment	 (i) Reticulocyte count rise; (ii) mean Hb at the time of delivery; (iii) side effect; (iv) perinatal outcomes
Hedenus et al, ⁹³ 2007	Multicenter RCT (n = 15) (Sweden)	Adults with Non-Hodgkin's Lymphoma, Chronic Lymphocytic Leukaemia or myeloma, Hb 9-11 g/dL, evidence of stainable iron on bone marrow aspirate within 1 month prior to inclusion n = 67	Iron sucrose 100mg weekly from weeks 0 to 6, every second week from weeks 8 to 14	No iron	Mean change in Hb from baseline to end of treatment	 (i) Hb response (increase >2 g/dL); (ii) time to Hb response; (iii) changes in iron profiles; (iv) EPO requirements
Hedenus et al ^{.94} 2014	Multicenter RCT (n = 11) (Europe)	Adults with lymphoid malignancies, Hb 8.5-10.5 g/dL, Tsat <20% and ferritin >30 ng/mL, received chemotherapy for >8 weeks prior to inclusion n = 17	Ferric carboxymaltose 1000mg	Usual medical care	Mean change in Hb from baseline to week 8 post-treatment	(i)Safety; (ii) Hb response (increase >1 g/dL) and correction (Hb >11 g/dL)

Henry et al, ⁹⁵ 2007	Multicenter study (USA)	Age >18 years, due to start chemotherapy for a non- myeloid malignancy, Hb <11 g/dL, ferritin >100 ng/ml or Tsat >15%. n = 187	Ferrous gluconate IV 125mg once weekly for 8 weeks	Comparator 1: Ferrous sulphate 325mg t.d.s Comparator 2: No iron	Mean change in Hb from baseline to endpoint, first RBC transfusion or study withdrawal	(i)Hb response (>2 g/dL); (ii) safety
Holm et al, ⁹⁶ 2017	Single center RCT (Denmark)	Postpartum haemorrhage >700 ml and <1000 ml, or PPH >1000ml and Hb >6.5 g/dL at least 12 hours after delivery n = 196	Iron isomaltoside 1200mg, single dose	Oral iron 100mg daily	Change in physical fatigue scores of MFI questionnaire within 12 weeks postpartum	(i) Changes in Hb, ferritin, iron; (ii) changes in other dimensions of MFI and symptoms of depression; (iii) time to lactogenesis; (iv) time to discontinuation of breastfeeding; (v) transfusion
Iyoke et al, ⁹⁷ 2017	Multicenter RCT (n = 2) (Nigeria)	Postpartum anaemia Hb 6 - 7.9 g/dL, red cell features of iron deficiency at 48 hours or later following vaginal delivery n = 284	Iron dextran, calculated as hemoglobin required to reach 10 g/dL multiplied by 250 mg of parenteral iron	100mg oral elemental iron for 6 weeks	Proportion of women who attained a Hb of at least 10 g/dL by 6 weeks postpartum	
Jain et al, ⁹⁸ 2013	Single center RCT (India)	Postpartum Hb <8 g/dL within 48h of delivery n = 40	Iron sucrose calculated to total iron deficit, given over three separate doses in one weeks	Ferrous fumarate 300 mg daily for 14 days	Change in Hb at14 days postpartum	Safety and tolerability
Johansson et al, ⁹⁹ 2015	Single center RCT (Denmark)	Age >18 years, undergoing elective or subacute CABG, valve or combination without anaemia (Hb >12 g/dL for women, Hb >13 g/dL for men)	Iron isomaltoside 1000mg once only	0.9% saline IV placebo (opaque infusion kits)	Less decrease in postoperative Hb level in non-anaemic patients undergoing cardiac surgery	(i)RBC transfusion requirements; (ii) changes in iron profiles; (iii) safety

		n = 60				
Kalra et al, ¹⁰⁰ 2016	Multicenter RCT (n = 67) (Europa, Asia, USA)	Age >18 years, Hb <11 g/dL, serum ferritin mcg/L, Tsat <20%, not received EPO in previous 8 weeks n = 351	Iron isomaltoside calculated according to Ganzoni formula	Iron sulphate 100 mg x2/day for 8 weeks	Change in Hb from baseline from baseline to week 4 post- randomisation	(i)Change in Hb from weeks 2 to 8; (ii) changes in iron profiles; (iii) changes in HRQoL from baseline to weeks 4 and 8; (iv) safety
Karkouti et al, ¹⁰¹ 2006	Single center RCT (Canada)	Adults >18 years, postoperative open-heart surgery, total hip arthroplasty or spinal fusion, Hb 70-90 g/dL n = 38	Intervention 1: Iron sucrose 600mg (given over 3 split doses) Intervention 2: Iron sucrose 600mg (given over 3 split doses) and EPO (1200 IU/kg)	0.9% saline IV placebo (opaque infusion kits)	Change in Hb from postoperative day 1 to day 7	 (i) Hb up to 6 weeks postoperatively; (ii) changes in iron profiles on day 7; (iii) RBC transfusion requirements; (iv) hospital length of stay; (v) changes in HRQoL (SF-36)
Kasper et al, ¹⁰² 1998	Single center RCT (Germany)	Age >18 years, Hb <12.0 g/dL, scheduled to undergo major surgery and eligible for autologous blood donation n = 108	Ferric gluconate 102.5 mg IV (once) and oral iron (ferric succinate) 92.5mg x3/day for 21 days	Oral iron (ferric succinate) 92.5mg x3/day for 21 days and IV placebo	Improvement in Hb during the study period	(i) Changes in iron profiles; (ii) volume of blood donated; (iii) adverse events
Keeler et al, ¹⁰³ 2017	Multicenter RCT (n = 7) (UK)	Scheduled to undergo colorectal cancer excision with anaemia, defined as Hb <11 g/dL in women and <12 g/dL in men n = 116	Ferric carboxymaltose 1000mg, stratified on Hb (if Hb <10 g/dL, 2000mg could be given	Ferrous sulphate 200mg x2/day until surgery	Transfusion requirements from preoperative recruitment until postoperative outpatient review	 (i) Changes in hemoglobin and haematinic profiles; (ii) postoperative complications; (iii) RBC transfusion requirements

Keller et al, ¹⁰⁴ 2020 Khalafallah et al, ¹⁰⁵ 2010	Single center RCT (Switzerland) Single center RCT (Australia)	Blood donors with evidence of non-anaemic iron deficiency (ferritin <50 mcg/L) n = 203 Pregnant women <28 weeks' gestation with Hb 8.5 – 11.5 g/dL and ferritin <30 mcg/L	Ferric carboxymaltose 800mg Iron polymaltose, dose calculated according to	0.9% saline IV placebo (opaque infusion kits) Ferrous sulphate 80mg daily until delivery	Self-rated average fatigue during the past 7 days, assessed 6-8 weeks post- randomisation Predelivery Hb and iron stores	 (i) Changes in other self-reported fatigue and HRQoL measures; (ii) changes in Hb and ferritin; (iii) safety reporting Safety, tolerability and compliance
Khalafallah et al, ¹⁰⁷ 2016	Multicenter RCT (n = 2) (Australia)	n = 200 Age >18 years, requiring major elective surgery with at least planned hospital stay of 2 nights, Hb 70-120 g/L, ferritin <100 or Tsat 20% n = 201	weight and target Hb Ferric carboxymaltose 1000mg	Usual medical care	Changes in Hb and iron stores at 4 weeks postoperatively	(i) Safety and tolerability; (ii) length of hospital stay; (iii) infections; (iv) HRQoL at 4 and 12 weeks postoperatively
Khalafallah et al, ¹⁰⁶ 2018*	Single center RCT (Australia)	Pregnant women in second/third trimester of pregnancy, Hb 8.5- 12 g/dL, ferritin <100 mcg/L or Tsat <20% n = 166	Intervention 1: Ferric carboxymaltose 1000mg Intervention 2: Iron polymaltose 1000mg	Ferrous sulphate 105mg daily until delivery	Change in Hb and ferritin from baseline to 4 weeks post- randomisation	(i) Tolerability and adverse events; (ii) transfusion requirements; (iii) changes in HRQoL; (iv) fetal outcomes
Kim et al, ¹¹⁰ 2007	Single center RCT (Korea)	Age>18 years, Hb <12 g/dL, undergoing chemotherapy for cervical cancer n = 75	Iron sucrose 200mg at each chemotherapy cycle	Usual medical care	RBC transfusion requirements	(i) Changes in Hb; (ii) proportion of patients with resolution of anaemia (defined as Hb >12 g/dL)
Kim et al, ¹⁰⁹ 2009	Multicenter RCT (n = 3) (South Korea)	Women experiencing menorrhagia with Hb <9 g/dL, scheduled to undergo elective surgery	Iron sucrose 200mg 3 days a week, for 3 weeks prior to surgery	Iron succinylate 80mg once daily for 3 weeks prior to surgery	Changes in Hb preoperatively	Safety

		n = 76				
Kim et al, ¹¹¹ 2017	Multicenter RCT (n = 7) (South Korea)	Adults (age >20 years) with acute isovolemic anaemia (Hb 7-10 g/dL) at 5-7 days post- gastrectomy n = 454	Ferric carboxymaltose 1000mg	0.9% saline IV placebo (opaque infusion kits)	No. of hemoglobin responders (Hb rise >2 g/dL) at 12 weeks post- randomisation	(i) Percentage of patients with Hb >10 g/dL, 11 g/dL and 12 g/dL by weeks 3 and 12; (ii) self-reported HRQoL; (iii) changes in Hb and iron profiles over the study duration
Kochhar et al, ¹¹² 2013	Single center RCT (India)	Singleton pregnant women between 24-34 weeks' gestation, moderate iron deficiency anaemia (Hb 7 -9 g/dL, MCV <85 fl, ferritin <15 ng/mL) n = 100	Iron sucrose, calculated to total iron deficit and targeted to Hb >12 g/dL, given over three separate doses	Ferrous sulphate 200 mg x3/day for 4 weeks	Change in Hb from baseline up to day 30 post-randomisation	(i) Requirement for RBC transfusion; (ii) adverse events; (iii) neonatal outcomes
Krayenbuehl et al, ¹¹³ 2020	Multicenter RCT (n = 4) (Switzerland)	Premenopausal, menstruating women aged 18 years with fatigue and non-anaemic iron deficiency (Hb >12 g/dL, ferritin <50 mcg/L) n = 90	Iron sucrose 800 mg over multiple doses)	0.9% saline IV placebo (opaque infusion kits)	Changes in fatigue scores 6 weeks after treatment initiation	(i) Changes in Hb and ferritin; (ii) Safety
Kulnigg et al, ¹¹⁴ 2008	Multicenter RCT (n = 36) (Europe and South America)	IBD with iron deficiency anaemia (Hb <10 g/dL and Tsat <20% or ferritin <100 mcg/L) n = 200	Ferric carboxymaltose, dose calculated according to Ganzoni formula	Ferrous sulphate 100mg x2/day for 12 weeks	Change in Hb from baseline to week 12	(i) Changes in Hb and iron profiles from baseline to weeks 2, 4 and 8; (ii) treatment responses, defined as Hb rise >2 g/dL and/or proportion of participants with resolution of anaemia; (iii) tolerability

Kulnigg- Dabsch et al, ¹¹⁵ 2013	Multicenter RCT (Austria and Germany)	IBD associated thrombocytosis and Hb >10.5 g/dL, age 18 and 60 years, ferritin <100 ng/mL, Tsat <30% n = 26	Intervention 1: Ferric carboxymaltose 500mg single dose Intervention 2: Ferric carboxymaltose 1000mg single dose	0.9% saline IV placebo (opaque infusion kits)	Decrease in platelet count of at least 25% at 6 weeks	 (i) Effect on ferric carboxymaltose on platelet count, disease activity and HRQoL; (ii) safety at week 6
Kuo et al, ¹¹⁶ 2008	Multicenter RCT (n = 2) (Taiwan)	CKD on long-term haemodialysis, ferritin <800 mcg/L n = 110	Iron sucrose 100mg once weekly for 12 weeks	0.9% saline IV placebo	Not specified. Outcomes measurements included: (i) oxidative damage to peripheral blood lymphocytes; (ii) changes in ferritin	
Li et al, ¹¹⁷ 2008	Single center RCT (China)	CKD on maintenance haemodialysis, Hb 6-9 g/dL, ferritin <500 mcg/L, Tsat <30% n = 46	Iron sucrose 100mg twice a week for 8 weeks, once a week for 4 weeks after	Ferrous succinate 200mg x3/day for 12 weeks	Increase in Hb >3 g/dL or Hct >10% during therapy	
Lindgren et al, ¹¹⁸ 2009	Multicenter RCT (n = 11) (Sweden)	Age 18-85 years, IBD, Hb <11.5 g/dL, ferritin <300 mcg/L n = 91	Iron sucrose 1000mg split over 200mg doses on alternate days	Ferrous sulphate 200mg x2/day over 20 weeks	Hb response (>2 g/dL) at 20 weeks post- treatment	
Litton et al, ¹⁰⁸ 2016	Multicenter RCT (n = 4) (Australia)	Age >18 years, within 48hrs of ICU admission, anticipated to require ICU beyond next calendar day, Hb <100 g/L at any time in the preceding 24 hours n = 140	Ferric carboxymaltose 500mg, redosing 4 days later if still eligible (max 4 doses allowed)	0.9% saline IV placebo (opaque infusion kits)	Number of RBCs transfused per patient between randomisation and hospital discharge	(i) Hb at hospital discharge; (ii) ICU and hospital LOS; (iii) proportion of patients receiving a transfusion; (iv) mortality; (v) infection

Maccio et al, ¹¹⁹ 2010	Single center RCT (Italy)	Age >18 years, advanced cancer, Hb <10 g/dL, ferritin 100-800 ng/ml, Tsat >15% n = 148	Ferric gluconate 125mg once weekly for 12 weeks	Oral lactoferrin 200mg daily for 12 weeks	Change in Hb from baseline until end of study period	(i) Hb response (Hb rise of >2 g/dL or Hb >12 g/dL); (ii) changes in iron profiles, CRP and ESR
Macdougall et al, ¹²¹ 1996	Single center RCT (UK)	CKD on regular haemodialysis, Hb <8.5 g/dL, ferritin 100-800 mcg/L n = 37	Iron dextran 250mg every two weeks	Comparator 1: Ferrous sulphate 200mg x3/day Comparator 2: No iron	Changes in Hb, iron status and EPO dosage requirements from baseline until end of study period (16 weeks)	
Macdougall et al, ¹²⁰ 2014	Multicenter RCT (n = 193) (USA, Europe)	Age >18 years, non-dialysis CKD, Hb 9-11 g/dL, ferritin <100 ng/ml or <200 ng/mL with Tsat 20%, eGFR <60 n = 626	Ferric carboxymaltose adjusted to target ferritin in two groups: (i) High: 400-600; (ii) Low: 100-20	Ferrous sulfate 304mg x2/day for 52 weeks	Time to initiation of other anaemia management of occurrence of an Hb trigger (Hb <10 g/dL during weeks 8-52)	(i) Changes in Hb and iron profiles; (ii) transfusion requirements (iii) safety
Madi-Jebara et al, ¹²² 2004	Single center RCT (Lebanon)	Postoperative cardiac surgery critical care, Hb 7-10 g/dL n = 120	Iron sucrose 200mg daily until calculated total iron deficit reached	0.9% saline IV placebo (opaque infusion kits)	Change in Hb from baseline until postoperative day 30	(i) Changes in iron profiles; (ii) RBC transfusion requirements; (iii) In- hospital mortality
McMahon et al, ¹²³ 2010	Multicenter RCT (n = 6) (Australia)	Age 18-80 years, CKD stages 3- 5, Hb >11 g/dL, ferritin <300 mcg/L, Tsat <25% n = 100	Iron sucrose 200mg every 2 months to maintain ferritin between 300-500 mcg/L	Ferrous sulphate 105mg daily to maintain ferritin between 100- 150 mcg/L	Changes in Hb at 12 months or at termination (e.g. starting dialysis, adverse event, starting ESA)	(i) Changes in renal function; (ii) HRQoL; (iii) time to commencement of dialysis/ESA
Meyer et al, ¹²⁴ 1996	Single center RCT (South Africa)	Pre-term infants (<33 weeks' gestation, <1.5kg), venous Hct <0.38 n = 42	Iron sucrose 6mg/kg per week	Ferrous sulphate 12 mg/kg/day	Specific a priori endpoints not reported	

Michael et al, ¹²⁵ 2002	Multicenter RCT (n = 69) (USA)	Adults with CKD on chronic haemodialysis, established on EPO, Hb <12.3 g/dL, ferritin <800 ng/mL, Tsat <50% n = 2534	Ferric gluconate 125mg	0.9% saline IV placebo (opaque infusion kits)	Drug intolerance and life-threatening adverse events	(i) Rate of all adverse events; (ii) cross- reactivity to previously exposed iron dextran
Montano- Pedroso et al, ¹²⁶ 2018	Multicenter RCT (n = 2) (Brazil)	Adult women (18-55 years), post-bariatric surgery with a BMI <32 kg/m ² and stabilised weight loss for at least 6 months n = 56	Iron sucrose 400mg (given over two doses)	Iron hydroxide 100mg x2/day for 8 weeks	Hb at postoperative day 56	 (i) Changes in iron profiles; (ii) adverse effects; (iii) postoperative complications on days 7,28 and 56; (iv) changes in HRQoL (SF-36 and FACIT-F)
Moppett et al, ¹²⁷ 2019	Multicenter RCT (n = 2) (UK)	Age >70 years, emergency admission with hip fracture n = 80	Iron sucrose 200mg on three separate occasions perioperatively	Usual medical care	Difference in mean reticulocyte count at day 7 after randomization	(i) Cardiovascular or infective complications; (ii) changes in Hb and iron parameters; (iii) length of stay; (iv) mortality; (v) transfusion requirements; (vi) postoperative mobility
Mudge et al, ¹²⁸ 2012	Single center RCT (Australia)	Adults (age >18 years) scheduled to undergo living- donor or deceased donor kidney transplant surgery n = 104	Iron polymaltose 500mg single dose on postoperative day 4	Ferrous sulphate 210 mg x2/day until Hb >11 g/dL	Time to Hb more than or equal to 11 g/dL	(i) Adverse events; (ii) acute rejection episodes; (iii) infections; (iv) blood transfusions or EPO
Na et al, ¹²⁹ 2011	Single center RCT (South Korea)	Scheduled for bilateral total knee arthroplasty, Hb >10 g/dL, ferritin 100-300 mcg/L and Tsat <20% n = 108	Iron sucrose 200mg – one dose intraoperatively, followed by single dose on post-op days 1,2,3 and 5 if postoperative Hb	No iron	Changes in postoperative Hb and RBC transfusion requirements up to 6 weeks postoperatively	Changes in iron profiles

			was between 7-8 g/dL			
Nanthini et al, ¹³⁰ 2017	Single center RCT (India)	Age 18-45 years, singleton pregnancy 12-32 weeks' gestation, Hb 7-9 g/dL n = 127	Iron sucrose 48 hourly, dose calculated to iron deficit	Intramuscular iron every 8 weeks	Proportion achieving target Hb of 11 g/dL up to 8 weeks post- treatment	Safety and tolerability
Neeru et al, ¹³¹ 2012	Single center RCT (India)	Pregnant women 14-36 weeks' gestation, Hb 6.5-10.9 g/dL, ferritin <27 ng/dL n = 100	Iron sucrose on alternate days, dose calculated to iron deficit	Ferrous fumarate 300mg	Efficacy defined as improvement in Hb by 1 g/dL at 4 weeks post- treatment	Tolerability
Neogi et al, ¹³² 2019	Multicenter RCT (n = 4) (India)	Pregnant women age >18 years, Hb 5-8 g/dL if gestation 20 and 28 weeks, Hb 5-9 g/dL if gestation >28 weeks n = 2018	Iron sucrose on alternate days, dose calculated to target Hb	Oral iron 100mg x2/day until 6 weeks postpartum	Composite of postpartum haemorrhage, puerperal sepsis, shock, prolonged hospital LOS, need for transfusion, ICU admission and referral to another centre	(i) Components of maternal primary outcomes; (ii) composite fetal outcome (low birthweight, preterm labour, perinatal death); (iii) changes in Hb and ferritin
Ng et al, ¹³³ 2018	Multicenter RCT (n = 2) (UK)	Adult with oesophageal cancer and treatment decision for palliative chemotherapy (Hb <12 g/dL in females, Hb <13 g/dL in men) n = 27	Iron maltoside - dose calculated according to Ganzoni formula	Usual medical care	Feasibility (screen failure rates, acceptability, non- concordance, retention rates)	(i) Changes in Hb and iron profiles post- chemotherapy; (ii) transfusion requirements; (iii) mortality; (iv) HRQoL scores
Noronha et al, ¹³⁴ 2018	Single center RCT (India)	Age >18 years, malignancy requiring chemotherapy, Hb <12 g/dL, ferritin <100 ng/mL or Tsat <20% n = 192	Iron sucrose every 3 weeks, calculated as per iron deficit formula	Ferrous sulfate 100mg x3/day for 6 weeks	Change in hemoglobin from baseline to 6 weeks post-treatment	 (i) Proportion of patients with Hb rise >1g/dL; (ii) RBC transfusion requirements; (iii) quality of life (FACT- An questionnaires); (iv) response to cancer

						therapy and overall survival; (v) safety profile of iron
Okonko et al, ¹³⁵ 2008	Multicenter RCT (n = 2) (UK and Poland)	Age >21 years, NYHA Class II or III, Hb <12.5 g/dL (anaemic group) or Hb 12.5 to 14.5 g/dL (non-anaemic group), ferritin <100 mcg/L or 100-300 mcg/L if Tsat <20%, LVEF <45%	Iron sucrose administered every 4 weeks up to 16 weeks, calculated to iron deficit	Usual medical care	Change in absolute pVO2 from baseline to week 18 post-treatment	(i) Changes in Hb, iron profiles; (ii) changes in LVEF, NYHA class; (iii) changes in global HRQoL and fatigue
Olijhoek et al, ¹³⁶ 2001	Multicenter RCT (n = 18) (Europe)	n = 35 Age >18 years, scheduled to undergo orthopaedic surgery that was estimated to require 2 to 4 units of blood, Hb 10-13 g/dL, ferritin >50 mcg/L	Intervention 1: EPO and iron saccharate 200mg on days 1 and 8	Comparator 1: EPO + oral iron 200mg daily for 14 days	Total RBC production from day 1 to day 14 (day before scheduled surgery)	Changes in Hb
		n = 110	Intervention 2: Placebo and iron saccharate 200mg on days 1 and 8	Comparator 2: Placebo + oral iron 200mg daily for 14 days		
Onken et al, ¹³⁷ 2014#	Multicenter RCT (n = 84) (USA)	Age >18 years, iron deficiency anaemia of varying aetiology (heavy uterine bleeding, GI disorders, nutritional deficiencies), Hb <11 g/dL, ferritin <100 ng/mL or ferritin <300 ng/mL with Tsat <30%, who did not respond to a two-week run-in with oral iron	Ferric carboxymaltose 30 mg/kg (max 1.5 kg)	Ferrous sulphate 325 mg x3/day for two weeks	Mean change from baseline to highest observed Hb	(i) Proportion of patients achieving Hb >12 g/dL; (ii) proportion of patients achieving an increase of at least 2 g/dL at any point (iii) changes in ferritin; (iv) adverse events
Padmanabhan	Single center	n = 507 Scheduled for open heart	Ferric	Ferrous sulphate	Change in Hb 3 weeks	(i) Changes in iron
et al, ¹³⁸ 2018	RCT (UK)	surgery with WHO definition of	carboxymaltose 1000mg	200mg daily until surgery	after iron therapy	profiles and CRP; (ii) transfusion

		anaemia (male, Hb <13 g/dL; female, Hb <12 g/dL) n = 50				requirements; (iii) postoperative complications (atrial fibrillation, renal failure, infection); (iv) HRQoL (EQ-5D-5L, SF-36)
Park et al, ¹³⁹ 2019	Single center RCT (South Korea)	Scheduled to undergo elective hip or knee arthroplasty, Hb >10 g/dL within 4 weeks of surgery n = 58	Ferric carboxymaltose 1000mg (following induction of anaesthesia)	0.9% saline IV placebo (opaque infusion kits)	Change in Hb from preoperative value to 1 month after surgery	 (i) Changes in Hb and iron profiles from preoperative values to postoperative day 5; (ii) RBC transfusion requirements; (iii) changes in perioperative oxygenation; (iv) adverse events
Pedrazolli et al, ¹⁴⁰ 2008	Multicenter RCT (n = 33) (Italy)	Adults with solid organ malignancy planned to have chemotherapy for 12 weeks, Hb <11 g/dL, ferritin>100 mcg/L and Tsat >40% n = 149	Ferric gluconate 125mg per week for 6 weeks	No iron	Proportion of patients with response at 12 weeks (Hb rise >2 g/dL or Hb >12 g/dL)	(i) Time to response;(ii) transfusionrequirements; (iii)changes in Hb overtime; (iv) safety
Pieracci et al, ¹⁴² 2014	Multicenter RCT (n = 4) (USA)	Adults >18 years, critically ill trauma with Hb <12 g/dL, expected ICU length of stay >5 days n = 150	Iron sucrose 100mg thrice weekly for up to six doses or until ICU discharge	0.9% saline IV placebo (opaque infusion kits)	Number of participants requiring an RBC transfusion	 (i) Changes in iron profiles and markers of erythropoiesis; (ii) infection at 28 days; (iii) 28-day mortality
Perello et al, ¹⁴¹ 2014	Single center RCT (Spain)	Postpartum anaemia within 48 hours of delivery, Hb 6-8 g/dL n = 72	Iron sucrose 200mg on two consecutive days and ferrous sulphate 105mg x2/day for 30 days	0.9% saline on two consecutive days (opaque infusion kits) and ferrous sulphate 105mg x2/day for 30 days	Changes in Hb at one, two and six weeks postpartum	(i) changes in iron profiles (ferritin, TIBC, retic count); (ii) Symptoms of anaemia, depression and anxiety; (iii) tolerability

Pollak et al, ¹⁴³ 2001	Single center RCT (Austria)	Preterm infants gestational age <31 weeks, Hct >30%, phlebotomy <1 ml/day N = 29	Iron sucrose 2mg/kg/day	Comparator 1: Oral iron Comparator 2: Oral iron + IV EPO	Unclear	
Ponikowski et al, ¹⁴⁵ 2015	Multicenter RCT (n = 41) (Europe)	Age >18 years, Stable NYHA II-III congestive heart failure, LVEF <45%, BNP > 100 pg/ml, able to perform 6-MWT, ferritin < 100 ng/mL or < 300 ng/mL with Tsat < 20% n = 304	Ferric carboxymaltose, calculated on Hb and body weight (administered 6- weekly for three doses, then 12 weekly for 36 weeks	0.9% saline IV placebo (opaque infusion kits)	Change in 6-MWT from baseline to week 24	(i) Patient global assessments regularly up to week 52; (ii) changes in NYHA class; (iii) changes in fatigue scores and HRQoL (EQ-5D; (iv) adverse events; (v) hospitalisation rate; (vi) mortality; (v) changes in laboratory markers (Hb, iron status, cardiac biomarkers); (vi) adverse events
Ponikowski et al, ¹⁴⁴ 2020	Multicenter RCT (n = 121) (Europe, South America, Singapore)	Age >18 years, hospitalised for acute heart failure with LVEF <50%, evidence of iron deficiency defined as ferritin <100 ng/mL or 100-299 ng/mL with Tsat <20% n = 1132	Ferric carboxymaltose 500mg, two doses (repletion and maintenance), subsequent doses based if ID persisted	0.9% saline IV placebo (opaque infusion kits)	Composite of recurrent heart failure hospitalisations and cardiovascular death up to 52 weeks post- randomisation	 (i) Composite of recurrent cardiovascular hospitalisations and cardiovascular death; (ii) heart failure hospitalisation; (iii) cardiovascular mortality; (iv) days lost due to heart failure hospitalisations or cardiovascular death; (v) safety
Price et al, ¹⁴⁶ 2014	Multicenter RCT (USA)	Age >65 year, Hb 9.0-11.5 g/dL (females), Hb 9.0-12.7 g/dL (males), unexplained anemia,	Iron sucrose 200mg per week for five 5 weeks	No iron	Change in 6-MWT from baseline to 12	(i) Change in Hb; (ii) changes in Geriatric Evaluation Panel

Provenzano et al, ¹⁴⁷ 2009	Multicenter RCT (n = 50) (USA)	serum ferritin between 20 and 200 ng/mL n = 19 Adults with CKD requiring haemodialysis for at least 90 days, Hb <11.5 g/dL, Tsat <30%	Ferumoxytol 510mg, two infusions	Ferrous fumarate 50mg daily for 21 days	weeks post- randomisation Change in Hb from baseline to day 35	(i) Proportion of patients achieving Hb >1 g/dL; (ii) changes in iron profiles
Quinibi et al, ¹⁴⁸ 2011	Multicenter RCT (n = 47) (USA, Australia)	n = 230 Age >12 years, non-dialysis dependent CKD, Hb <11 g/dL, ferritin <300 mcg/L, Tsat <25% n = 255	Ferric carboxymaltose 1000mg (further 500mg doses on day 17 and day 31 if Tsat <30% and ferritin <500 mcg/L)	Ferrous sulphate 195mg x3/day for 56 days	Percentage of patients with Hb response >1 g/dL	(i) Changes in Hb during the course of the study; (ii) adverse events
Rathod et al, ¹⁴⁹ 2015^	Single center RCT (India)	Postpartum anaemia, Hb <10 g/dL n = 366	Intervention 1: Iron sucrose, dose calculated for total iron deficit using Ganzoni formula Intervention 2: Ferric carboxymaltose 1000mg single dose	Ferrous ascorbate 100mg daily for six weeks	Changes in Hb and ferritin at two and six weeks	Adverse effects
Razzaq et al, ¹⁶⁸ 2017	Single center RCT (Pakistan)	Postpartum anaemia, Hb <10 g/dL n = 82	Formulation not reported, up to 1000mg weekly	Ferrous sulfate 325mg x3/day for 6 weeks	Proportion of participants with rise in Hb >3.5 g/dL	

Reinisch et al, ¹⁵⁰ 2013	Multicenter RCT (n = 36) (Europe and Asia)	Age >18 years with IBD, Hb <12 g/dL, Tsat <20% n = 338	Iron isomaltoside, dose calculated according to Ganzoni formula	Iron sulfate 200 m.g. once daily for 8 weeks	Change in Hb from baseline to week 8	(i) Change in Hb at weeks 2 and 4; (ii) changes in ferritin and Tsat at week 8; (iii) HRQoL (IBD-Q); (iv) safety and adverse events
Richards et al, ¹⁵¹ 2020	Multicenter RCT (n = 46) (UK)	Age >18 years scheduled to undergo major abdominal surgery with WHO definition of anaemia (Hb <12 g/dL for females, <13 g/dL for males) n = 487	Ferric carboxymaltose 1000mg (between 10 – 42 days before surgery)	0.9% saline IV placebo (opaque infusion kits)	Composite of RBC transfusion or death 30 days after the index operation	 (i)) Total number of RBC units transfused; (ii) changes in Hb from randomisation to day of surgery and 8 weeks and 6 months postoperatively; (iii) ICU and hospital LOS; (iv) postoperative complications; (v) readmissions; (vi) HRQoL
Rudra et al, ¹⁵² 2016	Single center RCT (India)	Pregnant women 24 to 34 weeks' gestation, Hb 7-9 g/dL n = 200	Iron sucrose, dose calculated to achieve target Hb of 11 g/dL	Ferrous ascorbate 100mg x2/day until 6 weeks postpartum	Efficacy, safety and acceptability of iron sucrose	
Santer et al, ¹⁵³ 2020	Single center RCT (UK)	Age >18 years, COPD with no exacerbation in previous 4 weeks n = 48	Ferric carboxymaltose 1000mg	0.9% saline IV placebo (opaque infusion kits)	Change in resting peripheral oxygen saturations from baseline to 1 week after infusion	 (i) Changes from baseline to follow-up visits in oxygenation; (ii) 6-MWT; (iii) laboratory parameters (Hb, CRP, iron profiles); (iv) COPD exacerbations; (v) HRQoL (MRC Dyspnoea, Fatigue Severity); (vii) echocardiography changes

Schijns et al, ¹⁵⁴ 2020	Multicenter RCT (n = 3) (Netherlands)	Women aged 18-65 years, preoperative ferritin >20 mcg/L and then developed iron deficiency post-gastric bypass n = 120	Ferric carboxymaltose 1000mg	Comparator 1: Ferrous fumarate 200mg x3/day Comparator: Ferrous gluconate 695mg x2/day	Percentage of patients with ferritin >20 mcg/L at 3- and 12-months following treatment	
Schroder et al, ¹⁵⁵ 2005	Multicenter RCT (Germany)	Adult patients aged 18-85 years with IBD, iron deficiency anaemia defined as Hb <10.5 g/dL (females) or <11 g/dL (males) and Tsat <20% or ferritin <20 mcg/L	Iron sucrose 7 mg/kg loading dose, followed by 200mg weekly for 5 weeks	Iron sulfate 100- 200mg daily for 6 weeks	Maximal change in Hb from baseline until 6 weeks	(i) Adverse events; (ii) changes in HRQoL;(iii) changes in Tsat or ferritin
Sedighi et al, ¹⁵⁶ 2013	Multicenter RCT (n = 3) (Iran)	n = 46 Age >18 years, CKD established on haemodialysis for more than 3 months, Hb <11 g/dL, ferritin >500 ng/mL, Tsat <25%	Iron sucrose 100mg twice weekly for 5 weeks	Ascorbic Acid for 12 weeks	Change in Hb from baseline to week 12	Changes in ferritin, serum iron, TIBC and Tsat
Seid et al, ¹⁵⁸ 2008	Multicenter RCT (n = 28) (USA)	n = 40 Postpartum anaemia (Hb <10 g/dL) within 10 days of delivery n = 291	Ferric carboxymaltose, dose calculated according to Ganzoni formula	Ferrous sulphate 65mg x3/day for 6 weeks	Percentage of participants with Hb >12g/dL between baseline and end of study	(i) Percentage of participants with Hb rise >3 g/dL; (ii) time taken to achieve Hb rise >3 g/dL; (iii) changes in Hb, ferritin, and Tsat; (iv) Safety
Seid et al, ¹⁵⁷ 2017	Multicenter RCT (n = 130)	Heavy menstrual bleeding or post-partum anaemia, Hb <11	Ferric carboxymaltose	Usual medical care	Safety (Incidence of AEs, death, hospitalisation, disability, congenital	Changes in Hb and ferritin from baseline

		g/dL, iron deficiency (definition not provided) n = 2045	15mg/kg once only		anomaly/birth defect, life-threatening events)	to highest post- randomisation value
Serrano- Trenas et al, ¹⁵⁹ 2011	Single centre RCT (Spain)	Age >65 years, scheduled to undergo hip fracture surgery n = 200	Iron sucrose 600mg - given in 200mg every 48 hours (first dose pre-operatively)	Usual medical care	RBC transfusion requirements	(i) Changes in iron profiles; (ii) hospital length of stay; (iii) infection; (iv) 30-day mortality; (v) side- effects
Singh et al, ¹⁶¹ 1998	Single center RCT (Singapore)	Pregnant women age >16 years, 20-28 weeks' gestation, Hb <9 g/dL, ferritin <20 mg/L n = 100	Iron polymaltose, dose calculated to Hb deficit	Iron fumarate 200mg x3/day for 12 weeks	Changes in Hb at 36 weeks, delivery and 6 weeks postpartum	Changes in iron profiles
Singh et al, ¹⁶⁰ 2006	Multicenter RCT (n = 21) (USA & Mexico)	Age >18 years, CKD on peritoneal dialysis, Hb 9.5-11.5 g/dL, established on EPO, Tsat <25%, ferritin <500 ng/ml n = 121	Iron sucrose 1000mg, divided over a 28-day period	No iron	Change from baseline to highest Hb during study period	(i) Changes in Tsat and ferritin; (ii) time to anaemia intervention; (iii) safety events
Sloand et al, ¹⁶² 2004	Single center RCT (USA)	CKD (end stage) and Restless leg syndrome n = 25	Iron dextran 1000mg (over multiple doses)	0.9% saline IV placebo (opaque infusion kits)	Changes in International RLS score from baseline to 4 weeks post-infusion	Adverse events
Spahn et al, ¹⁶³ 2019	Single center RCT (Switzerland)	Age >18 years, undergoing CABG and/or valve surgery, Hb <130 g/L (males) or <120 g/L (females) or ferritin <100 mcg/L n = 1006	Ferric carboxymaltose 1000mg once only and Eprex 40,000 units (preoperatively) B12 and folate also supplemented	0.9% saline IV placebo (opaque infusion kits)	Numbers of RBCs transfused within 7 days	 (i) Percentage with any RBC transfusion in 90 days; (ii) duration of mechanical ventilation; (iii) acute kidney injury; (iv) infection (7 days); (v) VTE (90 days); (vi) 30 and 90-day mortality; (vii) hospital LOS; (viii) changes in peri-

						operative Hb concentrations
Spinowitz et al, ¹⁶⁴ 2008	Multicenter RCT (n = 13) (USA)	Age >18 years, CKD stages 1-5, Hb <11 g/dL n = 304	Ferumoxytol 510mg – two doses	Ferrous fumarate 200mg daily for 21 days	Changes in Hb from baseline to day 35	(i) Changes in iron profiles; (ii) proportion of patients increasing Hb by >1 g/dL
Steensma et al, ¹⁶⁵ 2011	Multicenter RCT (USA)	Age >18 years, receiving chemotherapy for non-myeloid neoplasm, Hb <11 g/dL, ferritin >20 mcg/L, Tsat <60% n = 502	Ferric gluconate 187.mg every 3 weeks (for 5 doses)	Comparator 1: Ferrous sulphate 325mg for 16 weeks Comparator 2: Oral placebo for	Proportion of patients with Hb response >2 g/dL from baseline	(i) Transfusion requirements; (ii) ESA dose; (iii) changes in HRQoL; (iv) adverse events
				16 weeks		
Stoves et al, ¹⁶⁶ 2001	Single center RCT (UK)	Adults with progressive CKD and worsening anaemia Hb <11 g/dL	Iron sucrose 300mg - repeated monthly according to	Ferrous sulphate 200mg x3/day	Changes in ferritin and EPO dose requirements Average follow-up: 5.2	
		n = 45	serum ferritin		months	
Toblli et al, ¹⁶⁸ 2007	Single center RCT (Argentina)	Adults with LVEF <35%, anaemia (Hb <12.5 g/dL for men, <11.5 g/dL for women) with ferritin <100 ng/mL and Tsat <20% n = 40	Iron sucrose 200mg weekly for 5 weeks	0.9% saline IV placebo (opaque infusion kits)	Improvement in Hb and renal function	(i) Changes in BNP and inflammation; (ii) no. of hospitalisations;(iii) changes in exercise tolerance and changes in HRQoL
Trenkwalder et al, ¹⁶⁹ 2017	Multicenter RCT (n = 13) (Finland, Germany, Switzerland)	Adults with restless leg syndrome, International RLS >15, Hb <11.5 g/dL (females); <12.5 g/dL (males) n = 110	Ferric carboxymaltose 1000mg	0.9% saline IV placebo (opaque infusion kits)	Mean change in International RLS score from baseline to week 4 post- randomisation	(i) Changes in IRLS score from baseline to week 12; (ii) changes in ferritin, Tsat; (iii) Adverse events

Vadhan-Raj et al, ¹⁷⁰ 2013	Multicenter RCT (n = 192) (Europe, Asia, North America)	Anaemia (Hb 7-10 g/dL) secondary to any underlying condition (gastric bleed, cancer, postpartum anaemia, heart failure, rheumatoid arthritis) n = 812	Ferumoxytol 510mg - two doses	0.9% saline IV placebo (opaque infusion kits)	Proportion of patients achieving Hb rise of >2 g/dL at any point from baseline to week 5	(i) Proportion of patients with Hb >12 g/dL; (ii) changes in iron profiles; (iii) changes in fatigue scales and SF-36; (iv) safety
Van Iperen et al, ¹⁷¹ 2000	Single center RCT (Netherlands)	Age >18 years, expected ICU length of stay >7 days, Hb <11.2 g/dL (or 12.1 g/dL if ischaemic heart disease) n = 36	Iron sucrose 20mg daily from day 1-14	No iron	Changes in Hb and reticulocyte counts at 14 days	(i) Changes in EPO and iron profiles; (ii) blood loss; (iii) RBC transfusion requirements; (iv) ICU length of stay; (v) mortality
van Veldhuisen et al, ¹⁷² 2017	Single center RCT (n = 28) (Europe)	Age >18 years, clinically stable heart failure NYHA II to III, LVEF <45%, Ferritin <100 ng/ml or <300 ng/ml with Tsat <20% n = 172	Ferric carboxymaltose, administered at week 0 and week 6, based on screening Hb and weight	Usual medical care	Change in peak oxygen consumption from baseline to week 24	 (i) Effect on haematinic and cardiac biomarkers; (ii) HRQoL; (iii) safety
Van Wyck et al, ¹⁷⁵ 2005	Multicenter RCT (n = 35) (USA)	Adults, Stage 3-5 CKD, Hb <11 g/dL, Tsat <25%, ferritin <300 ng/mL n = 188	Iron sucrose 1000mg in divided doses over 14 days	Ferrous sulphate 195mg x3/day for 56 days	Proportion of patients with an Hb increase of 1 g/dL	Changes in Hb and iron profiles
Van Wyck et al, ¹⁷⁴ 2007	Multicenter RCT (n = 43) (USA and Mexico)	Postpartum anaemia, Hb <10 g/dL within 10 days of delivery n = 361	Ferric carboxymaltose, dose calculated to target Hb	Ferrous sulphate 65mg x3/day for 42 days	Change in Hb by > 2g/dL after treatment	(i) Proportion of patients with Hb >12 g/dL; (ii) time to achieve to primary outcome; (iii) changes in iron profiles; (iv) transfusion requirements; (v) HRQoL

Van Wyck et al, ¹⁷³ 2009	Multicenter RCT (n = 79) (USA and Mexico)	Adult females age >18 years, Hb <11 g/dL due to heavy uterine bleeding, Tsat <25%, ferritin <100 ng/mL n = 477	Ferric carboxymaltose, dose calculated to target Hb	Ferrous sulphate 65mg x3/day for 42 days	Proportion of patients with Hb increase >2 g/dL	i) Proportion of patients with Hb >12 g/dL; (ii) time to achieve to primary outcome; (iii) changes in iron profiles; (iv) RBC transfusion requirements; (v) HRQoL
Vanobberghen et al, ¹⁷⁶ 2020	Multicenter RCT (n = 2) (Tanzania)	Pregnant women within 14 days of delivery with IDA (Hb <11 g/dL, ferritin <50 mcg/L) n = 230	Ferric carboxymaltose, doses based on weight and Hb	Ferrous sulphate 60mg once daily for 6 weeks	Proportion of patients with normalisation of Hb (>11.5 g/dL)	 (i) Proportion of patients with corrected ID (raised serum ferritin >100 mcg/L); (ii) adverse events; (iii) SF-36; (iv) adherence to study medication
Verma et al, ¹⁸⁴ 2011	Single center RCT (India)	Postpartum anaemia Hb < 8 g/dL, within 24 hours of delivery n = 150	Iron sucrose 200mg every 48 hours (3 doses)	Oral iron 200 mg ferrous sulphate x2/day for one month	Changes in Hb for the first 4 weeks postpartum	
Warady et al, ¹⁷⁷ 2004	Multicenter RCT (n = 5) (USA)	Paediatric patients with ESRD (age 1-20 years), haemodialysis for >2 months, Tsat >20% n = 35	Iron dextran, (weight based) weekly for 6 weeks	Ferrous fumarate 4-6 mg/kg/day for 6 weeks	Maintenance of target Hct between 33% and 36%, reduction of EPO dose and prevention of iron deficiency	(i) Changes in iron status; (ii) parathyroid hormone levels and blood urea nitrogen levels during the study
Weisbach et al, ¹⁷⁸ 1999	Single center RCT (Germany)	Age >18 years, scheduled for autologous blood donation (minimum of 3 units) prior to major orthopaedic or cardiovascular surgery	Iron sucrose 200mg after each donation	Comparator 1: Ferrous fumarate 100mg x3/day up to day before surgery	Net RBC production during the donation period	(i) Changes in Hb values and iron profiles; (ii) postoperative erythropoiesis; (iii) adverse events
		n = 123		Comparator 2: No iron		

Westad et	Multicenter RCT	Postpartum anaemia, Hb 6.5-8.5	Iron sucrose	Ferrous sulphate	Change in Hb at 4	(i) Changes in Hb and
al, ¹⁷⁹ 2008	(n = 5) (Norway)	g/dL within 48 hours after delivery n = 129	600mg (split over 3 doses)	100 mg x2/day from inclusion until 12 weeks	weeks postpartum	iron profiles at 8 and 12 weeks postpartum; (ii) HRQoL (SF-36) after four, eight and 12 weeks
Woods et al, ¹⁸⁰ 2014	Single center RCT (Australia)	Elite runners with non-anaemic iron deficiency (Hb >12 g/dL, ferritin 30-100 mcg/L) n = 14	Ferric carboxymaltose 100mg twice a week for 4 weeks	0.9% saline IV placebo (opaque infusion kits)	Changes in fatigue (Brief Fatigue Inventory) and mood (Brunel Mood Scale)	(i) Changes in exercise performance;(ii) changes in Hb and iron profiles
Xu et al, ¹⁸¹ 2020	Single center RCT (China)	Age 20-70 years, postoperative anaemia following cardiac surgery WHO criteria (male, Hb <13 g/dL; female, Hb <12 g/dL), ferritin 30-100 mcg/L or Tsat <20% n = 150	Iron sucrose 200mg on alternate days until calculated total iron deficit met, started day after surgery on cardiac ICU	0.9% saline IV placebo (opaque infusion kits)	Changes in Hb on postoperative day 7 and 14	(i) Changes in iron profiles; (ii) clinical – infection, length of ventilation, ICU and hospital stay; (iii) adverse events
Yeo et al, ¹⁸² 2018	Multicenter RCT (n = 2) (Singapore)	Adults admitted with decompensated heart failure, ferritin <100 ng/ml, Tsat <20%, Hb <14 g/dL n = 50	Ferric carboxymaltose 1000mg	0.9% saline (unblinded)	Change in 6-MWT from baseline to 12 weeks	(i) Changes in NYHA class and Kansas City Cardiomyopathy Questionnaire (KCCQ) (ii) hospital admission for heart failure; (iii) serious adverse events
Yoo et al, ¹⁸³ 2011	Single center RCT (South Korea)	Adults scheduled for valvular heart surgery, preoperative anaemia according WHO definition n = 74	Iron sucrose 200mg and EPO (500 IU/kg) 16-24 prior to surgery	0.9% saline IV placebo (opaque infusion kits)	RBC transfusion requirements during surgery and for first 4 postoperative days	(i) Changes in Hb and iron profiles; (ii) postoperative complications

Abbreviations: 6-MWT, six minute walk test; BI, Barthel's index; CRP, C-reactive protein; COPD, Chronic Obstructive Pulmonary Disease; DVT, deep vein thrombosis; CKD, chronic kidney disease; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; ESR, Erythrocyte sedimentation rate; ESRD, End-stage renal disease; FIQR, fibromyalgia impact questionnaire; Hb, haemoglobin; HD, haemodialysis; HRQoL, health-related quality of life; IBD, inflammatory bowel disease; ICU, intensive care unit;

IV, intravenous; LOS, length of stay; LVEF, left ventricular ejection fraction; MFI, Multidimensional fatigue inventory; MI, myocardial infarction; s.c., subcutaneous; NYHA, New York Heart Association; PFS, Piper Fatigue Scale; RBC, red blood cell; RLS, restless leg syndrome; SF-36, Short-Form 36; Tsat, transferrin saturation; VTE, venous thromboembolism

*Trial analysed as two separate studies

^ Data for both IV iron groups were combined

This trial had an oral iron run-in period with two parallel randomisations after this based on tolerance of oral therapy -- in the results we have only included the participants in the randomisation of oral-tolerant participants (FCM vs oral iron) and not the other randomisation (FCM vs other IV standard of care)

eTable 2. Characteristics of ongoing RCTs

Study details and status	Sample	Participants]	Intervention(s)		Primary	Secondary	Infection
-	size	_	Arm 1	Arm 2	Arm 3	outcome	outcome	reporting
Surgery			-					
NCT03817957; IDA-II; Germany (Recruiting)	407	Age >18 years; following major surgery (orthopedic/trauma vascular, visceral, cardiac), Hb <12 g/dL for females and <13 g/dL for males or non- anemic ID (ferritin <100 mcg/L, confirmed 28 days before surgery)	Ferric carboxymaltose 1000mg	Polyglucoferron 500-2000 mg IV	Ferrous sulphate 50-200mg x2/day for 28 days	Proportion of patients who achieve normal Hb or Hb rise >1.5 g/dL at 30 days: pre- and post- volume- corrected urine iron levels	Changes in Hb and iron profiles; adverse events and tolerability; all-cause mortality; changes in SF-36	Not specified
NCT02972294; HiFIT; France (Recruiting)	780	Age >18 years, NOF fracture; Hb 9.5-13 g/dL	Iron isomaltoside 1000mg + tranexamic acid	Iron isomaltoside + IV placebo	IV placebo + tranexamic acid Arm 4: IV placebo x2	Peri-operative transfusion requirements	No. of blood products per patients; changes in Hb up to day 30 post-op; peri- operative blood loss; proportion of patients home at day 30; all-cause mortality; postoperative complications (cardiovascular, infection, transfusion- related, anaphylaxis); QoL (EQ-5D-5L, PQOL, IADL);	Yes – 'infectious complications'

						all-cause mortality	
KCT0004020; South Korea; (Recruiting)	80	Age >60 years, scheduled to undergo total shoulder arthroplasty; post- op Hb <10 g/dL or fall greater than 3 g/dL from pre- operative value.	Ferric carboxymaltose 1000mg	IV placebo (0.9% saline)	Changes in Hb up to 3 months postoperatively	Changes in ferritin, iron, total iron binding capacity, Tsat	Not specified
NCT04083755 IRONPAD; Spain (Recruiting)	230	Age >18 years; Hb <130 g/L (males); Hb <120 g/L (females), symptomatic lower limb ischaemia; >1 week prior to surgery	Ferric carboxymaltose 1000mg	No treatment or oral iron	Transfusion requirements	Changes in Hb; length of stay; hospital mortality; adverse events; SF-36 at day 30 post-op	Not specified
NCT03528564; HOPE-Hb; Canada (Recruiting)	74	Age >18 years, scheduled to undergo primary total hip or knee arthroplasty; Hb <12 g/dL	Iron sucrose 900mg + EPO 40000 IU	Iron sucrose 900mg + SC placebo	Feasibility and pre-operative Hb on day of surgery	Postoperative Hb; changes in Hb and iron profiles; transfusion requirements; DVT; postoperative morbidity; surgical wound infection; HADS; cognitive assessments; cost analysis	Yes – part of composite of postoperative morbidity up to 3 months post- surgery and surgical wound infection (superficial and deep) 6 weeks from surgery
EudraCT 2018-004213-41; RIPAC; Belgium (Recruiting)	60	Age >18 years, scheduled to undergo colonic cancer resection; Hb <12 g/dL in women and <13	Ferric carboxymaltose 1000mg	Usual care	Change in Hb at time of surgery	Peri-operative transfusion requirements; change in Hb at 1 month postoperative;	Yes – as part of postoperative morbidity assessment using Clavien-

		g/dL in men; Tsat <20%				postoperative complications; length of stay; QoL (EORTC QLQ-C30)	Dindo classification
NCT03565354; Hong Kong (Completed – results awaited)	40	Age >18 years, scheduled to undergo colorectal cancer surgery; Hb <13 g/dL, ferritin <30 mcg/L or ferritin 100-300 mcg/L with Tsat <20%	Iron isomaltoside 1000mg	Usual care	Changes in pre-operative Hb and ferritin	Peri-operative transfusion requirements; hospital length of stay, quality of recovery; surgical complication; DAOH-30	Yes – as part of postoperative morbidity assessment using Clavien- Dindo classification
NCT03574311; PREFER- CABG; Finland (Recruiting)	210	Age >18 years; open heart surgery	Ferric carboxymaltose 1000mg pre- operatively	IV placebo (0.9% saline)	Composite of incidence of RBC transfusion and/or nosocomial infection	Mortality at 90- days; length of stay; peri- operative MI; organ support requirements; HRQoL at one year	Yes – part of composite of primary outcome (incidence of RBC transfusion and/or nosocomial infection)
ACTRN12618001437257; ADEPT; Australia (Recruiting)	40	Scheduled to undergo elective open/laparoscopic abdominal surgery; Non-anemic iron deficiency	Ferric carboxymaltose 1000mg pre- operatively	IV placebo (0.9% saline)	Changes in peak VO ₂ measured by CPEX	Changes in AT; changes in Hb; changes in EQ- 5D-5L and WHODAS V2.0 (30 days post- operatively); peri- operative transfusion requirements; post-operative complications (including infection); DAOH-90	Yes – part of postoperative complication assessment

ICTRP EUCTR2018- 002571-18-NL; EFFECT KTx; Netherlands (Recruiting)	158	Age >18 years; Kidney transplant recipients (at least 4 months after transplant); ID (defined as ferritin < 100 μ g/L or ferritin between 100 and 300 μ g/L in combination with a transferrin saturation < 20%);	Ferric carboxymaltose 1000mg	IV placebo (0.9% saline)	Changes in 6MWT at 24 weeks post- intervention	Changes in Hb and iron profiles; changes in LVEF; HRQoL (SF-36, EQ-5D, KDQOL- SF); infection; cardiovascular events; graft rejection; mortality	Yes – defined as 'occurrence of infectious diseases'
NCT03662789; IronIC; Norway (Complete – results awaited)	102	Age >18 years, presentation at least one year post- cardiac transplant; ID (ID (defined at Tsat <20% with ferritin 100-300 µg/L or ferritin <100 µg/L)	Iron isomaltoside 20mg/kg	IV placebo (0.9% saline)	Peak oxygen consumption at 6 months	Changes in iron profiles; muscle strength (hand- grip dynamometer); changes in HRQoL (SF-36); changes in laboratory CRP, troponin and NT- proBNP	Not specified
NCT04268849; USA (Recruiting)	104	Age >18 years, undergone bariatric surgery >3 months ago, IDA (ferritin<30 mcg/L, Tsat <20%, Hb <13 g/dL)	Ferumoxytol 1020mg + oral placebo	Ferrous sulphate 60mg and vitamin C for 6 weeks + IV placebo (0.9% saline)	Changes in Clinical Global Impression at 6 weeks post- treatment; Changes in Hb	Changes in ferritin and Tsat; QoL measured by visual linear analogue scale	Not specified
Oncology							
ICTRP KCT0004311; South Korea (Recruiting)	341	Adults >19 years, solid cancer or lymphoma, Hb 8.0- 10.5 g/dL, recent chemotherapy	Ferric carboxymaltose 1000mg	Usual care	Change in Hb	Adverse events, quality of life with EORTC QLQ-C30	Not specified

ISRCTN13370767 ICARAS; UK (Recruiting)	40	Age \geq 18 years; Solid tumours not amenable to curative treatment; Hb <130 g/L (males) / <120 g/L (females)' moderate-severe fatigue	Iron isomaltoside (20 mg/kg)	IV placebo (0.9% saline)	Feasibility (recruitment, randomisation, protocol adherence, retention)	Quality of life (FACIT-F, EQ- 5D, EORTC QOQ-C30 and baseline, 4 and 8 weeks post- infusion); transfusion requirements; changes in Hb, iron profiles, cytokine activity; gut microbiome; daily steps	Not specified
Eudra CT 2014-000246-30; FERINJECT; Germany (Complete – results awaited)	64	Age >18 years; inoperable colorectal cancer; iron deficiency anaemia: $Hb \le 10.5$ g/dL and transferrin saturation < 20 % and/or serum ferritin < 20 ng/mL	Ferric carboxymaltose 1000mg	Ferrous sulphate 100mg	Rise in Hb by 2 g/dL at 12 weeks	QoL (EORTC- QLQ-C30), hand grip via dynamometer; transfusion requirements; changes in iron profiles; adverse events; overall survival	Not specified
NCT04206228 IIISAS; Norway (Recruiting)	100	Age>18 years, Aortic stenosis and scheduled for TAVI, ID (ferritin < $100 \mu g/L$ or ferritin between 100 and $300 \mu g/L$ in combination with a transferrin saturation < 20%)	Iron isomaltoside (20mg/kg)	IV placebo (0.9% saline)	Baseline- adjusted 6- minute walk test (6 months after intervention)	Changes in iron status, NT- proBNP, and Troponin; muscle strength; SF-36; EQ-VAS, HADS, Kansas City Cardiomyopathy Questionnaire; adverse events	Not specified
Obstetrics / Women's healt		W	T	E	T	Channel III	Nut and Cu 1
NCT03188445; Denmark (Recruiting)	200	Women aged >18 years; Pregnant >14 weeks gestation;	Iron isomaltoside 1000mg	Ferrous fumarate + ascorbic acid	Time to achieve Hb >11 g/dL	Changes in Hb and iron biomarkers	Not specified

		Ferritin <30 µg/L after 4 weeks of			(baseline to 18 weeks after		
		oral iron			treatment)		
ACTRN12619000283178p; IRONWOMAN; Australia (Not yet open)	50	Pregnant women aged >18 years; Hb 80-105 g/dL and ferritin <30 µg/L; between 26-33 weeks' gestation	Ferric carboxymaltose 1000mg + oral placebo capsules	Oral iron 80 mg once daily + IV placebo	Feasibility – adequacy of blinding	Patient and clinician acceptability; changes in SF-36 from baseline to 4 weeks; treatment side effects; oral iron compliance; proportion of women with Hb <105 g/dL at 4 weeks; changes in Hb and iron profiles; maternal outcomes (PPH, mode of delivery, transfusion requirements); fetal outcomes (SGA, birth weight, preterm labour, death, NICU admission)	Not specified
ACTRN12618001268235; REVAMP; Malawi (Recruiting)	862	Pregnant women 13-26 weeks' gestation; Hb <10 g/dL; negative malaria test	Ferric carboxymaltose 1000mg	Ferrous sulphate 200mg x2/day for 90 days	Prevalence of Hb <10 g/dL at timepoint closest to delivery	Maternal fatigue (1 month postpartum); changes in Hb and iron profiles; incidence of PPH, length of stay post-delivery; maternal cognitive function; transfusion requirements;	Yes – incidence of malaria and /or parasitaemia

NCT04505514; IVIronPPH; Malaysia (Recruiting)	60	Age >18 years; PPH >500 mls; Hb <10 g/dL	Iron isomaltoside 1000mg + oral iron preparation (Iberet-Folic 500)	IV placebo + oral iron preparation (Iberet-Folic 500)		Changes in Hb, serum iron and ferritin at 6 weeks	adverse events; neonatal outcomes (birth weight, preterm birth, still birth) General fatigue score; adverse events; transfusion requirements	No
NCT04205266; USA (Not yet recruiting)	76	Women aged 18- 50; heavy menstrual bleeding; Hb <11 g/dL	Ferumoxytol 510 mg (2 infusion)	Ferrous sulphate 325mg once daily for 60 days		Changes in Hb at 60 points	Patient satisfaction with treatment; quality of life score	No
NCT03957057; Slovenia (Recruiting)	300	PPH with Hb 7-10 g/dL within 48 hours after delivery	Ferric carboxymaltose 1000mg	Iron isomaltoside 1500mg	Ferrous sulphate 160 mg once daily for 6 weeks	MFI score at 6 weeks postpartum	Edinburgh Postnatal Depression score; changes in Hb and iron profiles; side effects; compliance with oral iron	Yes – part of composite of adverse events listed as 'upper respiratory tract infection'
CTRI/2020/02/023125; India (Recruiting)	80	Women age 18-45 years, postpartum Hb 8-10 g/dL	Ferric carboxymaltose 1000mg	Ferrous fumarate 152mg x2/day for 6 weeks		Changes in Hb at 2 and 6 weeks postpartum	Safety and acceptability	No
Cardiology / heart failure ISRCTN16403302;	1300	$A_{ro} > 19$ years	Iron	Usual care		Cardiovascular	All-cause	Yes -
IRONMAN; UK (Recruiting)	1300	Age >18 years, LVEF <45%; NYHA class II-IV; ID (defined at Tsat <20% with ferritin 100-300 µg/L or ferritin <100 µg/L)	isomaltoside (calculated to body weight)	Usual care		Cardiovascular mortality or hospitalisation for heart failure throughout follow-up period (approx. 3 years)	All-cause mortality; all- cause hospitalisation; HRQoL (Minnesota Living with Heart Failure; EQ-5D) at 4 and 20	Yes - Hospitalisation primarily for infection is assessed through review of case notes and reporting of patient, relative,

							months; QALY at 2.5 years; Death / hospitalisation primarily due to infection; 6MWT	carer or clinician throughout the follow up period
EudraCT 2019-002912-25; HEART-FID; USA (Recruiting)	1508	Age >18 years, reduced LVEF; ID ((defined at Tsat <20% and/or ferritin <100 µg/L); Hb between 9 g/dL and 13.5 g/dL, able to perform 6-MWT	Ferric carboxymaltose 1000mg	IV placebo (0.9% saline)		Composite of death, hospitalisation for heart failure (1 year) or change in 6- MWT (6 months)	Time to first composite event; cardiovascular death; time to cardiovascular death; cardiovascular hospitalization; urgent heart failure visits	No
NCT03833336; PREFER- HF; Spain (Recruiting)	72	Stable, chronic HF; LVEF >45%; ID (defined at Tsat <20% with ferritin 100-300 µg/L or ferritin <100 µg/L), able to perform 6- MWT	Ferric carboxymaltose 500-1000 mg at 0,6,12 and 24 weeks	Oral iron: Ferrous sulphate 100mg b.d. until week 24 OR Sucrosomial iron 30mg until week 24	IV and oral placebo	Changes in 6- MWT at 24 weeks	Changes in NYHA; hospitalisation; mortality; QoL (Kansas City Cardiomyopathy Questionnaire) – all at 24 weeks	No
ACTRN126200000285954; IRON-AF; Australia (Recruiting)	84	Age >18 years, persistent or paroxysmal AF, Hb <15 g/dL, ID (defined at Tsat <20% with ferritin 100-300 µg/L or ferritin <100 µg/L)	Ferric carboxymaltose 1000mg at weeks 0,1,4 and 8	IV placebo (0.9% saline)		Changes in VO ₂ at 12 weeks	Changes in QoL (SF-36, AF Effect of QoL, Patient Global Assessment, AF severity scale); changes in 6- MWT; changes in NYHA and echocardiography; mortality; hospitalisations	No

NCT04291690; TARGET- EFT; Canada (Recruiting)	144	Age >65 years, frail or pre-frail defined by EFT score >1, admission to cardiovascular unit	Multi- component- IV iron (Iron sucrose 300mg daily for 3 doses) if presence of IDA (Hb<13 g/dL, ferritin <100 µg/L or ferritin <300 µg/L and Tsat <20%) physical training; cognitive stimulation; nutritional support	Usual care	Changes in EQ-5D-5L from randomisation to 6 weeks	Changes in hospital-acquired disability; all- cause mortality; delirium; length of stay, mobility, step counts; HADS	Yes – part of composite of adverse events assessed up to 6 weeks post treatment
NCT03523117; USA (Recruiting)	72	Age 1-17 years; Hb <11 g/dL; ferritin <300 ng/mL, Tsat <30%, inadequate response to oral iron	Ferric carboxymaltose 15mg/kg (max 750 mg) at day 0 and day 7	Ferrous sulphate dose adjusted for age, for 28 days	Changes in Hb at day 35	Changes in ferritin, Tsat and Retic Hb	No
ChiCTR18000019815; China (Recruiting)	268	Children aged <14 years, scheduled to undergo major abdominal surgery; ferritin <15 mcg/L, Tsat <15%	I.v iron infusion (no further details)	Usual care	Incidence of RBC transfusion		No
Chronic Kidney Disease NCT04464850; IVO-IRON Thailand (Recruiting)	124	Age >18 years; Haemodialysis for at least 3 months; Hb 8-11.5 g/dL; Tsat <50% and ferritin <800 mg/dL	Iron sucrose 200mg every 2 weeks for 24 weeks	Ferrous fumarate 600 mg/day for 24 weeks	Change / reduction in EPO dose at 24 weeks	Changes in Hb; MACE; hospitalisations due to infection; Changes in HRQoL	Yes – secondary outcome of hospitalizations due to infection

						(KDQOL, EQ- 5D-5L), cost- effectiveness of oral	
Critical care							
NCT02276690; HEPCIDANE France (Completed – results awaited)	408	Age >18 years, required ICU care for at least 5 days, anaemia as per WHO definition	Intravenous iron +/- EPO according ferritin and hepcidin levels	Usual care	Hospital costs	Hospital and ICU LOS; fatigue; changes in Hb and iron profiles; 90- day mortality	No
ISRCTN13721808; INTACT UK (Completed – results awaited)	130	Age >18 years, required ICU care for at least 24 hours, Hb <100 g/L prior to hospital discharge	Ferric carboxymaltose 1000mg	Usual care	Feasibility – recruitment, randomisation and follow-up rates	Changes in Hb and iron profiles; nosocomial infection, in- hospital mortality; changes in fatigue and HRQoL up to 90 days post- randomisation; readmissions	Yes – secondary outcome defined as 'commencement of new antibiotic therapy or escalation from prophylactic antibiotics for a confirmed or strongly suspected new infection.

Abbreviations: 6-MWT, 6-minute walk test; CPEX, Cardiopulmonary Exercise Testing; CRP, C-reactive protein; DAOH, Days Alive and Out of Hospital; DVT, Deep Vein Thrombosis; EFT, Essential Frailty Toolset; EORTC, European Organisation for Research and Treatment of Cancer; EPO, erythropoietin; EQ-5D-5L, Euroqol-5D-5L; EQ-VAS, EuroQol Visual Analogue Scale; Hb, HADS, Hospital Anxiety and Depression Scale; Hemoglobin; HRQoL, Health-related quality of life; IADL, Instrumental Activities of Daily Living; ICU, Intensive Care Unit; ID, Iron deficiency; IDA, Iron deficiency anemia; IV, intravenous; KDQOL, Kidney Disease Quality of Life Instrument; LOS, Length of stay; LVEF, left ventricular ejection fraction; MACE, Major adverse cardiovascular events; MFI; Multidimensional Fatigue Inventory; MI, myocardial infarction; NICU, Neonatal Intensive Care Unit; NOF, Neck of femur; NYHA, New York Heart Association; PPH, Postpartum Hemorrhage; PQOL, Perceived Quality of Life; QALY, Quality adjusted life year; RBC, red blood cell; SF-36, Short Form-26; TAVI, Transcatheter Aortic Valve Implantation; Tsat, Transferrin saturation; WHO, World Health Organization; WHODAS, WHO Disability Assessment Schedule.

eTable 3. Characteristics of included NRS

Study ID	Study design	Participants	Exposure	Comparator	Key findings
Ikuta et al, ¹⁸³ 2019	Prospective cohort study Multicenter (n = 12) (Japan)	Iron deficiency anaemia (Hb <12 g/dL in women and <13 g/dL in men, ferritin <12 ng/mL) secondary to digestive diseases n = 39	Ferric carboxymaltose 1000mg or 1500mg depending on weight	N/A	10/39 (25.6%) experienced an 'infection or infestation' MedDRA coding definition
Ishida et al, ¹⁸⁴ 2015	Retrospective observational registry- based cohort Multicenter (USA)	CKD patients who had received IV iron in the 14 days preceding their first hospitalisation n = 2463	Receipt of IV iron of any dose, frequency, or type	No IV iron received	IV iron was not associated with hospital admission for infection or death within 30 days (OR 1.08; 95% CI: 0.96 to 1.22) ICD-9 Classification used to define infection
Kim et al, ¹⁸⁵ 2018	Retrospective propensity-matched cohort study Single center (South Korea)	Elective hip arthroplasty and hip fracture with postoperative anaemia (Hb <10 g/dL) n = 300	Ferric carboxymaltose 1000mg	Usual medical care	No statistically significant differences in postoperative infections between those who received iron compared with usual care (7/150 (4%) vs. 6/150 (3%), p>0.05) Investigator defined – 'positive bacterial culture and the need for antibiotics'
Kuragano et al, ¹⁸⁶ 2014	Prospective observational study Single center (Japan)	Stable CKD on maintenance dialysis for a period of 1 year n = 1086	IV iron, high dose (>50mg per week) or low dose (<50mg per week)	No iron	IV iron (both cohorts) associated with increased risk of infection when compared with no iron (HR 1.78; 95% CI: 2.24 to 12.14). High ferritin levels also associated with increased risk of infection when compared with low ferritin (HR 1.76; 95% CI: 1.29 to 2.4) No definition provided

Munoz et al, ¹⁹⁰ 2014 (1)	Retrospective study, data obtained from previous publications, doctorate theses and unpublished databases Multicenter (n = 4) (Spain)	Underwent either hip fracture surgery, total knee replacement or total hip replacement n = 2547	IV iron, either iron sucrose (100-200mg, 3 doses) or ferric carboxymaltose (600mg single dose) +/- EPO	Oral iron or no iron	Lower infection rates in patients who received IV iron (+/- EPO) when compared with control (107/1000 (10.7%) vs. 97/361 (26.9%), p<0.01) CDC definition used
Munoz et al, ¹⁸⁷ 2014 (2)	Retrospective matched cohort study Single center (Spain)	Lower limb arthroplasty n = 394	IV iron, either iron sucrose (100-200mg, 3 doses) or ferric carboxymaltose (600mg single dose)	Usual medical care	No statistically significant differences in postoperative infection between those who received iron compared with usual care (3/182 (1.6%) vs. 6/182 (3.3%), p=0.502) No definition provided
Peters et al, ¹⁸⁸ 2008	Retrospective, matched cohort study Multicenter (n = 5) (Germany)	Elective / emergency to perioperative ICU with anaemia n = 95	Ferric carboxymaltose 500mg	Usual medical care	No statistically significant differences in postoperative infections between those who received iron compared with usual care (n=78) (6/26 (23%) vs. 14/52 (27%), p>0.05) No definition provided
Zitt et al, ¹⁸⁹ 2014	Prospective, observational cohort study Single center (Austria)	CKD scheduled to start chronic dialysis treatment n = 222	IV iron, ferric gluconate weekly	No iron	Iron therapy was associated with reduced cardiovascular and sepsis- related mortality (HR 1.76; 95% CI: 1.29 to 2.4) No definition provided

Abbreviations: CDC, Centers for Disease Control and Prevention; CI, Confidence Interval; CKD, Chronic Kidney Disease; EPO, erythropoietin; HR, Hazard Ratio; ICD, International Classification of Diseases; ICU, Intensive Care Unit; IV, intravenous; OR, Odds Ratio.

eTable 4. Summary of risk of bias assessment for NRS

Study ID	Confounding	Selection	Intervention classification	Deviation from intervention	Missing data	Measurement of outcome	Selection of reported result	Overall
Munoz 2014 (1)	Serious	Moderate	Low	Low	Low	Moderate	Low	Moderate
Munoz 2014 (2)	Serious	Moderate	Low	Low	Low	Moderate	Low	Moderate
Zitt 2014	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Kurugano 2014	Moderate	Low	Moderate	Low	Low	Moderate	Low	Moderate
Ishida 2015	Moderate	Low	Low	Low	Low	Low	Low	Low
Kim 2018	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Peters 2018	Moderate	Low	Low	Moderate	Low	Moderate	Low	Moderate
Ikuta 2019	Serious	Moderate	Low	Low	Low	Moderate	Low	Moderate

eTable 5. Risk of bias assessments for individual RCTs

Study ID	Random sequence generation	Allocation concealment	Blinding of participants and	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other
	generation	conceannent	personnel	ussessment	outcome unu		
Abdelazim 2017			•				
Abhilashini 2014							
Adhikary 2011							
Agarwal 2006							
Agarwal 2015							
Aggarwal 2003							
Akhtar 2018							
A1 2005							
Allen 2011							
Al-Momen 1996							
Anker 2009							
Athibovonsuk 2013							
Auerbach 2004							
Auerbach 2010							
Bager 2014							
Baillie 2010							
Barish (1) 2012							
Barish (2) 2012							
Bastit 2008							
Batool 2018							
Bayoumeu 2002							
Beck-da-Silva 2013							
Beguin 2013							
Bencaiova 2009							
Bernabeu-Wittel 2016							
Bhandal 20006							
Bhavi 2017							
Biboulet 2018							
Bielza 2020							
Birgegard 2010							
Birgegard 2016							
Bisbe 2014							

Boomershine 2018				
Breymann 2008				
Breymann 2016				
Burden 2015				
Burns 1996				
Charles-Edwards 2019				
Charytan 2005				
Charytan 2012				
Cho 2016				
Cho 2018				
Coyne 2007				
Dalal 2018				
Damineni 2016				
Dangsuwan 2010				
Darwish 2019				
Deeba 2012				
Deng 2017				
Drexler 2020				
Dubey 2013				
Edwards 2009				
El Khouly 2017				
Evstatiev 2013				
Favrat 2014				
Ferrero-Barcelo 2019				
Fishbane 1995				
Friel 1995				
Froessler 2013				
Froessler 2016				
Garrido-Martin 2012				
Grote 2009				
Gupta 2014				
Hedenus 2007				
Hedenus 2014				
Henry 2007				
Holm 2017				
Iyoke 2017				
Jain 2013				

Johansson 2015				
Kalra 2016				
Karkouti 2006				
Karkouti 2000 Kasper 1998				
Keeler 2017				
Keller 2020				
Khalafallah 2010				
Khalafallah 2016				
Khalafallah 2018 (1)				
Khalafallah 2018 (2)				
Kim 2007				
Kim 2009				
Kim 2009				
Kochhar 2013				
Krayenbuehl 2011				
Kulnigg 2008				
Kulnigg-Dabsch 2013				
Kuo 2008				
Li 2008				
Lindgren 2009				
Litton 2016				
Maccio 2010				
MacDougall 1996				
MacDougall 2014				
Madi-Jebara 2004				
McMahon 2010				
Meyer 1996				
Michael 2002				
Montano-Pedroso 2018				
Moppett 2019				
Mudge 2012				
Na 2011				
Nanthini 2017				
Neeru 2012				
Neogi 2019				
Ng 2018				
Noronha 2018				

Okonko 2008				
Olijhoek 2001				
Onken 2014				
Padmanabhan 2019				
Park 2019				
Pedrazzoli 2008				
Perello 2014				
Pieracci 2014				
Pollak 2001				
Ponikowski 2015				
Ponikowski 2020				
Price 2014				
Provenzano 2009				
Quinibi 2011				
Rathod 2015				
Razzaq 2017				
Reinisch 2013				
Richards 2020				
Roger 2017				
Rudra 2016				
Santer 2020				
Schijns 2020				
Schroder 2005				
Sedighi 2003				
Seid 2008				
Seid 2017				
Serrano-Trenas 2011				
Singh 1998				
Singh 2006				
Sloand 2004				
Spahn 2019				
Spinowitz 2008				
Steensma 2011				
Stoves 2001				
Toblli 2007				
Trenkwalder 2017				
Vadhan-Raj 2013				

Van Iperen 2000				
Vanobbergen 2020				
Van Veldhuisen 2017				
Van Wyck 2005				
Van Wyck 2007				
Van Wyck 2009				
Verma 2011				
Warady 2004				
Weisbach 1999				
Westad 2008				
Woods 2014				
Xu 2020				
Yeo 2018				
Yoo 2011				

Key:

Low risk

Unclear risk

High risk

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eTable 6. Meta-regression analyses

Variable	No. of studies	Coefficient	95% Confidence Interval	p value
Ferritin	40	0000359	-0.0011785 to 0.0011067	0.950
Transferrin saturation	29	.0084419	-0.022902 to 0.0397858	0.585
Hemoglobin	36	0005157	-0.0054991 to 0.0044677	0.835
Study year	51	0083708	-0.0341953 to 0.0174536	0.518

Meta-regression analyses of ferritin, transferrin saturation, haemoglobin and study year on log risk ratio on infection.

eTable 7. Summary of reporting of infection in included RCTs

Definition	Intravenous iron vs. oral iron, n	Intravenous iron vs. no iron, n	Total
Clinical discretion / not specified	23	26	49
Investigator defined	1	6	7
Classification system			
- Clavien Dindo	1		1
- MedDra	1	3	4
- CDC		2	2
- POMS		1	1
Characterisation			
- Anatomical sites (any)	9	18	24
Lung	6	15	20
Gastrointestinal	2	3	4
Genitourinary	6	7	35
Skin	4	1	4
Surgical wound	1	4	5
Other	4	3	6
Line related		1	1
- Pathogens	0		
- Antibiotic use	1		1

Abbreviations: CDC, Centers for Disease Control; MedDRA, Medical Dictionary for Regulatory Activities; POMS, Postoperative Morbidity Survey

Examples of investigator-defined definitions:

Administration of IV antibiotic along with H/o fever, abdominal pain and foul-smelling vaginal discharge

One of 'bronchitis, cellulitis, conjunctivitis, fungal infections, furuncles, C.difficile, line infections, pneumonia, nasopharyngitis, sepsis, skin infections, URI, UTI

'If clinical symptoms were evident, or positive blood CSF culture, or local lesions

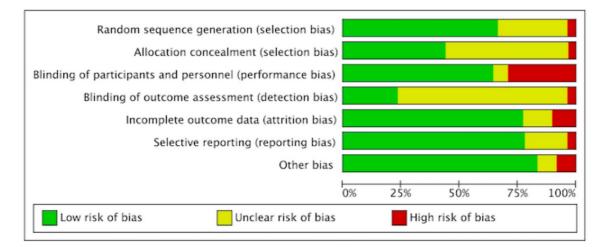
Increase in body temperature to >38 degrees C with a requirment for IV antibiotics

Commencement, escalation or change of IV antibiotics for a confirmed or strongly suspected infection

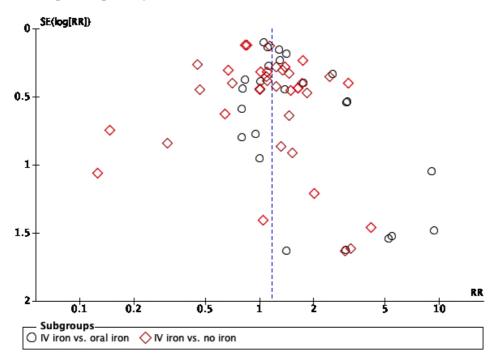
Commencement, escalation or change of IV antibiotics for a confirmed or strongly suspected infection

Antibiotic upgrade

eFigure 1. Risk of bias summary for RCTs



eFigure 2. Funnel plot for primary outcome



Funnel plot of standard error by log risk ratio for infection for the included studies in the meta-analysis. Abbreviations: SE, Standard error; RR, Risk ratio eFigure 3. Sensitivity analysis for primary outcome

	Experim	ental	Cont	rol		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M–H, Random, 95% Cl	ABCDEFG
1.9.1 IV iron vs. oral ir	on							
Keeler 2017	36	55	31	61	11.7%	1.29 [0.94, 1.76]		9997999
MacDougali 2014	114	304	111	312	15.6X	1.05 [0.86, 1.30]	+	~~~
Mudge 2012	10	51	12		3.7%	0.83 [0.40, 1.75]		~~~
Subtotal (95% CI)		410		424	31.0%	1.10 [0.93, 1.31]	*	
Total events	160		154					
Heterogeneity: Tau ² = 0				P = 0.4	2); i² = 0	×		
Test for overall effect: Z	= 1.15 (P	e = 0.25	•					
1.9.2 IV iron vs. no iro	n							
Anker 2009	50	305	24	254	7.7%	1.73 [1.10, 2.74]		
Baille 2010	27	559	22	559	6.0%	1.23 [0.71, 2.13]	- - -	9799999
Bernabeu-Wittel 2016	20	203	9	100	3.7%	1.09 [0.52, 2.32]	_ \ _	9299999
Coyne 2007	13	145	8	145	3.0%	1.63 [0.69, 3.80]	+	666? 666
Kim 2017	1	228	0	226	0.2%	2.97 [0.12, 72.62]		666666 6
Krayenbuchi 2011	10	43	6	47	2.6%	1.82 [0.72, 4.59]	+	
Litton 2016	22	70	16	70	5.9%	1.38 [0.79, 2.39]	+	
Michael 2002	3	1240	2		0.6%	1.51 [0.25, 9.03]		9799999
Moppett 2019	6	39	12	41	3.5%	0.70 [0.32, 1.53]		
Ponikowski 2020	103	559	121	551	14.5X	0.84 [0.66, 1.06]	-	666666 6
Richards 2020	7	234	15		2.6%	0.47 [0.19, 1.12]		
Serrano-Trenas 2011	16	100	13	199	4.2%	2.45 [1.23, 4.89]	—	0000000
Spahn 2019	66	243	77		14.0%	1.13 [0.88, 1.45]	+-	
Subtotal (95% CI)		3968		3917	69.0%	1.19 [0.95, 1.49]	•	
Total events	368		325					
Heterogeneity: $Tau^2 = 0$				2 (P = (0.03); 1² =	- 46X		
Test for overall effect: Z	= 1.54 (P	· = 0.12	.)					
Total (95% CI)		4378		4341	100.0%	1.15 [0.98, 1.35]	•	
Total events	528		479					
Heterogeneity: Tau ² = (5 (P = I	0.07); l ² =	37%	0.01 0.1 1 10 100	
Test for overall effect: Z							Favours comparator Favours intervention	
Test for subgroup differ	rences: Ch	r ² = 0.2	9, df = 1	(P = 0	.59), P =	0%	ratours comparator ratours intervention	
Risk of bias legend								
(A) Random sequence g	eneration	(selectio	n bias)					
(B) Allocation concealme	ent (selecti	on bias)						
(C) Blinding of participa	nts and pe	rsonnel	(perform	ance bi	ias)			
(D) Blinding of outcome	assessme	nt (dete	ction bias	;)				
(E) Incomplete outcome	data (attri	tion bias	5)					
(F) Selective reporting (r	eporting b	ias)						
(m) out 11								

(G) Other bias

Association between risk of infection and intravenous iron by removing studies at high risk of bias. The risk ratios were calculated using a random-effects model with Mantel-Haenszel weighting. The size of the data markers indicates the weight of the study. Error bars indicate 95% CIs. Risk of bias assessments for each study are displayed on the right

eFigure 4. Subgroup analysis by clinical setting

Study or Subgroup 1.10.1 Heart failure	Experim	Total		Total		Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl
Anker et al, ⁴¹ 2009 Okonko et al, ²²⁴ 2008 Ponikowski et al, ²²³ 2020 Subtotal (95% Cl)	50 2 102	305 24 559 888	24 3 121	254 11 551 816	3.1% 0.4% 4.9% 8.5%	1.73 [1.10, 2.74] 0.31 [0.06, 1.58] 0.83 [0.66, 1.05] 0.98 [0.50, 1.95]	
Total events Heterogeneity: Tau ⁴ = 0.25; C Test for overall effect: Z = 0.0	154 hi ^z = 9.78 S (P = 0.9	, df = 2	148 (P = 0.00			0.98 [0.50, 1.95]	T
1.10.2 Chronic Kidney Disea: Agarwal et al, ³⁴ 2015					2.00		
Covne et al.72 2007	37 13 2	67 145 25	27 8 5	69 145 50	3.8% 1.4% 0.5%	1.41 [0.98, 2.03] 1.63 [0.69, 3.80] 0.80 [0.17, 3.84]	
Fishbane et al, ⁸⁶ 1995 Kaira et al, ⁹⁹ 2016 Kuo et al, ¹¹⁵ 2008	56	112	53	117	4.6%	1.10 [0.84, 1.45]	
MacDougail et al, ¹¹⁹ 2014 Michael et al, ¹²⁴ 2002	114	55 304	1 111	55 312	0.2%	2.00 [0.19, 21.42] 1.05 [0.86, 1.30]	+ .
Qunibi et al, ¹⁴⁷ 2002 Qunibi et al, ¹⁴⁷ 2011 Singh et al, ¹⁵⁹ 2006	3 20	1240 147	2	1250 103	0.4% 1.6%	1.51 [0.25, 9.03] 1.75 [0.80, 3.82]	
Van Wyck et al. ¹⁷³ 2005	9 2	75 79	9 0	75 82	1.3% 0.1%	1.00 [0.42, 2.38] 5.19 [0.25, 106.38] 1.15 [1.00, 1.33]	
Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 0.00; Cl	258 hl² = 5.32	2249 , df = 9	224	2258 1); l ² =	19.1% 0%	1.15 [1.00, 1.33]	•
Test for overall effect: Z = 1.9 1.10.3 Critical care	7 (P = 0.0	5)					
Litton et al, ¹⁰⁷ 2016 Pieracci et al, ¹⁴¹ 2014	22 44	70 75	16 52	70 75	2.5% 4.9%	1.38 [0.79, 2.39]	
Xu et al. ¹⁷⁹ 2020 Subtotal (95% Cl)	14	75 220	21	75 220	2.3%	0.85 [0.66, 1.08] 0.67 [0.37, 1.21] 0.90 [0.65, 1.26]	- <u>+</u>
Total events	80		89			0.90 [0.03, 1.20]	Ť
Heterogeneity: Tau ² = 0.04; C Test for overall effect: Z = 0.5	hi" = 3.48 9 (P = 0.5	l, df = 2 6)	(P = 0.1)	8); 1² =	43%		
1.10.4 Inflammatory bowel d Evstatiev et al, ⁰² 2013 Kulnigg et al, ¹¹³ 2008	isease 20	105	13	99	2.1%	1.45 [0.76, 2.76]	<u> </u>
Kulnigg-Dabsch et al. ²¹⁴ 2013	18 3	137 16	6 0	63 9	1.3% 0.2%	1.38 [0.58, 3.31] 4.12 [0.24, 71.78]	
Lindgren et al. ¹¹⁷ 2009 Reinisch et al. ¹¹⁹ 2013 Schroder et al. ¹⁵⁴ 2005	12	45 233	4	46 109	1.0%	3.07 [1.07, 8.80] 1.41 [0.06, 34.34]	
Schroder et al, ⁵⁵⁴ 2005 Subtotal (95% Cl)	2	22 558	0	24 350	0.1% 4.8%	5.43 [0.28, 107.33] 1.73 [1.11, 2.71]	·
Total events Heterogeneity: Tau ² = 0.00; C Test for overall effect: Z = 2.4	56 hi ² = 2.64 0 (P = 0.0	, df = 5	23 (P = 0.76	5); I ² =	0%		
1.10.5 Mixed/Medical				_			
Baille et al, ⁴⁶ 2010 Barish (1) et al, ⁴⁷ 2012	27 23	559 343	22 18	559 360	2.5% 2.3%	1.23 [0.71, 2.13] 1.34 [0.74, 2.44]	
Barish (1) et al, ⁴⁷ 2012 Barish (2) et al, ⁴⁷ 2012 Burns et al, ⁴⁵ 1996 Favrat et al, ⁴⁴ 2014	1	366 11	8 3	369 12	0.3%	0.13 [0.02, 1.00] 1.45 [0.42, 5.10]	
Kravenbuehl et al. ¹¹² 2011	13 10	145 43	8 6	145 47	1.4% 1.2%	1.63 [0.69, 3.80] 1.82 [0.72, 4.59]	
Santer et al. ⁴⁵² 2020	7 33	24 608	7 10	24 200	1.3%	1.00 [0.41, 2.42]	
Vadhan-Raj et al. ¹⁶⁸ 2013 Subtotal (95% Cl) Total events	118	2099	82	1716	11.6%	1.09 [0.54, 2.16] 1.24 [0.94, 1.64]	•
Heterogeneity: Tau ² = 0.00; C Test for overall effect: Z = 1.5	hi² = 6.32	, df = 7 3)	(P = 0.50	0); I ² =	0%		
1.10.5 Obstetrics Bencaiova et al. ⁵³ 2009	9	130	1	130	0.3%	9.00 [1.16, 70.03]	
Breymann et al. ⁶¹ 2008 Khalafallah et al. ⁸⁰⁴ 2010	19 0	277 92	4	177 91	1.0%	3.04 [1.05, 8.77] Not estimable	
Neogi et al, ¹³¹ 2019 Sinoh et al, ¹⁶⁰ 1998	13	934 30	13	947 30	1.6%	1.01 [0.47, 2.18] Not estimable	
Van Wyck et al ¹⁷² 2007 Vanobberghen et al ¹⁷⁴ 2020	24 32	174 114	22 25	178 116	2.6% 3.1%	1.12 [0.65, 1.91] 1.30 [0.83, 2.05]	
Verma et al. ¹⁸² 2011 Subtotal (95% Cl)	1	75	0	75	0.1%	3.00 [0.12, 72.49] 1.42 [0.95, 2.13]	
Total events Heterogeneity: Tau ² = 0.07; C Test for overall effect: Z = 1.7.	98 hi ² = 7.03	. df = 5	65				20
1.10.7 Oncology	2 (F = 0.0	9)					
Bastit et al, ⁴⁸ 2008 Beguin et al, ⁵² 2013	18 10	200 50	39 7	196 52	2.7% 1.3%	0.45 [0.27, 0.76] 1.49 [0.61, 3.60]	
Hedenus et al, ⁹³ 2007 Henry et al, ⁹⁴ 2007	18	33 41	6 16	34 88	1.6%	3.09 [1.40, 6.81] 0.80 [0.34, 1.91]	· · · · · · · · · · · · · · · · · · ·
Pedrazzoli et al, ¹¹⁹ 2008 Steensma et al, ¹¹⁴ 2011	1 28	73	1	76	0.2%	1.04 [0.07, 16.34]	
Subtotal (95% CI) Total events	28 81	561	80	609	9.1%	2.53 [1.30, 4.91] 1.30 [0.61, 2.76]	
Heterogeneity: Tau ² = 0.65; C Test for overall effect: Z = 0.6	hi² = 24.8	7, df = 5 0)	(P = 0.0	0002);	² = 80%		
1.10.8 Paedlatrics					2.24	1.10 [0.59, 2.04]	
Friel et al, ⁸⁷ 1995 Meyer et al, ¹²³ 1996 Pollak et al ¹⁴² 2001	2	14 21	7 2	12 21	2.2%	1.00 [0.16, 6.45]	
Subtotal (95% CI)	2	10 45	4	19 52	0.5% 3.1%	0.95 [0.21, 4.32] 1.07 [0.62, 1.85]	-
Total events Heterogeneity: Tau ² = 0.00; C Test for overall effect: 2 = 0.2	13 hi ² = 0.04 5 (P = 0.8	, df = 2 0)	13 (P = 0.94	8); I ² =	0%		
1.10.9 Restless leg syndrome							- 2021
Allen et al, ¹⁰ 2011 Grote et al, ²¹ 2009 Trenkwalder et al, ²³⁸ 2017	3	24 29	2	21 31	0.4%	1.31 [0.24, 7.12] 3.20 [0.14, 75.55]	
Subtotal (95% Cl)	11	58 111	8	52 104	1.4% 2.0%	1.23 [0.54, 2.83] 1.31 [0.63, 2.71]	
Total events Heterogeneity: Tau ³ = 0.00; C Test for overall effect: Z = 0.7	15 hi ² = 0.33 3 (P = 0.4	, df = 2 6)	10 (P = 0.8)	5); I² =	0%		
1.10.10 Surgery/perioperativ Sernabeu-Wittel et al. ⁵¹ 2016		203	~	100	1.7%	1.00 (0.50, 0.00)	
sielza et al.5# 2020	17	126	9 17	127	2.2%	1.09 [0.52, 2.32] 1.01 [0.54, 1.88]	
Bisbe et al, ^{si} 2014 Froessleret al, ^{si} 2016	4	60 40	0 5	62 32	0.1% 0.8%	9.30 [0.51, 169.01] 0.64 [0.19, 2.19]	
Johansson et al. ⁹⁸ 2015 Keeler et al. ¹⁰² 2017	12 36	30 55	7 31	30 61	1.6% 4.2%	1.71 [0.78, 3.75] 1.29 [0.94, 1.76]	
Khalafallah et al, ³⁰⁵ 2016 Kim et al, ¹¹⁰ 2017	2	103 228	13 0	98 226	0.6% 0.1%	0.15 [0.03, 0.63] 2.97 [0.12, 72.62]	· · · · · · · · · · · · · · · · · · ·
Moppett et al, ¹²⁶ 2019 Mudge et al, ¹²⁷ 2012	8 10	39 51	12 12	41 51	1.6% 1.7%	0.70 [0.32, 1.53] 0.83 [0.40, 1.75]	
Padmanabhan et al, ¹³⁷ 2019 Richards et al, ¹³⁰ 2020	4	20 234	5	20 234	0.8%	0.80 [0.25, 2.55] 0.47 [0.19, 1.12]	
Serrano-Trenas et al, ¹⁵⁸ 2011 Spahn et al, ¹⁶² 2019	16 88	100 243	13 13 77	199 241	1.9%	2.45 [1.23, 4.89] 1.13 [0.88, 1.45]	Ļ
Subtotal (95% CI) Total events	229	1532		1522	4.6% 23.4%	1.04 [0.80, 1.36]	+
Heterogeneity: Tau ² = 0.09; C	hi² = 24.6		.3 (P = 0	.03); I²	= 46%		
Test for overall effect: Z = 0.3 Total (95% Cl)		10089		9391	100.0%	1.17 [1.04, 1.31]	•
Test for overall effect: Z = 0.3	1102 hi ² = 96.3	10089 8. df = 6	950			1.17 [1.04, 1.31]	+ 0.05 0.2 1 5 2

eFigure 5. Subgroup analysis by (a) dosing schedule (b) type of preparation and (c) iron profile at enrolment on the risk of infection.

Verma 2011 Ku 2020		= 73.02).0005); 100.0%	² = 48% 1.17 [1.04, 1.31]	•
Verma 2011 Ku 2020 Subtotal (95% CI) Fotal events Heterogenetty: Tau ² = 0.	.09; Chl ²	= 73.02	, df = 3	6 (P = ().0005);	² = 46%	
Verma 2011 Ku 2020 Subtotal (95% CI) Total events				6 (P = ().0005): I	² = 48%	
Vanobberghen 2020 Verma 2011 Xu 2020 Subtotal (95% CI)		3302	-				
Verma 2011		5382		5072	63.1%	1.20 [1.02, 1.40]	◆
	1 14	75 75	0 21	75 75	0.1X 2.3X	3.00 [0.12, 72.49] 0.67 [0.37, 1.21]	
	32	114	25	116	3.1%	1.30 [0.83, 2.05]	+
Van Wyck 2005	2	79	0	82	0.1%	5.19 [0.25, 106.38]	
iteensma 2011 /adhan-Raj 2013	28 33	164 608	11 10	163 200	2.0% 1.9%	2.53 [1.30, 4.91] 1.09 [0.54, 2.16]	
ingh 2006	9	75	9	75	1.3%	1.00 [0.42, 2.36]	
Serrano-Trenas 2011	16	100	13	199	1.9%	2.45 [1.23, 4.89]	
Qunibi 2011 Schroder 2005	20 2	147 22	6 0	103 24	1.6% 0.1%	1.75 [0.80, 3.82] 5.43 [0.28, 107.33]	
onikowski 2020	102	559	121	551	4.9%	0.83 [0.66, 1.05]	
Pollak 2001	2	10	4	19	0.5%	0.95 [0.21, 4.32]	
Pedrazzoli 2008 Pieracci 2014	1 44	73 75	1 52	76 75	0.2% 4.9%	1.04 [0.07, 16.34] 0.85 [0.66, 1.08]	
Okonko 2008	2	24	3	11	0.4%	0.31 [0.06, 1.58]	•
Neogi 2019	13	934	13	947	1.6%	1.01 [0.47, 2.18]	
Weyer 1996 Woppett 2019	2 8	21 39	2 12	21 41	0.4% 1.6%	1.00 [0.16, 6.45] 0.70 [0.32, 1.53]	
MacDougali 2014	114	304	111	312	5.2%	1.05 [0.86, 1.30]	+
Litton 2016	22	70	16	70	2.5%	1.38 [0.79, 2.39]	·
(uo 2006 Jindgren 2009	2 12	55 45	1	55 46	0.2% 1.0%	2.00 [0.19, 21.42] 3.07 [1.07, 8.60]	
Crayenbuehl 2011	10	43	6	47	1.2%	1.82 [0.72, 4.59]	-
lenry 2007	6	55 41	16	54 66	1.4%	0.60 [0.34, 1.91]	·
Grote 2009 Hedenus 2007	1 16	29 33	0	31 34	0.1% 1.6%	3.20 [0.14, 75.55] 3.09 [1.40, 6.81]	
Friel 1995	9	14	7	12	2.2%	1.10 [0.59, 2.04]	<u> </u>
Evstatlev 2013 Fishbane 1995	20 2	105 25	13 5	99 50	2.1× 0.5×	1.45 [0.76, 2.76] 0.80 [0.17, 3.84]	
Coyne 2007	13	145	6	145	1.4%	1.63 [0.69, 3.80]	
Burns 1996	4	11	3	12	0.7%	1.45 [0.42, 5.10]	<u> </u>
Sencalova 2009 Sletza 2020	9 17	130 126	1 17	130 127	0.3%	9.00 [1.16, 70.03] 1.01 [0.54, 1.88]	
Seguin 2013	10	50	7	52	1.3%	1.49 [0.61, 3.60]	
Bastit 2008	18	200	39	196	2.7%	0.45 [0.27, 0.76]	· ·
Anker 2009 Barish (2) 2012	50 1	305 366	24 8	254 369	3.1× 0.3×	1.73 [1.10, 2.74] 0.13 [0.02, 1.00]	•
Allen 2011	3	24	2	21	0.4%	1.31 [0.24, 7.12]	
Agarwal 2015	37	67	27	69	3.6%	1.41 [0.96, 2.03]	↓
1.12.2 Multiple dosing	- 6 .11 ()	- 0.04	,				
Heterogeneity: Tau ² = 0. Fest for overall effect: Z :				2 (P = ().41); l ² =	4%	
Fotal events	393	4707	324	-313	30.5%	1.15 [1.01, 1.32]	T
Van Wyck 2007 Subtotal (95% CI)	24	174 4707	22	176 4319	2.6% 36.9%	1.12 [0.65, 1.91] 1.15 (1.01, 1.32]	
Frenkwakter 2017	11	58	6	52	1.4%	1.23 [0.54, 2.83]	<u> </u>
Singh 1998 Spahn 2019	0 66	30 243	0 77	30 241	4.6%	Not estimable 1.13 [0.66, 1.45]	<u> </u>
Santer 2020	7	24	7	24	1.3%	1.00 [0.41, 2.42]	
Richards 2020	7	235	15	234	1.3%	0.47 [0.19, 1.12]	_
Padmanabhan 2019 Reinisch 2013	4 1	20 233	5	20 109	0.6% 0.1%	0.80 [0.25, 2.55] 1.41 [0.06, 34.34]	· · · · · · · · · · · · · · · · · · ·
Mudge 2012	10	51	12	51	1.7%	0.83 [0.40, 1.75]	
Kuinigg-Dabsch 2013 Michael 2002	3	16 1240	0	9 1250	0.2%	4.12 [0.24, 71.78] 1.51 [0.25, 9.03]	
Kulnigg 2008	18	137	6	63	1.3%	1.38 [0.58, 3.31]	
Kim 2017	1	228	0	226	0.1%	2.97 [0.12, 72.62]	· · · · · · · · · · · · · · · · · · ·
Khalafallah 2010 Khalafallah 2016	0 2	92 103	0 13	91 96	0.6%	Not estimable 0.15 [0.03, 0.63]	•
Keeler 2017	36	55	31	61	4.2%	1.29 [0.94, 1.76]	+
ohansson 2015 Kalra 2016	12 56	30 112	7 53	30 117	1.6% 4.6%	1.71 [0.78, 3.75] 1.10 [0.84, 1.45]	
Froessler 2016	4	40	5	32	0.6%	0.64 [0.19, 2.19]	
Breymann 2008 Favrat 2014	13	145	8	145	1.4%	3.04 [1.05, 8.77] 1.63 [0.69, 3.80]	
Bisbe 2014	4 19	60 277	04	62 177	0.1% 1.0%	9.30 [0.51, 169.01]	
	20	203	9	100	1.7%	1.09 [0.52, 2.32]	
	27 23	559 343	22 16	559 360	2.5% 2.3%	1.23 [0.71, 2.13] 1.34 [0.74, 2.44]	
Barish (1) 2012						, , , , , , , , , , , , , , , , , , , ,	
Study or Subgroup 1.12.1 Single dosing Balle 2010 Barlsh (1) 2012 Bernabeu-Wittel 2016	Events				Weight	M–H, Random, 95% CI	M–H, Random, 95% Cl

(b) Type of preparation

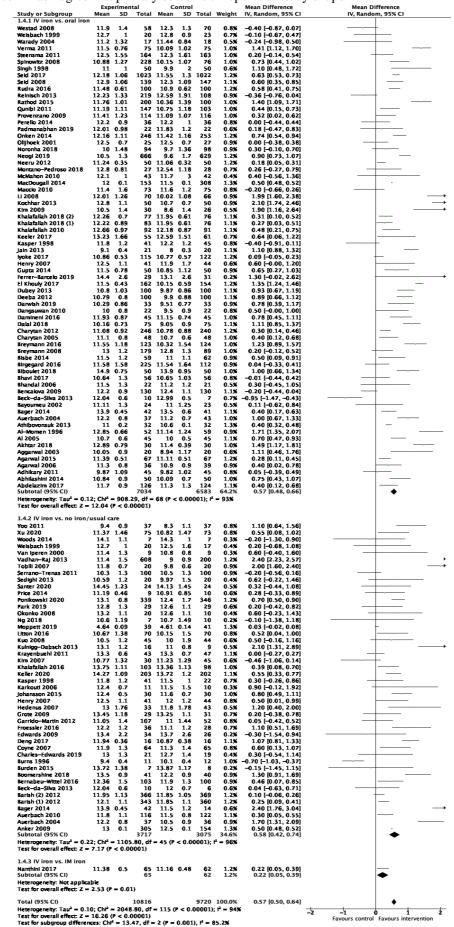
Allen 2011	Events Itose			Total		Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Anker 2009	3 50	24 305	2 24	21 254	0.4% 3.1%	1.31 [0.24, 7.12] 1.73 [1.10, 2.74]	
Baille 2010	27	559	22	559	2.5%	1.23 [0.71, 2.13]	
Barish (1) 2012	23	343	16	360	2.3%	1.34 [0.74, 2.44]	
larish (2) 2012	1	366	6	369	0.3%	0.13 [0.02, 1.00]	· · · · · · · · · · · · · · · · · · ·
iernabeu–Wittel 2016 lisbe 2014	20 4	203 60	9 0	100 62	1.7% 0.1%	1.09 [0.52, 2.32] 9.30 [0.51, 169.01]	
ireymann 2008	19	277	Ă,	177	1.0%	3.04 [1.05, 8.77]	
vstatlev 2013	20	105	13	99	2.1%	1.45 [0.76, 2.76]	
avrat 2014	13	145	8	145	1.4%	1.63 [0.69, 3.60]	
roessier 2016 (eeler 2017	4 36	40 55	5 31	32 61	0.6% 4.2%	0.64 [0.19, 2.19] 1.29 [0.94, 1.76]	
(halafallah 2016	2	103	13	98	0.6%	0.15 [0.03, 0.63]	·
(im 2017	1	228	Ō	226	0.1%	2.97 [0.12, 72.62]	
Culnigg 2008	16	137	6	63	1.3%	1.38 [0.58, 3.31]	
(uinigg-Dabsch 2013 Jitton 2016	3 22	16 70	0 16	9 70	0.2% 2.5%	4.12 [0.24, 71.78] 1.38 [0.79, 2.39]	
AacDougall 2014	114	304	111	312	5.2%	1.05 [0.86, 1.30]	_ _ _
admanabhan 2019	4	20	5	20	0.6%	0.80 [0.25, 2.55]	
onikowski 2020	102	559	121	551	4.9%	0.63 [0.66, 1.05]	
Qunibi 2011 Nichards 2020	20 7	147 234	8 15	103 234	1.6% 1.3%	1.75 [0.80, 3.82] 0.47 [0.19, 1.12]	
anter 2020	7	24	7	24	1.3%	1.00 [0.41, 2.42]	
ipahn 2019	88	243	77	241	4.6%	1.13 [0.66, 1.45]	+
renkwakter 2017	11	58		52	1.4%	1.23 [0.54, 2.83]	
/an Wyck 2007 /anobberghen 2020	24 32	174 114	22 25	178 116	2.6% 3.1%	1.12 [0.65, 1.91] 1.30 [0.83, 2.05]	
(u 2020	14	75	21	75	2.3%	0.67 [0.37, 1.21]	
ubtotal (95% CI)		4988		4611	54.0%	1.13 [0.98, 1.31]	◆
otal events leterogeneity: Tau ² = 0.0 lest for overall effect: Z =				7 (P = 1).04); I ² =	34%	
.11.2 Iron sucrose							
Agarwal 2015 Lastit 2008	37 18	67 200	27	69 196	3.6% 2.7%	1.41 [0.98, 2.03]	
iastit 2008 Jeguin 2013	10	200	39 7	52	1.3%	0.45 [0.27, 0.76] 1.49 [0.61, 3.60]	·
iencalova 2009	9	130	1	130	0.3%	9.00 [1.16, 70.03]	
ileiza 2020	17	126	17	127	2.2%	1.01 [0.54, 1.88]	
irote 2009 Iedenus 2007	1 16	29 33	0	31 34	0.1% 1.6%	3.20 [0.14, 75.55]	
rayenbuchi 2011	10	43	6	47	1.2%	3.09 [1.40, 6.81] 1.82 [0.72, 4.59]	
up 2008	2	55	ī	55	0.2%	2.00 [0.19, 21.42]	· · · · · · · · · · · · · · · · · · ·
Indgren 2009	12	45	4	46	1.0%	3.07 [1.07, 8.80]	
Aeyer 1996	2	21	2	21	0.4%	1.00 [0.16, 6.45]	
Aoppett 2019 Jeogi 2019	6 13	39 934	12 13	41 947	1.6% 1.6%	0.70 [0.32, 1.53] 1.01 [0.47, 2.18]	
konko 2008	2	24	3	11	0.4%	0.31 [0.06, 1.58]	
leracci 2014	44	75	52	75	4.9%	0.85 [0.66, 1.08]	
chroder 2005	2	22	0	24	0.1%	5.43 [0.28, 107.33]	
ierrano-Trenas 2011 ilngh 2006	16 9	100 75	13 9	199 75	1.9% 1.3%	2.45 [1.23, 4.89] 1.00 [0.42, 2.38]	
/an Wyck 2005	2	79	ő	82	0.1%	5.19 [0.25, 106.38]	
/erma 2011	1	75	Ó	75	0.1%	3.00 [0.12, 72.49]	
iubtotal (95% Cl) Fotal events	233	2222	212	2337	26.9%	1.28 [0.95, 1.74]	-
leterogeneity: Tau ² = 0.2 Fest for overall effect: Z =	20; Chf ²		df = 1!) (P = ().0005); f	⁴ = 59%	
1.11.3 Iron isomaltoside	,					1 71 10 78 3 761	
observes 201C		90	-				
ohansson 2015 Calca 2016	12	30 112	7	30	1.6%	1.71 [0.76, 3.75]	
Calra 2016	12 56	112	53	117	4.6%	1.10 [0.84, 1.45]	
taira 2016 teinisch 2013 tubtotal (95% CI)	12 56 1		53 0				◆
Caira 2016 Steinisch 2013 Subtotal (95% CI) Fotal events Heterogenetty: Tau ² = 0.0	12 56 1 69 00; Chi ²	112 233 375 - 1.12, 4	53 0 df = 2 (1	117 109 256	4.6% 0.1% 6.3%	1.10 [0.84, 1.45] 1.41 [0.06, 34.34] 1.16 [0.90, 1.50]	•
Caira 2016 teinisch 2013 subtotal (95% CI) fotal events leterogeneity: Tau ² = 0.0 fest for overall effect: Z =	12 56 1 69 00; Chi ²	112 233 375 - 1.12, 4	53 0 df = 2 (1	117 109 256	4.6% 0.1% 6.3%	1.10 [0.84, 1.45] 1.41 [0.06, 34.34] 1.16 [0.90, 1.50]	↓
caira 2016 teinsch 2013 subtotal (95% CI) otal events teterogenetty: Tau ² = 0.0 est for overall effect: Z = 1.1.4 Ferric gluconate Coyne 2007	12 56 1 69 00; Chi ²	112 233 375 - 1.12, 4	53 0 df = 2 (1	117 109 256	4.6% 0.1% 6.3%	1.10 [0.84, 1.45] 1.41 [0.06, 34.34] 1.16 [0.90, 1.50]	• •
aira 2016 leinisch 2013 lubtotal (95% Cl) Total events leterogenehy: Tau ² = 0.0 rest for overall effect: Z = 11.4 Ferric gluconate xoyne 2007	12 56 1 69 00; Chi ² 1.13 (P 13 6	112 233 375 = 1.12, (= 0.26) 145 41	53 0 df = 2 (1 8 16	117 109 256 • - 0.5 145 88	4.6% 0.1% 6.3% 7); ² = 0 1.4% 1.4%	1.10 [0.84, 1.45] 1.41 [0.06, 34.34] 1.16 [0.90, 1.50] 4 1.63 [0.69, 3.80] 0.80 [0.34, 1.91]	• •
alra 2016 leinisch 2013 uibtotal (95% CI) fotal events leterogeneity: Tau ² – 0.0 est for overall effect: 2 – 11.4 Ferric gluconate xoyne 2007 lenny 2007 lenny 2007	12 56 1 69 00; Chi ² - 1.13 (P 13 6 3	112 233 375 = 1.12, (= 0.26) 145 41 1240	53 0 df = 2 (1	117 109 256 • = 0.5 145 88 1250	4.6% 0.1% 6.3% 7); ² = 0 1.4% 1.4% 0.4%	1.10 [0.84, 1.45] 1.41 [0.06, 34.34] 1.16 [0.90, 1.50] 4 1.63 [0.69, 3.80] 0.80 [0.34, 1.91] 1.51 [0.25, 9.03]	
aira 2016 ieinisch 2013 iubtotal 95% CI) foral events leterogenehy: Tau ² = 0.0 est for overall effect: Z = .11.4 Ferric gluconate Soyne 2007 ilenar 2007 ilenar 2007 ilenar 2008	12 56 1 00; Chi ² • 1.13 (P 13 6 3 1	112 233 375 = 1.12, 4 = 0.26) 145 41 1240 73	53 0 df = 2 (1 8 16 2 1	117 109 256 • = 0.5 145 88 1250 76	4.6% 0.1% 6.3% 7); ² = 0 1.4% 1.4% 0.4% 0.2%	1.10 [0.84, 1.45] 1.41 [0.06, 34.34] 1.16 [0.90, 1.50] 4 1.63 [0.69, 3.80] 0.80 [0.34, 1.91] 1.51 [0.25, 9.03] 1.04 [0.07, 16.34]	
alra 2016 ielnisch 2013 uibtotal (95% Cl) fotal events leterogeneity: Tau ² = 0.0 iest for overall effect: Z = .11.4 Ferric gluconate toyne 2007 fichael 2002 edrazzoli 2008 teensma 2011	12 56 1 69 00; Chi ² - 1.13 (P 13 6 3	112 233 375 = 1.12, (= 0.26) 145 41 1240	53 0 df = 2 (1	117 109 256 • = 0.5 145 88 1250	4.6% 0.1% 6.3% 7); ² = 0 1.4% 1.4% 0.4%	1.10 [0.84, 1.45] 1.41 [0.06, 34.34] 1.16 [0.90, 1.50] 4 1.63 [0.69, 3.80] 0.80 [0.34, 1.91] 1.51 [0.25, 9.03]	
aira 2016 ieinisch 2013 uibtotal (95% CI) iotal events leterogenehy: Tau ² – 0.0 est for overall effect: 2 – 	12 56 1 69 00; Ch ² 113 6 3 1 28 51 03; Ch ²	112 233 375 = 1.12, 4 = 0.26) 145 41 1240 73 164 1663 = 4.36, 4	53 0 df = 2 (1 1 11 38 df = 4 (1	117 109 256 = 0.5 145 88 1250 76 163 1722	4.6% 0.1% 6.3% 7); f ² = 07 1.4% 1.4% 1.4% 0.2% 2.0% 5.3%	1.10 (0.84, 1.45) 1.41 (0.06, 34.34) 1.16 (0.90, 1.50) 4 1.63 (0.69, 3.80) 0.80 (0.34, 1.91) 1.51 (0.25, 9.03) 1.04 (0.07, 16.34) 2.53 (1.30, 4.91) 1.59 (1.00, 2.53)	
ohansson 2015 calra 2016 teinisch 2013 iubtotal (95% CI) foral events teterogenethy: Tau ² = 0.0 fest for overall effect: Z = L.11.4 Ferric gluconate Zoyne 2007 tenny 2007 vichael 2002 vedrazzoli 2008 teterosma 2011 subtotal (95% CI) foral events teterogenethy: Tau ² = 0.0 fest for overall effect: Z = L.11.5 Ferumoxytol	12 56 1 69 00; Ch ² 113 6 3 1 28 51 03; Ch ²	112 233 375 = 1.12, 4 = 0.26) 145 41 1240 73 164 1663 = 4.36, 4	53 0 df = 2 (1 1 11 38 df = 4 (1	117 109 256 = 0.5 145 88 1250 76 163 1722	4.6% 0.1% 6.3% 7); f ² = 07 1.4% 1.4% 1.4% 0.2% 2.0% 5.3%	1.10 (0.84, 1.45) 1.41 (0.06, 34.34) 1.16 (0.90, 1.50) 4 1.63 (0.69, 3.80) 0.80 (0.34, 1.91) 1.51 (0.25, 9.03) 1.04 (0.07, 16.34) 2.53 (1.30, 4.91) 1.59 (1.00, 2.53)	
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alra 2016 alra 2016 leinisch 2013 ubtotal (95% CI) oral events leterogeneity: Tau ² = 0.0 iest for overall effect: Z = .11.4 Ferric gluconate come 2007 lichael 2002 deny 2007 lichael 2002 derazzoli 2008 teensma 2011 ubtotal (95% CI) oral events leterogeneity: Tau ² = 0.0 iest for overall effect: Z = .11.5 Ferumoxytol (adhan-Raj 2013 ubtotal (95% CI) oral events leterogeneity: Not applica iest for overall effect: Z = .11.6 Iron dextran ums 1996 Ishbane 1995 lich 1995 ligh 1998 ubtotal (95% CI) oral events leterogeneity: Tau ² = 0.0 est for overall effect: Z = .11.7 Iron polymaltose halafilah 2010 ludge 2012 olak 2001 ubtotal (95% CI) oral events	12 56 1 1 69 90; Ch ² + 1.13 (f 6 3 1 28 51 28 51 1.28 6 51 1.33 (ch ² + 1.98 (f 7 33 33 33 33 33 33 33 33 33 33 33 34 51 1.98 (f 7 9 0 0 1.57 (f 7 9 0 0 1.57 (f) 1.98 (f)	$\begin{array}{c} 112\\ 112\\ 233\\ 375\\ = 1.12, ($	53 0 df = 2 (1) 8 16 2 1 11 11 11 10 10 10 10 10 df = 4 (1) 10 df = 2 (1) 10 df = 2 (2) 10	117 109 256 88 1250 76 145 88 1250 76 163 1722 200 200 12 200 12 200 12 200 104 200 109 109 109 109 109 109 163 1722 1722 163 1722 163 1724 163 1724 163 1724 163 1724 163 1724 163 1744 163 1744 164 164 164 164 164 164 164 1	4.6% 0.1% 0.1% 6.3% 7); f ² = 07 1.4% 0.4% 0.4% 0.4% 0.4% 0.4% 0.4% 0.6%; f ² = 97 1.9% 1.9% 0.5% 2.2%	1.10 (0.84, 1.45) 1.41 (0.06, 3.4.34) 1.16 (0.90, 1.50) 4 1.63 (0.69, 3.80) 0.80 (0.34, 1.91) 1.51 (0.25, 9.03) 1.04 (0.07, 16.34) 2.53 (1.30, 4.91) 1.59 (1.00, 2.53) 4 1.09 (0.54, 2.16] 1.09 (0.54, 2.16] 1.00 (0.54, 2.16] 1.10 (0.54, 2.16] 1.10 (0.54, 2.16] 1.10 (0.54, 2.5] 1.10 (0.54, 2.	
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(c) Iron profile at enrolment

itudy or Subgroup	Experim Events		Conti Events		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M–H, Random, 95% Cl
1.13.1 Iron deficiency a		242	10	200	.	1 34 10 74 3 441	
Sarish (1) 2012 Sarish (2) 2012	23 1	343 366	18 6	360 369	2.4% 0.3%	1.34 [0.74, 2.44] 0.13 [0.02, 1.00]	
Favrat 2014	13	145	š	145	1.5%	1.63 [0.69, 3.80]	
roessler 2016	4	40	5	32	0.6%	0.64 [0.19, 2.19]	
Khalafallah 2010 Kulaian Dahash 2013	03	92 16	0	91 9	0.2%	Not estimable	
Kuinigg–Dabsch 2013 Reinisch 2013	3 1	233	ŏ	109	0.1%	4.12 [0.24, 71.78] 1.41 [0.06, 34.34]	
Schroder 2005	2	22	ŏ	24	0.2%	5.43 [0.28, 107.33]	
Singh 1998	0	30	0	30		Not estimable	
Spahn 2019	66	243	77	241	4.6%	1.13 [0.66, 1.45]	+-
Steensma 2011 Vanobberghen 2020	28	164	11	163	2.1%	2.53 [1.30, 4.91]	
Subtotal (95% CI)	32	114 1808	25	116 1689	3.2% 15.5%	1.30 [0.83, 2.05] 1.32 [0.98, 1.77]	•
Total events	195		152				•
Heterogeneity: Tau ² = 0 Test for overall effect: Z				(P = 0.	.17); i² = 3	0%	
1.13.2 Functional iron	deficiency	/					
Agarwal 2015	37	67	27	69	3.6%	1.41 [0.98, 2.03]	
Anker 2009 Baille 2010	50 27	305 559	24 22	254 559	3.2% 2.6%	1.73 [1.10, 2.74] 1.23 [0.71, 2.13]	
Bisbe 2014	4	60	6	62	0.2%	9.30 [0.51, 169.01]	
Coyne 2007	13	145	ŝ	145	1.5%	1.63 [0.69, 3.80]	
Kaira 2016	56	112	53	117	4.6%	1.10 [0.64, 1.45]	
Khalafallah 2016	2	103	13	98	0.6%	0.15 [0.03, 0.63]	
Kulnigg 2008	18 12	137	6	63	1.4%	1.38 [0.58, 3.31]	
⊔ndgren 2009 MacDougali 2014	114	45 304	111	46 312	1.0% 5.1%	3.07 [1.07, 8.80] 1.05 [0.86, 1.30]	
Michael 2002	3	1240	2	1250	0.4%	1.51 [0.25, 9.03]	
Okonko 2008	2	24	3	11	0.5%	0.31 [0.06, 1.58]	+
Ponikowski 2020	102	559	121	551	4.9%	0.83 [0.66, 1.05]	-+
Qunibi 2011	20	147	6	103	1.7%	1.75 [0.60, 3.62]	+
Singh 2006 Van Wyck 2005	9 2	75 79	9 0	75 82	1.4% 0.1%	1.00 [0.42, 2.38]	
van wyck 2005 Ku 2020	14	75	21	75	2.4%	5.19 [0.25, 106.38] 0.67 [0.37, 1.21]	
Subtotal (95% CI)		4036		3872	35.4%	1.15 [0.94, 1.41]	*
Total events	485		432				
Heterogeneity: Tau ² = 0 Test for overall effect: Z				i (P = 1	0.008); l ² ·	- 51%	
1.13.3 Anaemia only							
Bastit 2008	16	200	39	196	2.6%	0.45 [0.27, 0.76]	
Bernabeu-Wittel 2016	20	203 277	9	100	1.6%	1.09 [0.52, 2.32]	
Breymann 2006 Hedenus 2007	19 16	33	4	177 34	1.0× 1.6×	3.04 [1.05, 8.77] 3.09 [1.40, 6.81]	
Henry 2007	ĨĞ	41	16	66	1.4%	0.60 [0.34, 1.91]	
ohansson 2015	12	30	7	30	1.7%	1.71 [0.78, 3.75]	
Keeler 2017	36	55	31	61	4.3%	1.29 [0.94, 1.76]	+
Kim 2017	1	228	0	226	0.1%	2.97 [0.12, 72.62]	
Litton 2016 Manage 1996	22	70 21	16 2	70 21	2.6% 0.4%	1.36 [0.79, 2.39]	
Meyer 1996 Neogi 2019	13	934	13	947	1.7%	1.00 [0.16, 6.45] 1.01 [0.47, 2.18]	
Padmanabhan 2019	4	20	5	20	0.9%	0.80 [0.25, 2.55]	
Pedrazzoli 2008	1	73	1	76	0.2%	1.04 [0.07, 16.34]	
Pleracci 2014	44	75	52	75	4.6%	0.85 [0.66, 1.08]	
Richards 2020	.7	234	15	234	1.4%	0.47 [0.19, 1.12]	
Trenkwalder 2017 Vadhan–Raj 2013	11 33	58 608	6 10	52 200	1.5× 2.0×	1.23 [0.54, 2.83] 1.09 [0.54, 2.16]	
Verma 2011	1	75	ĩŏ	75	0.1%	3.00 [0.12, 72.49]	
Subtotal (95% CI)	-	3235	•	2682	30.3%	1.09 [0.85, 1.39]	◆
Total events Heterogeneity: Tau² = 0	268 .10; Chi ² ·	= 32.62	234 df = 13	7 (P = (0.01);	46%	
Test for overall effect: Z	= 0.68 (P	· = 0.50)					
1.13.4 Non-anaemic ir Burns 1996	on deficie 4	ncy 11	3	12	0.6%	1.45 [0.42, 5.10]	
Grote 2009	ī	29	0	31	0.1%	3.20 [0.14, 75.55]	
Krayenbuehl 2011	10	43	ě	47	1.3 %	1.82 [0.72, 4.59]	+
Subtotal (95% CI)		83		90	2.2%	1.74 [0.84, 3.59]	-
Total events Heterogeneity: Tau ² = 0 Taut for any call officer 7				• = 0.8	i9); i² = 0%	í	
Test for overall effect: Z	= 1.50 (P	· = 0.13)	•				
1.13.5 Non-anaemic		130	1	130	0.3%	9.00 [1.16, 70.03]	
	9		-	100	1.6×		
1.13.5 Non-anaemic Bencalova 2009 Evstatlev 2013	9 20	105	9		1.0/	2.12 [1.01, 4.42]	1
Bencalova 2009 Evstatlev 2013 Fishbane 1995	20 2	105 25	5	50	0.5%	0.80 [0.17, 3.84]	
Bencalova 2009 Evstatlev 2013 Fishbane 1995 Mudge 2012	20 2 10	105 25 51	5 12	50 51	0.5% 1.8%	0.60 [0.17, 3.84] 0.63 [0.40, 1.75]	
Bencalova 2009 Evstatiev 2013 Fishbane 1995 Mudge 2012 Pollak 2001	20 2 10 2	105 25	5 12 4	50 51 19	0.5% 1.8% 0.6%	0.80 [0.17, 3.84] 0.83 [0.40, 1.75] 0.95 [0.21, 4.32]	
Bencalova 2009 Evstatlev 2013 Fishbane 1995 Mudge 2012	20 2 10	105 25 51 10	5 12	50 51	0.5% 1.8%	0.60 [0.17, 3.84] 0.63 [0.40, 1.75]	
Bencalova 2009 Evstatlev 2013 Flshbane 1995 Mudge 2012 Pollak 2001 Santer 2020 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0	20 2 10 2 7 50 .15; Chi ²	105 25 51 10 24 345 = 7.67, 4	5 12 4 7 38 df = 5 (1	50 51 19 24 374	0.5% 1.8% 0.6% 1.4% 6.4%	0.80 [0.17, 3.84] 0.83 [0.40, 1.75] 0.95 [0.21, 4.32] 1.00 [0.41, 2.42] 1.29 [0.75, 2.23]	
sencalova 2009 ivstatkev 2013 isibhane 1995 Mudge 2012 Pollak 2001 Santer 2020 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0 Fest for overall effect: Z	20 2 10 2 7 50 .15; Chi ²	105 25 51 10 24 345 = 7.67, 4	5 12 4 7 38 df = 5 (1	50 51 19 24 374	0.5% 1.8% 0.6% 1.4% 6.4%	0.80 [0.17, 3.84] 0.83 [0.40, 1.75] 0.95 [0.21, 4.32] 1.00 [0.41, 2.42] 1.29 [0.75, 2.23]	
Sencalova 2009 Evstatiev 2013 Ifshbane 1995 Mudge 2012 Pollak 2001 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.13.6 Unclear	20 2 10 2 7 50 .15; Chi ² -	105 25 51 10 24 345 = 7.67, () = 0.35)	5 12 4 7 38 df = 5 (1	50 51 19 24 374	0.5% 1.8% 0.6% 1.4% 6.4% 8); i ² = 35	0.80 [0.17, 3.84] 0.83 [0.40, 1.75] 0.95 [0.21, 4.32] 1.00 [0.41, 2.42] 1.29 [0.75, 2.23]	
Sencalova 2009 Evstatiev 2013 Fishbane 1995 Mudge 2012 Pollak 2001 Santer 2020 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 Fest for overall effect: Z 1.13.6 Unclear Allen 2011	20 2 10 2 7 50 .15; Chi ²	105 25 51 10 24 345 = 7.67, 4	5 12 4 7 38 df = 5 (1	50 51 19 24 374	0.5% 1.8% 0.6% 1.4% 6.4%	0.80 [0.17, 3.84] 0.83 [0.40, 1.75] 0.95 [0.21, 4.32] 1.00 [0.41, 2.42] 1.29 [0.75, 2.23]	
Bencalova 2009 Evstatiev 2013 Fishbane 1995 Mudge 2012 Pollak 2001 Subtotal (95% CI) Total events Heterogenehty: Tau ² = 0 Test for overall effect: Z 1.13.6 Unclear Allen 2011 Beguin 2013 Bistra 2020	20 2 10 2 7 50 .15; Chi ² - = 0.93 (P 3 10 17	105 25 51 10 24 345 = 7.67, 6 = 0.35) 24 50 126	5 12 4 7 38 df = 5 (1 2 7 17	50 51 19 24 374 • = 0.1 21 52 127	0.5% 1.8% 0.6% 1.4% 6.4% 8); I ² = 35 0.5% 1.4% 2.2%	0.80 [0.17, 3.84] 0.83 [0.40, 1.75] 0.95 [0.21, 4.32] 1.00 [0.41, 2.42] 1.29 [0.75, 2.23] % 1.31 [0.24, 7.12] 1.49 [0.61, 3.60] 1.01 [0.54, 1.88]	• • •
sencalova 2009 Evstattev 2013 (ishbane 1995 Mudge 2012 Pollak 2001 Subtotal (95% CI) Total events Heterogenethy: Tau ² = 0 Fest for overall effect: Z 1.13.6 Unclear Allen 2011 Beguin 2013 Sietza 2020 Fiel 1995	20 2 10 2 7 50 .15; Chi ² - 0.93 (P 3 10 17 9	105 25 51 10 24 345 = 7.67, (= 0.35) 24 50 126 14	5 12 4 7 38 df = 5 (1 7 17 7	50 51 19 24 374 7 = 0.1 21 52 127 12	0.5% 1.8% 0.6% 1.4% 6.4% 8); ^p = 35 0.5% 1.4% 2.2% 2.3%	0.80 [0.17] 3.84 0.83 [0.40, 1.75] 0.95 [0.21, 4.32] 1.00 [0.41, 2.42] 1.29 [0.75, 2.23] * 1.31 [0.24, 7.12] 1.49 [0.61, 3.60] 1.01 [0.54, 1.88] 1.10 [0.55, 2.04]	
Bencalova 2009 Evstatiev 2013 Fishbane 1995 Mudge 2012 Pollak 2001 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.13.6 Unclear Allen 2011 Bieguin 2013 Bieguin 2013 Bieguin 2013	20 2 10 2 7 50 .15; Ch ² - 0.93 (P 3 10 17 9 9 2	105 25 51 10 24 345 = 7.67, 4 = 0.35) 24 50 126 14 55	5 12 4 7 38 df = 5 (1 7 17 7 1	50 51 19 24 374 7 = 0.1 21 52 127 12 55	$\begin{array}{c} 0.5\% \\ 1.8\% \\ 0.6\% \\ 1.4\% \\ 6.4\% \end{array}$ $\begin{array}{c} 6.4\% \\ 6.1\% \\ 1.4\% \\ 2.2\% \\ 2.2\% \\ 2.3\% \\ 0.2\% \end{array}$	0.80 [0.17, 3.84] 0.83 [0.40, 1.75] 0.95 [0.21, 4.32] 1.00 [0.41, 2.42] 1.29 [0.75, 2.23] % 1.31 [0.24, 7.12] 1.49 [0.61, 3.60] 1.01 [0.54, 1.88] 1.10 [0.59, 2.04] 2.00 [0.19, 21.42]	
Bencalova 2009 Evstatiev 2013 Fishbane 1995 Mudge 2012 Pollak 2001 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.13.6 Unclear Allen 2011 Beguin 2013 Bielza 2020 Friel 1995 Kuo 2008 Moppett 2019	20 2 10 2 7 50 .15; Chi ² = 0.93 (P 3 10 17 9 2 8	105 25 51 10 24 345 = 7.67, 4 = 0.35) 24 50 126 126 14 55 39	5 12 4 7 38 df = 5 (1 7 7 7 1 12	50 51 19 24 374 7 = 0.1 21 52 127 12 55 41	0.5% 1.8% 0.6% 1.4% 6.4% 8); l ² = 35 0.5% 1.4% 2.2% 2.2% 0.2% 1.7%	0.80 [0.17, 3.84] 0.83 [0.40, 1.75] 0.95 [0.21, 4.32] 1.00 [0.41, 2.42] 1.29 [0.75, 2.23] 34 1.31 [0.24, 7.12] 1.49 [0.61, 3.60] 1.01 [0.54, 1.88] 1.10 [0.54, 1.88] 1.10 [0.54, 1.88]	
Sencalova 2009 Evstattev 2013 Isishane 1995 Mudge 2012 Pollak 2001 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 Fest for overall effect: Z 1.13.6 Unclear Allen 2011 Biguin 2013 BigUa 2020 Friel 1995 Kuo 2008 Moppett 2019 Serrano-Trenas 2011	20 2 10 2 7 50 .15; Ch ² - 0.93 (P 3 10 17 9 9 2	105 25 51 10 24 345 = 7.67, 4 = 0.35) 24 50 126 14 55	5 12 4 7 38 df = 5 (1 7 17 7 1	50 51 19 24 374 7 = 0.1 21 52 127 12 55	0.5% 1.8% 0.6% 1.4% 6.4% 8); ² = 35 0.5% 1.4% 2.2% 2.3% 0.2% 1.7%	0.80 [0.17, 3.84] 0.83 [0.40, 1.75] 0.95 [0.21, 4.32] 1.00 [0.41, 2.42] 1.29 [0.75, 2.23] * 1.31 [0.24, 7.12] 1.49 [0.61, 3.60] 1.01 [0.54, 1.68] 1.10 [0.59, 2.04] 2.00 [0.19, 21.42] 0.70 [0.32, 1.53] 2.45 [1.23, 4.89]	
Sencalova 2009 Evistative 2013 Isishane 1995 Mudge 2012 Pollak 2001 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.13.6 Unclear Allen 2011 Bieguin 2013 Bielza 2020 Friel 1995 Kuo 2008 Moppett 2019 Serrano-Trenas 2011 Subtotal (95% CI) Total events	20 2 10 2 50 .15; Chr ² - - 0.93 (P 3 10 17 9 2 8 16 .02; Chr ² -	105 25 51 10 24 345 = 7.67, (50 126 14 55 39 100 408 = 6.70, (5 12 4 7 38 df = 5 (1 2 7 17 7 1 12 13 13 df = 6 (1	50 51 19 24 374 = 0.1 21 52 127 12 55 41 199 507	0.5% 1.8% 0.6% 1.4% 6.4% 8); ² - 35 0.5% 1.4% 2.2% 2.3% 0.2% 1.7% 2.0% 10.3%	0.80 [0.17, 3.84] 0.83 [0.40, 1.75] 0.55 [0.21, 4.32] 1.00 [0.41, 2.42] 1.29 [0.75, 2.23] 3% 1.31 [0.24, 7.12] 1.49 [0.61, 3.60] 1.01 [0.54, 1.88] 1.10 [0.59, 2.04] 2.00 [0.19, 21.42] 0.70 [0.32, 1.53] 2.45 [1.23, 4.89] 1.24 [0.89, 1.73]	
Sencalova 2009 Evstattev 2013 Sishbane 1995 Mudge 2012 Pollak 2001 Santer 2020 Subtotal (95% CI) Total events Heterogenethy: Tau ² = 0 Test for overall effect: Z 1.13.6 Unclear Allen 2011 Seguin 2013 Sietza 2020 Friel 1995 Kuo 2008 Moppett 2019 Serrano-Trenas 2011 Subtotal (95% CI) Total events	20 2 10 2 50 .15; Chr ² - - 0.93 (P 3 10 17 9 2 8 16 .02; Chr ² -	105 25 51 10 24 345 = 7.67, (50 126 14 55 39 100 408 = 6.70, (5 12 4 7 38 df = 5 (1 2 7 17 7 1 12 13 13 df = 6 (1	50 51 19 24 374 = 0.1 21 52 127 12 55 41 199 507	0.5% 1.8% 0.6% 1.4% 6.4% 8); ² - 35 0.5% 1.4% 2.2% 2.3% 0.2% 1.7% 2.0% 10.3%	0.80 [0.17, 3.84] 0.83 [0.40, 1.75] 0.55 [0.21, 4.32] 1.00 [0.41, 2.42] 1.29 [0.75, 2.23] 3% 1.31 [0.24, 7.12] 1.49 [0.61, 3.60] 1.01 [0.54, 1.88] 1.10 [0.59, 2.04] 2.00 [0.19, 21.42] 0.70 [0.32, 1.53] 2.45 [1.23, 4.89] 1.24 [0.89, 1.73]	
sencalova 2009 vstatkev 2013 isibhane 1995 Wudge 2012 vollak 2001 isibtotal (95% CI) fotal events Heterogeneity: Tau ² = 0 Test for overall effect: Z 1.13.6 Unclear Allen 2011 iseguin 2013 isejza 2020 riel 1995 Kuo 2008 Woppett 2019 iserrano-Trenas 2011 Subtotal (95% CI) Total events ieterogeneity: Tau ² = 0	20 2 10 2 50 .15; Chr ² - - 0.93 (P 3 10 17 9 2 8 16 .02; Chr ² -	105 25 51 10 24 345 = 7.67, (50 126 14 55 39 100 408 = 6.70, (5 12 4 7 38 df = 5 (1 2 7 17 7 1 12 13 13 df = 6 (1	50 51 19 24 374 • = 0.1 21 52 127 12 55 41 199 507 • = 0.3	0.5% 1.8% 0.6% 1.4% 6.4% 8); ² - 35 0.5% 1.4% 2.2% 2.3% 0.2% 1.7% 2.0% 10.3%	0.80 [0.17, 3.84] 0.83 [0.40, 1.75] 0.55 [0.21, 4.32] 1.00 [0.41, 2.42] 1.29 [0.75, 2.23] 3% 1.31 [0.24, 7.12] 1.49 [0.61, 3.60] 1.01 [0.54, 1.88] 1.10 [0.59, 2.04] 2.00 [0.19, 21.42] 0.70 [0.32, 1.53] 2.45 [1.23, 4.89] 1.24 [0.89, 1.73]	
sencalova 2009 vstatkev 2013 isibhane 1995 Mudge 2012 vollak 2001 hanter 2020 Subtotal (95% CI) fotal events Heterogeneity: Tau ² = 0 fest for overall effect: Z L.13.6 Unclear Allen 2011 iseguin 2013 isetza 2020 riel 1995 (up 2008 Moppett 2019 iserrano-Trenas 2011 Subtotal (95% CI) fotal events Heterogeneity: Tau ² = 0 fest for overall effect: Z	20 2 10 2 50 .15; Chr ² - - 0.93 (P 3 10 17 9 2 8 16 .02; Chr ² -	105 25 51 10 24 345 = 7.67, 4 = 0.35) 24 50 126 126 126 126 126 126 126 126 126 126	5 12 4 7 38 df = 5 (1 2 7 17 7 1 12 13 13 df = 6 (1	50 51 19 24 374 • = 0.1 21 52 127 12 55 41 199 507 • = 0.3	0.5% 1.8% 0.6% 1.4% 6.4% 8); ² - 35 0.5% 1.4% 2.2% 2.3% 0.3% 1.7% 2.0% 10.3% 5); ² - 10	0.80 [0.17, 3.84] 0.83 [0.40, 1.75] 0.55 [0.0, 1.74] 1.00 [0.41, 2.42] 1.29 [0.75, 2.23] 1.49 [0.61, 3.60] 1.01 [0.54, 1.88] 1.10 [0.59, 2.04] 2.00 [0.19, 21.42] 0.70 [0.32, 1.53] 2.45 [1.23, 4.89] 1.24 [0.89, 1.73]	

eFigure 6. Secondary outcomes - hemoglobin forest plots

(a) Difference in haemoglobin at primary outcome timepoint or study endpoint



(b) By treatment response, as defined by the study authors

	Experim Events		Contr Events		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% Cl
1.5.1 IV iron vs. oral iro	on						
Adhikary 2011	27	45	11	45	1.3%	2.45 [1.39, 4.32]	
Auerbach 2004	53	78	15	43	1.5%	1.95 [1.26, 3.01]	
Bager 2014	38	42	31	41	2.1%	1.20 [0.98, 1.46]	
Batool 2016	36	41	27	41	2.0%	1.33 [1.04, 1.71]	
	3	24	4	23	0.4%		
Bayoumeu 2002			-			0.72 [0.18, 2.87]	
Beguin 2013	23	23	20	25	2.0%	1.24 [1.01, 1.53]	
Bencalova 2009	97	130	104	130	2.2%	0.93 [0.82, 1.06]	-+
Bisbe 2014	20	59	13	62	1.2%	1.62 [0.89, 2.95]	
Sreymann 2006	152	179	73	69	2.2%	1.04 [0.92, 1.16]	+
Breymann 2016	103	124	87	123	2.2%	1.17 [1.02, 1.35]	
Charytan 2005	26	48	15	48	1.4%	1.73 [1.06, 2.84]	
Charytan 2012	64	249	55	249	1.6%	1.16 [0.85, 1.59]	
Jubey 2013	62	100	5	100	0.8%	12.40 [5.21, 29.54]	
· · · · ·	-		-				
vstatlev 2013	77	105	60	99	2.1%	1.21 [0.99, 1.47]	
errer-Barcelo 2019	29	39	19	31	1.6%	1.21 [0.87, 1.70]	
lenry 2007	30	41	20	44	1.7%	1.61 [1.11, 2.34]	
yoke 2017	110	115	115	122	2.3%	1.01 [0.96, 1.08]	+
(halafallah 2010	15	92	26	91	1.3%	0.57 [0.32, 1.00]	
(Im 2009	23	30	3	26	0.6%	6.64 [2.25, 19.61]	
	36	136	2	60	0.4%		
Cuinigg 2008						7.94 [1.96, 31.92]	
12008	45	70	19	66	1.6%	2.23 [1.47, 3.39]	
Indgren 2009	30	45	22	46	1.7%	1.39 [0.97, 2.01]	<u>├</u>
Maccio 2010	37	73	42	75	1.6%	0.91 [0.67, 1.22]	-+-
MacDougali 2014	139	305	99	308	2.1%	1.42 [1.16, 1.74]	
McMahon 2010	34	43	30	42	2.0%	1.11 [0.87, 1.41]	- +
Neogl 2019	240	666	128	629	2.1	1.77 [1.47, 2.13]	
	20	87		90	1.2%		
Noronha 2016			16			1.29 [0.72, 2.33]	
Onken 2014	139	244	73	251	2.0%	1.96 [1.57, 2.45]	
admanabhan 2019	1	22	2	22	0.2%	0.50 [0.05, 5.12]	• • • • • • • • • • • • • • • • • • • •
rovenzano 2009	56	114	29	116	1.7%	1.96 [1.36, 2.83]	
)unibi 2011	69	147	36	103	1.9%	1.73 [1.29, 2.32]	
tathod 2015	93	200	12	100	1.3×	3.88 [2.23, 6.72]	
	36	41	27	41	2.0%	1.33 [1.04, 1.71]	
Lazzaq 2017							
chijns 2020	26	33	16	26	1.6%	1.14 [0.83, 1.55]	
ichroder 2005	12	22	13	24	1.3×	1.01 [0.59, 1.71]	
ieki 2008	127	139	98	147	2.2%	1.37 [1.21, 1.55]	-
ipinowitz 2006	69	228	14	76	1.4%	2.12 [1.29, 3.49]	
iteensma 2011	114	164	109	163	2.2%	1.04 [0.90, 1.21]	+-
itoves 2001	15	22	14	23	1.5%	1.12 [0.73, 1.73]	
Van Wyck 2005	35	79	23	82	1.6×		
·		-	-			1.58 [1.03, 2.42]	
Van Wyck 2007	163	169	158	168	2.3%	1.03 [0.98, 1.08]	T T
Van Wyck 2009	167	228	139	225	2.2%	1.33 [1.18, 1.50]	
Vanobberghen 2020	75	94	47	92	2.0%	1.56 [1.25, 1.95]	
Neisbach 1999	6	30	5	60	0.6%	2.40 [0.80, 7.23]	
Subtotal (95% CI)		4965		4467	71.5%	1.41 [1.27, 1.56]	•
Total events	2832		1878				
				10 (m	A AAAA): P = 91%	
Heterogeneity: Tau ² = 0 Fest for overall effect: Z).09; Chl ² : = 6.36 (P	o.00 > ۲		13 (P <	0.00001		
Fest for overall effect: Z).09; Chl ² : = 6.36 (P	o.00 > ۲	001)		0.00001		
est for overall effect: Z 1.5.2 IV iron vs. no iror).09; Chl ² : = 6.36 (P	o.00 > ۲		36	1.2%	2.72 [1.51, 4.88]	
est for overall effect: Z L.5.2 IV iron vs. no iror Averbach 2004).09; Chi ² : = 6.36 (P n/compar	' < 0.00 ator	001)			2.72 [1.51, 4.88]	
est for overall effect: Z LS.2 IV iron vs. no iror Werbach 2004 Werbach 2010).09; Chi ² (= 6.36 (P n/compar 53 70	r < 0.00 ator 78 81	9 56	36 72	1.2% 2.1%	2.72 [1.51, 4.88] 1.11 [0.96, 1.29]	
est for overall effect: Z LS.2 IV iron vs. no iror Werbach 2004 Werbach 2010 Kastit 2008	0.09; Chi ² : = 6.36 (P n/compar 53 70 172	 < 0.00 rator 78 81 200 	9 56 143	36 72 196	1.2% 2.1% 2.2%	2.72 [1.51, 4.88] 1.11 [0.96, 1.29] 1.18 [1.06, 1.31]	
est for overall effect: Z L.S.2 IV iron vs. no iror werbach 2004 werbach 2010 lastit 2008 Belza 2020	0.09; Chi ² (= 6.36 (P n/compar 53 70 172 82	e < 0.00 rator 78 81 200 126	001) 9 56 143 92	36 72 196 127	1.2% 2.1% 2.2% 2.1%	2.72 [1.51, 4.88] 1.11 [0.96, 1.29] 1.18 [1.06, 1.31] 0.90 [0.76, 1.06]	
est for overall effect: Z LS.2 IV iron vs. no iror werbach 2004 werbach 2010 iastit 2008 lebza 2020 Joyne 2007	0.09; Chi ² - = 6.36 (P n/compar 53 70 172 82 30	e < 0.00 rator 78 81 200 126 64	001) 9 56 143 92 19	36 72 196 127 65	1.2% 2.1% 2.2% 2.1% 1.5%	2.72 [1.51, 4.88] 1.11 [0.96, 1.29] 1.18 [1.06, 1.31] 0.90 [0.76, 1.06] 1.60 [1.01, 2.54]	
est for overall effect: Z L.S.2 IV iron vs. no iror werbach 2004 werbach 2010 lastit 2008 lietza 2020 Soyne 2007 idwards 2009	0.09; Chi ² + = 6.36 (P n/compar 53 70 172 62 30 9	 < 0.00 rator 78 81 200 126 64 34 	001) 9 56 143 92 19 9	36 72 196 127 65 26	1.2% 2.1% 2.2% 2.1% 1.5% 0.9%	2.72 [1.51, 4.88] 1.11 [0.96, 1.29] 1.18 [1.06, 1.31] 0.90 [0.76, 1.06] 1.60 [1.01, 2.54] 0.76 [0.35, 1.65]	
est for overall effect: Z L.S.2 IV iron vs. no iror Auerbach 2004 Auerbach 2010 Jastit 2008 Jastit 2008 Jastit 2020 Goyne 2007 Javrat 2014	0.09; Chi ² - = 6.36 (P n/compar 53 70 172 62 30 9 144	 < 0.00 rator 78 81 200 126 64 34 144 	001) 9 56 143 92 19	36 72 196 127 65 26 146	1.2% 2.1% 2.2% 2.1% 1.5% 0.9% 2.2%	2.72 [1.51, 4.86] 1.11 [0.96, 1.29] 1.18 [1.06, 1.31] 0.90 [0.76, 1.06] 1.60 [1.01, 2.54] 0.76 [0.35, 1.65] 1.24 [1.14, 1.34]	
est for overall effect: Z L.S.2 IV iron vs. no iror Auerbach 2004 Auerbach 2010 Jastit 2008 Jastit 2008 Jastit 2020 Goyne 2007 Javrat 2014	0.09; Chi ² + = 6.36 (P n/compar 53 70 172 62 30 9	 < 0.00 rator 78 81 200 126 64 34 	001) 9 56 143 92 19 9	36 72 196 127 65 26	1.2% 2.1% 2.2% 2.1% 1.5% 0.9%	2.72 [1.51, 4.88] 1.11 [0.96, 1.29] 1.18 [1.06, 1.31] 0.90 [0.76, 1.06] 1.60 [1.01, 2.54] 0.76 [0.35, 1.65]	
est for overall effect: Z L.S.2 IV iron vs. no iror werbach 2004 werbach 2010 lastit 2008 liebza 2020 Coyne 2007 idwards 2009 avrat 2014 liedenus 2007	0.09; Chi ² - = 6.36 (P n/compar 53 70 172 62 30 9 144	 < 0.00 rator 78 81 200 126 64 34 144 	001) 9 56 143 92 19 9 116	36 72 196 127 65 26 146	1.2% 2.1% 2.2% 2.1% 1.5% 0.9% 2.2%	2.72 [1.51, 4.86] 1.11 [0.96, 1.29] 1.18 [1.06, 1.31] 0.90 [0.76, 1.06] 1.60 [1.01, 2.54] 0.76 [0.35, 1.65] 1.24 [1.14, 1.34]	
est for overall effect: Z LS.2 IV iron vs. no iror werbach 2004 werbach 2010 lastit 2008 letza 2020 loyne 2007 idwards 2009 lavrat 2014 iedenus 2007 iedenus 2014	0.09; Chi ² - = 6.36 (P n/compar 53 70 172 82 30 9 144 31 8	> < 0.00 rator 78 81 200 126 64 34 144 33 8	9 56 143 92 19 9 118 18 6	36 72 196 127 65 26 146 34 9	1.2% 2.1% 2.2% 2.1% 1.5% 0.9% 2.2% 1.6% 1.4%	2.72 [1.51, 4.88] 1.11 [0.96, 1.29] 1.18 [1.06, 1.31] 0.90 [0.76, 1.06] 1.60 [1.01, 2.54] 0.76 [0.35, 1.65] 1.24 [1.14, 1.34] 1.77 [1.28, 2.46] 1.45 [0.90, 2.35]	
est for overall effect: Z L.S.2 IV iron vs. no iror werbach 2004 werbach 2010 lastit 2008 lielza 2020 Joyne 2007 dwards 2009 avrat 2014 ledenus 2007 iedenus 2014 ledenus 2014	0.09; Chi ² - = 6.36 (P n/compar 53 70 172 82 30 9 144 31 8 30	P < 0.00 rator 78 81 200 126 64 34 144 33 8 41	9 56 143 92 19 9 118 18 6 18	36 72 196 127 65 26 146 34 9 44	1.2% 2.1% 2.1% 1.5% 0.9% 2.2% 1.8% 1.4%	2.72 [1.51, 4.88] 1.11 [0.96, 1.29] 1.18 [1.06, 1.31] 0.90 [0.76, 1.06] 1.60 [1.01, 2.54] 0.76 [0.35, 1.65] 1.24 [1.14, 1.34] 1.77 [1.28, 2.46] 1.45 [0.90, 2.35] 1.79 [1.20, 2.67]	
est for overall effect: Z L.S.2 IV iron vs. no iror werbach 2004 werbach 2010 lastit 2008 lietza 2020 Joyne 2007 dwards 2009 javrat 2014 ledenus 2007 ledenus 2014 ledenus 2014 ledenus 2014 ledenus 2007 lietdo 2007	0.09; Ch ² : = 6.36 (P 53 70 172 82 30 9 144 31 8 30 9 9	P < 0.00 rator 78 81 200 126 64 34 144 33 8 41 30	9 56 143 92 19 9 118 18 6 18 21	36 72 196 127 65 26 146 34 9 44	1.2% 2.1% 2.2% 2.1% 1.5% 0.9% 2.2% 1.8% 1.4% 1.6%	2.72 [1.51, 4.86] 1.11 [0.96, 1.29] 1.18 [1.06, 1.31] 0.90 [0.76, 1.06] 1.60 [1.01, 2.54] 0.76 [0.35, 1.65] 1.24 [1.14, 1.34] 1.77 [1.28, 2.46] 1.45 [0.90, 2.35] 1.79 [1.20, 2.67] 0.64 [0.34, 1.21]	
rest for overall effect: Z L.S.2 IV iron vs. no iror Auerbach 2004 Auerbach 2010 lastit 2008 letza 2020 Coyne 2007 dwards 2009 avrat 2014 ledenus 2007 ledenus 2014 ledenus 2014 leiny 2007 (Im 2007 (Im 2017	0.09; Ch ² (= 6.36 (P 53 70 172 82 30 9 144 31 8 30 9 200	> < 0.00 rator 78 81 200 126 64 34 144 33 8 41 30 217	0001) 9 566 143 92 19 9 118 18 6 6 18 21 21 115	36 72 196 127 65 26 146 34 9 44 45 213	1.2% 2.1% 2.2% 2.3% 1.5% 0.9% 2.2% 1.6% 1.6% 1.4% 1.1% 2.2%	2.72 [1.51, 4.88] 1.11 [0.96, 1.29] 1.18 [1.06, 1.31] 0.90 [0.76, 1.06] 1.60 [1.01, 2.54] 0.76 [0.35, 1.65] 1.24 [1.14, 1.34] 1.77 [1.28, 2.46] 1.45 [0.90, 2.35] 1.79 [1.20, 2.67] 0.64 [0.34, 1.21] 1.71 [1.50, 1.94]	
est for overall effect: Z 	0.09; Ch ² (= 6.36 (r/compar 53 70 172 62 30 9 144 31 8 30 9 200 56	> < 0.00 ator 78 81 200 126 64 34 144 33 8 41 30 217 73	9 56 143 92 19 9 116 18 6 18 6 21 115 47	36 72 196 127 65 26 146 34 9 44 45 213 76	1.2% 2.1% 2.1% 2.1% 1.5% 0.9% 2.2% 1.6% 1.4% 1.4% 1.1% 2.2%	2.72 [1.51, 4.88] 1.11 [0.96, 1.29] 1.18 [1.06, 1.31] 0.90 [0.76, 1.06] 1.60 [1.01, 2.54] 0.76 [0.35, 1.65] 1.24 [1.14, 1.34] 1.77 [1.28, 2.46] 1.45 [0.90, 2.35] 1.79 [1.20, 2.67] 0.64 [0.34, 1.21] 1.71 [1.50, 1.94] 1.24 [1.00, 1.54]	
est for overall effect: Z L.S.2 IV iron vs. no iror werbach 2004 werbach 2010 lastit 2008 lielza 2020 Joyne 2007 dwards 2009 avrat 2014 ledenus 2007 lim 2007 lim 2007 lim 2007 lim 2017 Vedrazzoli 2008 lichards 2020	0.09; Chr ² (= 6.36 (P n/compar 53 70 172 82 30 9 144 31 8 30 9 144 31 8 30 9 200 56 42	 < 0.00 ator 78 81 2000 126 64 34 144 33 8 41 30 217 73 244 	0001) 956 143 92 19 9 118 6 18 21 115 47 21	36 72 196 127 65 266 146 34 9 44 45 213 76 243	1.2% 2.1% 2.2% 2.1% 1.5% 0.9% 2.2% 1.6% 1.4% 1.6% 1.1% 2.2% 2.0%	2.72 [1.51, 4.88] 1.11 [0.96, 1.29] 1.18 [1.06, 1.31] 0.90 [0.76, 1.06] 1.60 [1.01, 2.54] 0.76 [0.35, 1.65] 1.24 [1.14, 1.34] 1.77 [1.28, 2.46] 1.45 [0.90, 2.35] 1.79 [1.20, 2.67] 0.64 [0.34, 1.21] 1.71 [1.50, 1.94] 1.24 [1.00, 1.54] 1.99 [1.22, 3.26]	
est for overall effect: Z L.S.2 IV iron vs. no iror werbach 2004 werbach 2010 lastit 2008 lielza 2020 Joyne 2007 dwards 2009 avrat 2014 ledenus 2007 lim 2007 lim 2007 lim 2007 lim 2017 Vedrazzoli 2008 lichards 2020	0.09; Chr ² - = 6.36 (P n/compar 53 70 172 82 30 9 144 31 8 30 9 244 31 8 30 9 246 144 31 8 30 9 144 31 8 30 9 144 31 8 30 9 144 31 8 30 9 144 31 8 30 9 144 31 8 30 9 144 31 8 30 9 144 31 8 30 9 144 31 8 30 9 144 31 8 30 9 144 31 8 30 9 144 31 8 30 9 144 31 8 30 9 144 31 8 30 9 144 31 8 30 9 144 31 8 30 9 144 31 8 30 9 144 31 8 30 9 144 8 30 9 144 31 8 30 9 200 56 148 31 8 30 9 200 56 148 31 8 30 9 200 56 148 30 9 200 56 148 31 8 30 9 200 56 56 200 56 56 56 56 56 56 56 56 56 56	> < 0.00 ator 78 81 200 126 64 34 144 33 8 41 30 217 73	9001) 956 143 92 19 9 118 6 18 21 115 47 21 11	36 72 196 127 65 26 146 34 45 213 76 243 60	1.2% 2.1% 2.1% 2.1% 1.5% 0.9% 2.2% 1.6% 1.4% 1.4% 1.1% 2.2%	2.72 [1.51, 4.86] 1.11 [0.96, 1.29] 1.18 [1.06, 1.31] 0.90 [0.76, 1.06] 1.60 [1.01, 2.54] 0.76 [0.35, 1.65] 1.24 [1.14, 1.34] 1.77 [1.28, 2.46] 1.45 [0.90, 2.35] 1.79 [1.20, 2.67] 0.64 [0.34, 1.21] 1.71 [1.50, 1.94] 1.24 [1.00, 1.54] 1.99 [1.22, 3.26] 1.96 [1.03, 3.76]	
est for overall effect: Z L.S.2 IV iron vs. no iror werbach 2004 werbach 2010 lastit 2008 lietza 2020 loyne 2007 idwards 2009 lavrat 2014 ledenus 2007 liedenus 2017 ledenus 2017 lim 2007 lim 2007 lim 2007 lim 2007 lim 2007 lim 2007 lim 2007 lim 2017 vedrazzoli 2008 lichards 2020 lerrano-Trenas 2011	0.09; Chr ² (= 6.36 (P n/compar 53 70 172 82 30 9 144 31 8 30 9 144 31 8 30 9 200 56 42	 < 0.00 ator 78 81 2000 126 64 34 144 33 8 41 30 217 73 244 	0001) 956 143 92 19 9 118 6 18 21 115 47 21	36 72 196 127 65 266 146 34 9 44 45 213 76 243	1.2% 2.1% 2.2% 2.1% 1.5% 0.9% 2.2% 1.6% 1.4% 1.6% 1.1% 2.2% 2.0%	2.72 [1.51, 4.88] 1.11 [0.96, 1.29] 1.18 [1.06, 1.31] 0.90 [0.76, 1.06] 1.60 [1.01, 2.54] 0.76 [0.35, 1.65] 1.24 [1.14, 1.34] 1.77 [1.28, 2.46] 1.45 [0.90, 2.35] 1.79 [1.20, 2.67] 0.64 [0.34, 1.21] 1.71 [1.50, 1.94] 1.24 [1.00, 1.54] 1.99 [1.22, 3.26]	
est for overall effect: Z LS.2 IV iron vs. no iror werbach 2004 twerbach 2010 lastit 2008 letza 2020 20yne 2007 idwards 2009 lavrat 2014 ledenus 2007 lidenus 2017 ledenus 2017 lim 2007 Lim 2017 lim 2016 lim 2016	0.09; Chr ² (= 6.36 (F n/compar 53 70 172 82 30 9 144 31 8 30 9 144 31 8 30 9 200 56 42 18 8 39	> < 0.00 rator 78 81 200 126 64 34 144 38 41 30 217 73 244 50 66	9001) 956 143 92 19 9 118 6 18 21 115 47 21 11	36 72 196 127 65 26 146 34 9 44 45 213 76 243 60 33	1.2% 2.1% 2.2% 2.3% 1.6% 1.6% 1.4% 1.4% 1.4% 1.1% 2.2% 2.0% 1.4% 1.1%	2.72 [1.51, 4.86] 1.11 [0.96, 1.29] 1.18 [1.06, 1.31] 0.90 [0.76, 1.06] 1.60 [1.01, 2.54] 0.76 [0.35, 1.65] 1.24 [1.14, 1.34] 1.77 [1.28, 2.46] 1.45 [0.90, 2.35] 1.79 [1.20, 2.67] 0.64 [0.34, 1.21] 0.64 [0.34, 1.21] 1.71 [1.50, 1.54] 1.24 [1.00, 1.54] 1.96 [1.03, 3.76] 1.97 [1.05, 2.99]	
est for overall effect: Z L.S.2 IV iron vs. no iror werbach 2004 werbach 2010 lastit 2008 letza 2020 loyne 2007 idwards 2009 lavrat 2014 iedenus 2007 lidednus 2014 iedenus 2014 iedenus 2017 ledenus 2017 lim 2007 lim 2006 lim 2006 lim 2006 lim 2005 lim 2005	0.09; Ch ² (= 6.36 (r/compar 53 70 172 82 30 9 144 31 8 30 9 200 56 42 18 39 200 56 42 18	> < 0.00 ator 78 81 200 126 64 34 144 33 8 41 30 217 73 244 50 668 608	9 56 143 92 19 118 6 18 6 18 21 115 47 21 11 11 11	36 72 196 127 65 26 146 34 9 44 45 213 76 243 60 33 200	1.2% 2.1% 2.2% 1.5% 0.9% 2.2% 1.6% 1.4% 1.6% 1.1% 2.2% 1.4% 1.1% 1.3%	2.72 [1.51, 4.88] 1.11 [0.96, 1.29] 1.18 [1.06, 1.31] 0.90 [0.76, 1.06] 1.60 [1.01, 2.54] 0.76 [0.35, 1.65] 1.24 [1.14, 1.34] 1.77 [1.28, 2.46] 1.45 [0.90, 2.35] 1.79 [1.20, 2.67] 0.64 [0.34, 1.21] 1.71 [1.50, 1.94] 1.24 [1.00, 1.54] 1.99 [1.22, 3.26] 1.96 [1.03, 3.76] 1.77 [1.05, 2.99] 14.74 [8.29, 26.22]	
rest for overall effect: Z L.S.2 IV iron vs. no iror Auerbach 2004 Auerbach 2010 Lastit 2008 Bielza 2020 Coyne 2007 Edwards 2009 avrat 2014 Hedenus 2017 Hedenus 2017 Vedrazzoli 2008 Kichards 2020 Berrano-Trenas 2011 Bingh 2006 /adhan-Raj 2013 (u 2020	0.09; Chr ² (= 6.36 (F n/compar 53 70 172 82 30 9 144 31 8 30 9 144 31 8 30 9 200 56 42 18 8 39	> < 0.00 rator 78 81 200 126 64 34 144 144 33 8 41 30 217 73 244 50 66 606 606 75	0001) 956 143 92 199 118 16 6 18 21 115 47 21 115 11	36 72 196 127 65 26 146 34 45 213 76 243 60 33 200 73	1.2% 2.1% 2.2% 1.5% 0.9% 2.2% 1.6% 1.4% 1.6% 1.1% 2.0% 2.0% 1.4% 1.1% 1.3% 1.2% 0.9%	2.72 [1.51, 4.88] 1.11 [0.96, 1.29] 1.18 [1.06, 1.31] 0.90 [0.76, 1.06] 1.60 [1.01, 2.54] 0.76 [0.35, 1.65] 1.24 [1.14, 1.34] 1.77 [1.28, 2.46] 1.45 [0.90, 2.35] 1.79 [1.20, 2.67] 0.64 [0.34, 1.21] 1.71 [1.50, 1.94] 1.24 [1.00, 1.54] 1.99 [1.22, 3.26] 1.96 [1.03, 3.76] 1.77 [1.05, 2.99] 14.74 [8.29, 26.22] 2.19 [1.02, 4.72]	
est for overall effect: Z L.S.2 IV iron vs. no iror werbach 2004 werbach 2010 lastit 2008 lietza 2020 loyne 2007 idwards 2009 iavrat 2014 ledenus 2007 lim 2	0.09; Chr ² (= 6.36 (P n/compar 53 70 172 82 30 9 144 31 8 30 9 144 31 8 30 9 200 56 42 8 39 493 18	> < 0.00 ator 78 81 200 126 64 34 144 33 8 41 30 217 73 244 50 668 608	9 56 143 92 19 9 118 18 21 115 47 21 11 11 11 11 11 8	36 72 196 127 65 26 146 34 9 44 45 213 76 243 60 33 200	1.2% 2.1% 2.2% 1.5% 0.9% 2.2% 1.6% 1.4% 1.6% 1.1% 2.2% 1.4% 1.1% 1.3%	2.72 [1.51, 4.88] 1.11 [0.96, 1.29] 1.18 [1.06, 1.31] 0.90 [0.76, 1.06] 1.60 [1.01, 2.54] 0.76 [0.35, 1.65] 1.24 [1.14, 1.34] 1.77 [1.28, 2.46] 1.45 [0.90, 2.35] 1.79 [1.20, 2.67] 0.64 [0.34, 1.21] 1.71 [1.50, 1.94] 1.24 [1.00, 1.54] 1.99 [1.22, 3.26] 1.96 [1.03, 3.76] 1.77 [1.05, 2.99] 14.74 [8.29, 26.22]	
est for overall effect: Z .5.2 IV iron vs. no iror werbach 2004 werbach 2010 iastit 2008 igetza 2020 isoyne 2007 idwards 2009 avrat 2014 iedenus 2007 idedenus 2014 iedenus 2017 iedenus 2017 iedrazzoli 2008 tichards 2020 ierrano-Trenas 2011 ingh 2006 iadhan-Raj 2013 (µ 2020 iubtotal (95% CI) otal events ieterogenety: Tau ² = 0	0.09; Chr ² (= 6.36 (F n/compar 53 70 172 82 30 9 144 31 8 30 9 200 56 42 18 39 200 56 42 18 39 200 56 42 18 39	> < 0.00 ator 78 81 200 126 64 34 144 33 8 41 30 217 73 244 50 66 608 75 2172 = 244.3	0001) 956 143 92 19 9 118 6 6 18 6 18 21 115 47 21 11 11 11 11 8 733 16, df = 1	36 72 196 127 65 26 146 9 44 45 213 34 9 44 45 243 60 33 200 0 33 200 0 33	1.2% 2.1% 2.2% 2.1% 1.5% 0.9% 2.2% 1.6% 1.4% 1.6% 1.4% 1.6% 1.4% 1.3% 1.2% 0.9% 28.5%	2.72 [1.51, 4.86] 1.11 [0.96, 1.29] 1.18 [1.06, 1.31] 0.90 [0.76, 1.06] 1.60 [1.01, 2.54] 0.76 [0.35, 1.65] 1.24 [1.14, 1.34] 1.77 [1.28, 2.46] 1.45 [0.90, 2.35] 1.79 [1.20, 2.67] 0.64 [0.34, 1.21] 0.64 [0.34, 1.21] 1.71 [1.50, 1.94] 1.24 [1.00, 1.54] 1.96 [1.02, 3.76] 1.96 [1.03, 3.76] 1.77 [1.05, 2.99] 14.74 [8.29, 26.22] 2.19 [1.02, 4.72] 1.58 [1.28, 1.95]	
Fest for overall effect: Z L.S.2 IV iron vs. no iror Auerbach 2004 Auerbach 2010 Sastt 2008 Siebz 2020 Coyne 2007 dwards 2009 dwards 2009 dwards 2014 Hedenus 2014 Hedenus 2014 Hedenus 2017 Hedenus 2017 Cim 2007 Cim 2008 Cim 2008 Cim 2008 Cim 2008 Cim 2006 Cim 2006 Cim 2005 Cim 2006 Cim 2006 Cim 2006 Cim 2006 Cim 2007 Cim 200	0.09; Chr ² (= 6.36 (F n/compar 53 70 172 82 30 9 144 31 8 30 9 200 56 42 18 39 200 56 42 18 39 200 56 42 18 39	< 0.00 ator 78 81 200 1266 64 34 144 33 8 41 30 217 73 244 50 66 608 608 75 2172 = 244.3 < 0.00	0001) 956 143 92 19 9 118 6 6 18 6 18 21 115 47 21 11 11 11 11 8 733 16, df = 1	36 72 196 127 65 26 146 34 44 45 213 36 60 33 200 73 1698	1.2% 2.1% 2.2% 2.1% 1.5% 0.9% 2.2% 1.6% 1.6% 1.6% 1.6% 1.6% 1.4% 1.6% 1.4% 1.3% 1.2% 0.9% 28.5% 0.000001	2.72 [1.51, 4.86] 1.11 [0.96, 1.29] 1.18 [1.06, 1.31] 0.90 [0.76, 1.06] 1.60 [1.01, 2.54] 0.76 [0.35, 1.65] 1.24 [1.14, 1.34] 1.77 [1.28, 2.46] 1.45 [0.90, 2.35] 1.79 [1.20, 2.67] 0.64 [0.34, 1.21] 0.64 [0.34, 1.21] 1.71 [1.50, 1.54] 1.24 [1.00, 1.54] 1.26 [1.03, 3.76] 1.77 [1.05, 2.99] 14.74 [8.29, 26.22] 2.19 [1.02, 4.72] 1.58 [1.28, 1.95]	
	0.09; Chr ² (= 6.36 (F n/compar 53 70 172 82 30 9 144 31 8 30 9 200 56 42 18 39 200 56 42 18 39 200 56 42 18 39	> < 0.00 ator 78 81 200 126 64 34 144 33 8 41 30 217 73 244 50 66 608 75 2172 = 244.3	0001) 956 143 92 19 9 118 6 6 18 6 18 21 115 47 21 11 11 11 11 8 733 16, df = 1	36 72 196 127 65 26 146 34 44 45 213 36 60 33 200 73 1698	1.2% 2.1% 2.2% 2.1% 1.5% 0.9% 2.2% 1.6% 1.4% 1.6% 1.4% 1.6% 1.4% 1.3% 1.2% 0.9% 28.5%	2.72 [1.51, 4.86] 1.11 [0.96, 1.29] 1.18 [1.06, 1.31] 0.90 [0.76, 1.06] 1.60 [1.01, 2.54] 0.76 [0.35, 1.65] 1.24 [1.14, 1.34] 1.77 [1.28, 2.46] 1.45 [0.90, 2.35] 1.79 [1.20, 2.67] 0.64 [0.34, 1.21] 0.64 [0.34, 1.21] 1.71 [1.50, 1.94] 1.24 [1.00, 1.54] 1.96 [1.02, 3.76] 1.96 [1.03, 3.76] 1.77 [1.05, 2.99] 14.74 [8.29, 26.22] 2.19 [1.02, 4.72] 1.58 [1.28, 1.95]	
Fest for overall effect: Z L.S.2 IV iron vs. no iror werbach 2004 Averbach 2010 lastit 2008 liebza 2020 Coyne 2007 diwards 2009 avrat 2014 tedenus 2007 liedenus 2014 tedenus 2017 liedenus 2017 liedenus 2017 liedenus 2017 liedenus 2018 lim 2007 Clim 2007 Clim 2007 Clim 2007 lim 2006 lim 2007 lim 2007 lim 2007 lim 2007 lim 2007 lim 2006 li	0.09; Chr ² (= 6.36 (F n/compar 53 70 172 82 30 9 144 31 8 30 9 200 56 42 18 39 200 56 42 18 39 200 56 42 18 39	< 0.00 ator 78 81 200 1266 64 34 144 33 8 41 30 217 73 244 50 66 608 608 75 2172 = 244.3 < 0.00	0001) 956 143 92 19 9 118 6 6 18 6 18 21 115 47 21 11 11 11 11 8 733 16, df = 1	36 72 196 127 65 26 146 34 44 45 213 36 60 33 200 73 1698	1.2% 2.1% 2.2% 2.1% 1.5% 0.9% 2.2% 1.6% 1.6% 1.6% 1.6% 1.6% 1.4% 1.6% 1.4% 1.3% 1.2% 0.9% 28.5% 0.000001	2.72 [1.51, 4.86] 1.11 [0.96, 1.29] 1.18 [1.06, 1.31] 0.90 [0.76, 1.06] 1.60 [1.01, 2.54] 0.76 [0.35, 1.65] 1.24 [1.14, 1.34] 1.77 [1.28, 2.46] 1.45 [0.90, 2.35] 1.79 [1.20, 2.67] 0.64 [0.34, 1.21] 0.64 [0.34, 1.21] 1.71 [1.50, 1.54] 1.24 [1.00, 1.54] 1.26 [1.03, 3.76] 1.77 [1.05, 2.99] 14.74 [8.29, 26.22] 2.19 [1.02, 4.72] 1.58 [1.28, 1.95]	
est for overall effect: Z .5.2 IV iron vs. no iror werbach 2004 werbach 2010 iastit 2008 ideta 2020 ioyne 2007 idwards 2009 iavrat 2014 iedenus 2007 idedenus 2014 iedenus 2007 idedenus 2014 ienry 2007 itim 2017 vedrazzoll 2008 tichards 2020 ierrano-Trenas 2011 ingh 2006 /adhan-Raj 2013 iu 2020 iubtotal (95% Cl) fotal events leterogeneity: Tau ² = 0 fest for overall effect: Z fotal (95% Cl)	0.09; Ch ² (= 6.36 (P n/compar 53 70 172 82 30 9 144 31 8 30 9 200 56 42 18 39 200 56 42 18 39 200 56 42 18 39 200 56 42 18 39 200 56 42 18 39 200 56 42 18 39 200 56 42 18 49 31 56 42 43 36 49 49 31 56 42 42 43 46 42 42 43 46 47 47 46 47 46 47 46 47 46 47 46 47 46 47 46 47 46 47 46 47 46 47 46 47 46 47 46 47 46 47 47 47 46 47 47 46 47 47 47 47 47 47 47 47 47 47 47 47 47	< 0.00 ator 78 81 200 126 64 34 144 33 8 41 30 217 73 244 50 66 608 75 2172 = 244.3 < 0.000 7137	0001) 9 56 143 92 19 9 118 6 18 21 115 47 21 11 11 8 733 16, df = 1 01) 2611	36 72 196 127 65 26 146 9 44 45 213 76 243 76 243 200 73 1698 17 (P < 6165	1.2% 2.1% 2.2% 2.2% 1.5% 0.9% 2.2% 1.4% 1.1% 2.2% 1.4% 1.1% 1.3% 2.0% 1.4% 1.2% 0.9% 28.5%	2.72 [1.51, 4.88] 1.11 [0.96, 1.29] 1.18 [1.06, 1.31] 0.90 [0.76, 1.06] 1.60 [1.01, 2.54] 0.76 [0.35, 1.65] 1.24 [1.14, 1.34] 1.77 [1.28, 2.46] 1.45 [0.90, 2.35] 1.79 [1.20, 2.67] 0.64 [0.34, 1.21] 1.71 [1.50, 1.94] 1.24 [1.00, 1.54] 1.99 [1.22, 3.26] 1.96 [1.03, 3.76] 1.77 [1.05, 2.99] 14.74 [8.29, 26.22] 2.19 [1.02, 4.72] 1.58 [1.28, 1.95] 3.7 ² = 93%	

Association between changes in hemoglobin and intravenous iron. The mean differences and risk ratios were calculated using a random-effects model with Mantel-Haenszel weighting. The size of the data markers indicates the weight of the study. Error bars indicate 95% CIs.

eFigure 7. Secondary outcomes - red blood cell (RBC) transfusion requirements

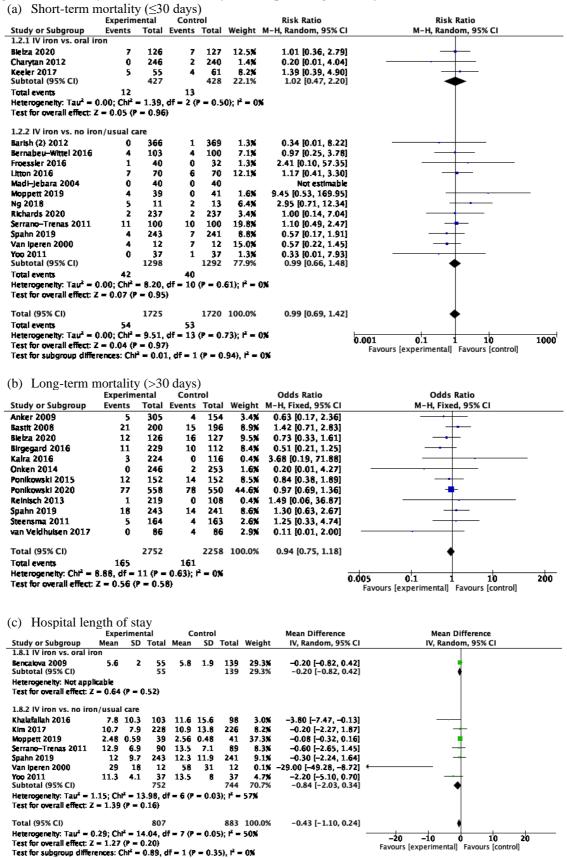
Ctudy on Cub	Experim		Cont		Wai-he	Risk Ratio	Risk Ratio
Study or Subgroup 1.5.1 IV iron vs. oral iro	Events	Iotal	Events	Iotal	weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Adhikary 2011	27	45	11	45	1.3×	2.45 [1.39, 4.32]	
Averbach 2004	53	78	15	43	1.6%	1.95 [1.26, 3.01]	
Bager 2014	38	42	31	41	2.1%	1.20 [0.98, 1.46]	
Batool 2018	36	41	27	41	2.0%	1.33 [1.04, 1.71]	
Bayoumeu 2002	3	24	4	23	0.4%	0.72 [0.18, 2.87]	
Beguin 2013	23	23	20	25	2.1%	1.24 [1.01, 1.53]	
Bencalova 2009 Bisbe 2014	97 20	130 59	104 13	130 62	2.2× 1.2×	0.93 [0.82, 1.06] 1.62 [0.89, 2.95]	
Breymann 2008	152	179	73	69	2.2%	1.04 [0.92, 1.16]	
Breymann 2016	103	124	87	123	2.2%	1.17 [1.02, 1.35]	
Charytan 2005	26	48	15	48	1.4%	1.73 [1.06, 2.84]	
Charytan 2012	64	249	55	249	1.9%	1.16 [0.85, 1.59]	
Dubey 2013	62	100	5	100	0.6%	12.40 [5.21, 29.54]	
Evstatlev 2013	77	105	60	99	2.1%	1.21 [0.99, 1.47]	
Ferrer-Barcelo 2019	29	39	19	31	1.6%	1.21 [0.87, 1.70]	
Henry 2007 hereka 2017	30 110	41 115	20 115	44 122	1.7% 2.3%	1.61 [1.11, 2.34]	
iyoke 2017 Khalafallah 2010	15	92	26	91	1.3%	1.01 [0.96, 1.08] 0.57 [0.32, 1.00]	
Kim 2009	23	30	3	26	0.6%	6.64 [2.25, 19.61]	
Kulnigg 2008	36	136	2	60	0.4%	7.94 [1.98, 31.92]	
LI 2008	45	70	19	66	1.6%	2.23 [1.47, 3.39]	
Undgren 2009	30	45	22	46	1.7%	1.39 [0.97, 2.01]	<u> </u>
Maccio 2010	37	73	42	75	1.9%	0.91 [0.67, 1.22]	<u> </u>
MacDougali 2014	139	305	99	308	2.1%	1.42 [1.16, 1.74]	
McMahon 2010	34	43	30	42	2.0%	1.11 [0.87, 1.41]	+
Neogi 2019 Nacasha 2018	240	666	128	629	2.1%	1.77 [1.47, 2.13]	
Noronha 2016 Onken 2014	20 139	87 244	16 73	90 251	1.2× 2.1×	1.29 [0.72, 2.33]	
Padmanabhan 2019	139	22	2	22	0.2%	1.96 [1.57, 2.45] 0.50 [0.05, 5.12]	· · · · · · · · · · · · · · · · · · ·
Provenzano 2009	56	114	29	116	1.7%	1.96 [1.36, 2.83]	·
Qunibi 2011	89	147	36	103	1.9%	1.73 [1.29, 2.32]	
Rathod 2015	93	200	12	100	1.3×	3.66 [2.23, 6.72]	
Razzaq 2017	36	41	27	41	2.0%	1.33 [1.04, 1.71]	
Schijns 2020	26	33	16	26	1.9%	1.14 [0.83, 1.55]	
Schroder 2005	12	22	13	24	1.4%	1.01 [0.59, 1.71]	
Seid 2008	127	139	98	147	2.2%	1.37 [1.21, 1.55]	-
Spinowitz 2008	89	228	14	76	1.4%	2.12 [1.29, 3.49]	
Steensma 2011	114	164	109	163	2.2%	1.04 [0.90, 1.21]	
Stoves 2001 Van Wyck 2005	15 35	22 79	14 23	23 62	1.6% 1.6%	1.12 [0.73, 1.73] 1.58 [1.03, 2.42]	
Van Wyck 2007	163	169	158	168	2.3%	1.03 [0.96, 1.06]	-
Van Wyck 2009	187	228	139	225	2.2%	1.33 [1.18, 1.50]	
Weisbach 1999	6	30	5	60	0.6%	2.40 [0.80, 7.23]	
Subtotal (95% CI)		4871		4375	70.9%	1.40 [1.26, 1.56]	•
Total events Heterogeneity: Tau ² = 0	2757 09· Chi ²	= 446 50	1831 0 df = .	47 (P e	0.00001	· F = 91%	
Test for overall effect: Z				•		• •	
1.5.2 IV iron vs. no iror	n/compai	ator					
Averbach 2004	53	78	9	36	1.2%	2.72 [1.51, 4.88]	
Averbach 2010	70	81	56	72	2.2%	1.11 [0.96, 1.29]	 -
Bastit 2006	172	200	143	196	2.3%	1.18 [1.06, 1.31]	
Sielza 2020	82 20	126	92	127	2.2%	0.90 [0.76, 1.06]	
Coyne 2007 Edwards 2009	30 9	64 34	19 9	65 26	1.5× 0.9×	1.60 [1.01, 2.54] 0.76 [0.35, 1.65]	
Favrat 2014	144	144	118	146	2.3%	1.24 [1.14, 1.34]	-
Hedenus 2007	31	33	18	34	1.6%	1.77 [1.28, 2.46]	
Hedenus 2014	8	8	ē	9	1.5%	1.45 [0.90, 2.35]	+
	30	41	16	44	1.7%	1.79 [1.20, 2.67]	———
Henry 2007	9	30	21	45	1.2%	0.64 [0.34, 1.21]	
Kim 2007		217	115	213	2.2%	1.71 [1.50, 1.94]	
Kim 2007 Kim 2017	200	73	47	76	2.1%	1.24 [1.00, 1.54]	<u> </u>
Kim 2007 Kim 2017 Pedrazzoli 2008	56	-		243	1.4%	1.99 [1.22, 3.26]	
Kim 2007 Kim 2017 Pedrazzoli 2008 Richards 2020	56 42	244	21		1.1%	1.96 [1.03, 3.76]	
Kim 2007 Kim 2017 Pedrazzoli 2008 Richards 2020 Serrano-Trenas 2011	56 42 18	244 50	11	60 33		1 77 11 05 2 001	
Kim 2007 Kim 2017 Pedrazzoli 2008 Richards 2020 Serrano-Trenas 2011 Singh 2006	56 42 18 39	244 50 66	11 11	33	1.4%	1.77 [1.05, 2.99] 14.74 [8.29, 26.22]	
Kim 2007 Kim 2017 Pedrazzoli 2008 Richards 2020 Serrano-Trenas 2011 Singh 2006 Vadhan-Raj 2013	56 42 18 39 493	244 50 66 608	11	33 200	1.4% 1.3%	14.74 [8.29, 26.22]	
Kim 2007 Kim 2017 Pedrazzoli 2008 Richards 2020 Serrano-Trenas 2011 Singh 2006 Vadhan-Raj 2013 Xu 2020	56 42 18 39	244 50 66	11 11 11	33	1.4%		·
Kim 2007 Kim 2017 Pedrazzoli 2008 Richards 2020 Serrano-Trenas 2011 Singh 2006 Vadhan-Raj 2013 Ku 2020 Subtotal (95% CI)	56 42 18 39 493	244 50 66 608 75	11 11 11	33 200 73	1.4% 1.3% 0.9%	14.74 [8.29, 26.22] 2.19 [1.02, 4.72]	•
Kim 2007 Kim 2017 Pedrazzoli 2008 Richards 2020 Serrano-Trenas 2011 Singh 2006 Vadhan-Raj 2013 Ku 2020 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0	56 42 18 39 493 18 1504 .16; Chr ²	244 50 66 608 75 2172 = 244.3	11 11 11 8 733 6, df =	33 200 73 1698	1.4% 1.3% 0.9% 29.1%	14.74 [6.29, 26.22] 2.19 [1.02, 4.72] 1.58 [1.28, 1.95]	•
Kim 2007 Kim 2017 Pedrazzoli 2008 Richards 2020 Serrano-Trenas 2011 Singh 2006 Vadhan-Raj 2013 Xu 2020 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z	56 42 18 39 493 18 1504 .16; Chr ²	244 50 66 608 75 2172 = 244.30 < 0.000	11 11 11 8 733 6, df =	33 200 73 1698 17 (P <	1.4% 1.3% 0.9% 29.1%	14.74 [6.29, 26.22] 2.19 [1.02, 4.72] 1.58 [1.28, 1.95] ; f ² = 93%	•
Kim 2007 Kim 2017 Pedrazzoli 2008 Richards 2020 Serrano-Trenas 2011 Singh 2006 Vadhan-Raj 2013 Xu 2020 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z Total (95% CI)	56 42 18 39 493 18 1504 .16; Chi ² = 4.26 (F	244 50 66 608 75 2172 = 244.3	11 11 11 6 733 6, df = 01)	33 200 73 1698 17 (P <	1.4% 1.3% 0.9% 29.1%	14.74 [6.29, 26.22] 2.19 [1.02, 4.72] 1.58 [1.28, 1.95]	 ▲ ▲
Henry 2007 Kim 2007 Kim 2017 Pedrazzoli 2008 Richards 2020 Serrano-Trenas 2011 Singh 2006 Vadhan-Raj 2013 Xu 2020 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 Total (95% CI) Total (95% CI) Total events Heterogeneity: Tau ² = 0	56 42 18 39 493 18 1504 .16; Chi ² = 4.26 (F	244 50 66 608 75 2172 = 244.34 < 0.000 7043	11 11 11 8 733 6, df =)1) 2564	33 200 73 1698 17 (P < 6073	1.4% 1.3% 0.9% 29.1% : 0.00001) 100.0%	14.74 [8.29, 26.22] 2.19 [1.02, 4.72] 1.58 [1.28, 1.95] ; I ² = 93% 1.45 [1.32, 1.60]	

(b) Mean number of RBCs transfused

	Expe	riment	al	С	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.6.1 IV iron vs. oral iror	n								
Subtotal (95% CI)			0			0		Not estimable	
Heterogeneity: Not applica	able								
Test for overall effect: Not	t applica	ble							
1.6.2 IV iron vs. no iron/	/usual c	are							
Beguin 2013	0	0	23	0.6	1.9	25		Not estimable	
Bernabeu-Wittel 2016	1.26	1.3	103	1.28	1.4	100	10.2%	-0.02 [-0.39, 0.35]	-+-
Garrido-Martin 2012	-0.085	0.74	107	-0.01	0.73	52	24.0%	-0.08 [-0.32, 0.17]	
Johansson 2015	1.25	0.5	30	2.2	1.64	30	3.6%	-0.95 [-1.56, -0.34]	
Kim 2007	1.87	2.7	30	3.58	3.89	45	0.6%	-1.71 [-3.20, -0.22]	·
Litton 2016	-0.27	1.1	70	0.016	1.15	70	10.2%	-0.29 [-0.66, 0.09]	
Richards 2020	0.65	1.3	243	0.61	1.3	244	26.5X	0.04 [-0.19, 0.27]	-
Serrano-Trenas 2011	0.76	1.16	100	0.87	1.12	100	14.2%	-0.11 [-0.43, 0.21]	
Spahn 2019	1.5	2.7	243	1.9	2.9	241	5.7%	-0.40 [-0.90, 0.10]	
Van Iperen 2000	1.07	1.04	12	2.06	0.93	12	2.3×	-0.99 [-1.78, -0.20]	
Yoo 2011	1.6	0.9	37	3.7	2.1	37		-2.10 [-2.84, -1.36]	
Subtotal (95% CI)			998			956	100.0%	-0.20 [-0.32, -0.08]	◆
Heterogeneity: Chi ² = 46.	31, df -	• 9 (P <	: 0.000)01); P	- 61%				
Test for overall effect: Z =	• 3.31 (P	P = 0.0	009)						
Total (95% CI)			998			956	100.0%	-0.20 [-0.32, -0.08]	•
Heterogeneity: $Chl^2 = 46$.	31, df -	• 9 (P <	: 0.000)01); P	- 61%				
Test for overall effect: Z =	• 3.31 (P	P = 0.0	009)						Favours intervention Favours control
Test for subgroup differen	nces: No	t applik	able						ravours mervention ravours control

Association between transfusion requirements and intravenous iron. The mean differences and risk ratios were calculated using a random-effects model with Mantel-Haenszel weighting. The size of the data markers indicates the weight of the study. Error bars indicate 95% CIs

eFigure 8. Secondary outcomes - mortality and hospital length of stay



Association between mortality and hospital length of stay and intravenous iron. The mean differences and risk ratios were calculated using a random-effects model with Mantel-Haenszel weighting. The size of the data markers indicates the weight of the study. Error bars indicate 95% CIs