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Interventions for treating iron deficiency anaemia in inflammatory bowel disease: a network meta-analysis (Protocol)

Iheozor-Ejiofor Z, Gordon M, Iqbal T, Allen P, Hoque S, Sinopoulou V, Engineer J, Akobeng AK

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[Intervention Protocol]

Interventions for treating iron deficiency anaemia in inflammatory bowel disease: a network meta-analysis

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

The primary objective will be to evaluate the efficacy and harms of the interventions for the treatment of iron deficiency anaemia in people with inflammatory bowel disease and rank the treatments in order of effectiveness in a network meta-analysis.

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BACKGROUND

Description of the condition

Anaemia in people with inflammatory bowel disease is an extraintestinal manifestation that historically has received little attention compared with other extraintestinal diseases such as arthritis or osteoarthritis (Stein 2012). Iron deficiency anaemia is a significant and common systemic manifestation of inflammatory bowel disease. Iron deficiency anaemia manifests as fatigue, shortness of breath, heart palpitations and pale skin (Niepel 2018). It significantly impacts on the quality of life of a person with inflammatory bowel disease and on the progression of their disease. Anaemia should not be accepted as an unavoidable manifestation of inflammatory bowel disease. Prompt diagnosis and effective management is paramount.

There are two predominant types of anaemia that have been identified and associated with inflammatory bowel disease, iron deficiency anaemia and anaemia of chronic disease. The cause of iron deficiency anaemia is multi-factorial; causes include, chronic blood loss, malnutrition and haemolysis (Wilson 2004). Folic acid deficiency is not an uncommon finding in these patients and the administration of bone marrow-suppressing medications can also affect erythropoiesis.

Studies have reported the prevalence of iron deficiency anaemia in people with inflammatory bowel disease to be as high as 36% to 90% (Kulnigg 2006). The wide range of prevalence fits with the fact that anaemia often mirrors disease activity in people with inflammatory bowel disease. Interestingly prevalence is lower in inflammatory bowel disease outpatients (Gomollon 2009), occurring in 10% and 6% of Crohn's disease and ulcerative colitis outpatients respectively (Antunes 2015), likely reflecting that this population have lower rates of active disease and lower severity of activity disease. Iron deficiency anaemia appears to be more common in children (88%) than adults (55%) with inflammatory bowel disease (Goodhand 2012).

Iron deficiency is the main cause of anaemia in inflammatory bowel disease (Gomollon 2009), often as a result of dietary restrictions, malabsorption, active bleeding and under-treatment of anaemia. In addition, chronic abdominal pain and nausea often results in poor oral intake, and mucosal inflammation in the gastrointestinal tract can lead to inadequate nutrient absorption. Although iron absorption tends to be normal in people with inflammatory bowel disease, the iron loss may exceed the capacity for iron absorption (Wilson 2004). This explains why activity levels of inflammatory bowel disease correlate with levels of iron deficiency anaemia.

Anaemia has a significant effect on the quality of life of people with inflammatory bowel disease, even if it is not noticeably symptomatic. Therefore it is important that anaemia is treated effectively and it should not be assumed that some element of anaemia is a normal finding of inflammatory bowel disease (Gomollon 2009). The World Health Organization's definitions of anaemia apply to people with inflammatory bowel disease. It is thought that people with inflammatory bowel disease without anaemia but with iron deficiency should be considered for treatment as it is of clinical relevance. Achieving normal haemoglobin levels does not necessarily mean that normal iron store levels have been restored.

Description of the intervention

There are various ways of treating iron deficiency anaemia and administering iron, however the most effective way in people with inflammatory bowel disease remains unclear. Iron can be administered orally, via intramuscular injection, intravenous infusion and it is also possible to deliver iron via blood transfusion or by using erythropoietin with iron. All of these routes require consideration and likely need consideration of some of the disease factors discussed above. This includes severity or activity levels of disease at the time of therapy initiation, with active disease potentially impacted by the efficacy or tolerability of oral interventions. Conversely, as both people with ulcerative colitis and Crohn's disease follow a similar pathophysiological route to iron deficiency anaemia (Wilson 2004), the specific disease type is likely less of a factor than in most other areas of inflammatory bowel disease management. Evidence has suggested that oral iron can cause gastrointestinal disturbances and irritation (Tolkien 2015), which may impact compliance. Intramuscular and intravenous preparations have been associated with allergic reactions and anaphylaxis (Akhuemonkhan 2018), as well as having different feasibility and practical considerations related to the need to deliver these either within a healthcare environment or by a healthcare professional. Blood transfusion carries the risk of transmitting infections including viral and parasitic infections. Historically oral administration of iron has been the preferred route especially for mild anaemia, and intravenous and intramuscular preparations have usually been reserved for more severe cases, where the benefit of treatment is thought to outweigh the associated risks and complications. Oral iron is inexpensive, however it is thought to have short-term effectiveness (Lee 2012). On the other hand, intravenous iron therapy requires more complex infrastructure and expertise to be administered. There are also variations on doses and preparations used and frequency of administration. The effectiveness and appropriateness of any iron therapy may depend on one or a combination factors for any given patient, such as previous reaction to the treatment, the severity of iron deficiency anaemia, disease activity or the use of adjunct therapy, such as erythropoiesis stimulating agents (Stein 2013).

How the intervention might work

The efficacy of intravenous iron therapy in people with inflammatory bowel disease has been the topic of recent investigation. Intravenous iron preparations that have been used include iron gluconate, iron sucrose, iron dextran, ferumoxytol and iron carboxymaltose. Iron dextran was the first parenteral iron formulation approved by the US Food and Drug Administration (FDA), however anaphylaxis has limited its use (Hassan 2011). Ferumoxytol was FDA-approved in 2009. It possesses low antigenic properties, so no test dose is required. The drug is phagocytosed by macrophages and slowly released into the circulation, which allows for rapid infusion in large doses (Hassan 2011). However no data exist regarding dosing or safety in children and adolescents. Proinflammatory cytokines are produced in increased amounts by peripheral-blood monocytes in people with inflammatory bowel disease (Schreiber 1996). Such cytokines can contribute to the development of anaemia by inducing a relative deficiency of erythropoietin (Schreiber 1996). It is thought that administering erythropoietin could be beneficial for people with inflammatory bowel disease; positive results have been observed in people with rheumatoid arthritis and chronic renal failure with associated anaemia (Gasche 1997; Schreiber 1996). Although recombinant

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human erythropoietin has been shown to be effective for treating anaemia that accompanies several chronic diseases (Goodnough 2000), it is costly and its benefits have not been shown to be greatly superior to other iron preparations. However, it has been suggested that its therapeutic potency can be maximised with co-administration of other intravenous iron preparations (Gasche 1997).

Why it is important to do this review

The most effective way of treating anaemia in people with inflammatory bowel disease remains unclear. There is little evidence to suggest that high doses of oral iron is beneficial. Only 10 mg to 20 mg of oral iron can be absorbed per day, therefore high doses of oral iron of up to 400 mg per day remains questionable (Gomollon 2009). With this rationale, a single tablet of most ferrous salt preparations such as ferrous sulphate provides more iron than can be absorbed. Additionally, non-absorbed iron salts can be toxic to intestinal mucosa (Kawai 1992), and there have been concerns that this can worsen disease activity or even activate disease. High doses of oral iron can also induce diarrhoea which, as well as impacting on quality of life can make distinguishing it from actual disease relapse problematic. This has necessitated the use of alternatives (Erichsen 2005; Lee 2017). These adverse events and tolerability issues are of interest to people with inflammatory bowel disease in general when considering options for therapy, but may be particular important in subgroups such as children and young people. In these groups acceptability can figure highly in decision making by families.

Evidently there are a range of different interventions that can be utilised in order to combat the problem of iron deficiency anaemia in people with inflammatory bowel disease. However, the efficacy and safety of each intervention remains poorly understood and currently no consensus has been reached amongst physicians as to which intervention is most beneficial. The European Crohn's and Colitis Organisation (ECCO) guideline recommends intravenous iron as first-line treatment in people with clinically active disease with previous intolerance to oral iron who need erythropoiesis stimulating agents (ECCO 2015). However, this recommendation is not based on systematic review evidence, but rather on a pragmatic consideration of these therapies for such patients. Given the range of methods for delivering iron and treating iron deficiency anaemia that clinicians and patients can choose from currently, we will employ a network meta-analysis approach for this review. This will allow ranking of therapies by both effectiveness and side-effect profiles; both key relative factors used to guide decision making from this portfolio of options.

For this reason we have identified a need for a Cochrane systematic review to be carried out in order to methodically evaluate and summarise the efficacy and safety of the interventions available for the treatment of iron deficiency anaemia in people with inflammatory bowel disease. We will look primarily at how the interventions affect the haemoglobin levels in the participants observed. We will also analyse how these interventions affect markers of iron stores, including transferrin saturation and serum ferritin levels, and also the changes in disease activity and the changes in reported quality of life.

OBJECTIVES

The primary objective will be to evaluate the efficacy and harms of the interventions for the treatment of iron deficiency anaemia in people with inflammatory bowel disease and rank the treatments in order of effectiveness in a network meta-analysis.

METHODS

Criteria for considering studies for this review

Types of studies

Published and unpublished randomised controlled trials (RCTs) irrespective of language or year of publication. We will exclude studies that used quasi-random methods in allocating participants (e.g. date of birth). We will only include cross-over RCTs if data are reported for the first treatment phase prior to cross-over. We do not anticipate finding any cluster-RCTs, but we will include cluster-RCTs if available.

Types of participants

People of any age and sex with a conventional diagnosis of Crohn's disease, ulcerative colitis or indeterminate colitis with confirmed iron deficiency anaemia as defined by the authors of the primary studies. Potential effect modifiers identified were age and disease activity. Therefore we will only assume that there is transitivity within specific age group and disease activity. For instance, adult with active disease, adult with inactive disease, etc.

Types of interventions

The administration of iron therapy by any route (e.g. orally, intramuscularly, intravenously, subcutaneously) for the treatment of iron deficiency anaemia. We will compare these interventions with control, placebo, no intervention or other interventions.

Types of outcome measures

Where possible we plan to collect data on the following outcomes.

Primary outcomes

Response (defined as the number of people with normalisation of haemoglobin levels or increase of haemoglobin at the end of treatment course). This definition is based on a previous systematic review by Aksan 2017, as well as scoping of the wider literature.

Secondary outcomes

- Time to response (survival data reported as a hazard ratio (HR) with standard error (SE))
- Change in haemoglobin levels
- Tolerability of treatment
- Non-compliance with treatment regimen
- Adverse events (such as constipation, abdominal pain, nausea, etc)
- Serious adverse events
- Withdrawal due to adverse events
- Health-related quality of life (measured using Inflammatory Bowel Disease Questionnaire (IBDQ) (Irvine 1994), Short IBDQ (SIBDQ) (Irvine 1996) or any other validated scale)

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We will note where outcome data are available for multiple time points, however we will only report outcome measures at the last time point available. We intend to produce network diagrams to show the amount of evidence for all selected studies contributing data to 'response' and 'withdrawal due to adverse events' and rank the interventions based on these outcomes.

Search methods for identification of studies

Electronic searches

We will search the following sources from inception of each database to the date of search and will place no restrictions on the language of publication:

- Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid Evidence-Based Medicine Reviews Database (EBMR);
- MEDLINE (Ovid MEDLINE ALL 1946 to Daily Update);
- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature);
- ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization International Clinical Trials Registry Platform (ICTRP; www.who.int/trialsearch/).

For detailed search strategies, see Appendix 1. We will adapt this search strategy and use it to search the proposed electronic databases. There is evidence to suggest that data from abstracts can be inconsistent with data published in articles (Pitkin 1999).

Searching other resources

- Reference searching: we will inspect the references of all identified studies for more relevant papers.
- Personal contacts: we will contact leaders in the field to identify other studies.
- Drug companies: we will contact manufacturers of appropriate iron preparations for additional information.

Data collection and analysis

Selection of studies

Using the above search strategy, two review authors will independently identify studies that appear to be potentially relevant. The two review authors will independently read the full texts to assess the eligibility of the papers identified. After reading the full texts, the two review authors will independently assess the eligibility of all studies identified based on the inclusion criteria above. Disagreement among reviewers will be discussed and agreement reached by consensus. We will implement this process in order to reduce the risk of bias and decrease the chances of any inaccuracies during the interpretation of the studies.

Data extraction and management

We will develop a data extraction form and use it to extract information on relevant features and results of the included studies. The two review authors will extract and record data on the predefined data extraction form, independently and in duplicate. Extracted data will include the following items:

- characteristics of participants: age, sex, disease distribution, disease duration, disease type and disease activity index;
- total number of participants originally assigned to each intervention group;
- intervention: type and dose; mode of administration;
- control: no intervention, placebo or other interventions;
- concurrent medications
- outcomes: time of assessment, length of follow-up, change in haemoglobin status, change in transferrin saturation, changes in serum ferritin levels, quality-of-life assessment, adverse events.

Assessment of risk of bias in included studies

Two review authors will independently assess bias using the Cochrane 'Risk of bias' tool (Higgins 2017). Since our review will only focus on data from the first treatment period before cross-over, 'Risk of bias' assessment for any cross-over trials identified will be the same as the parallel-group trials. For the cluster-RCTs, we will assess risk of bias following guidance listed in Table 23.1.a of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higigns 2019). The study features to be assessed include:

- random sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- completeness of outcome data;
- selective reporting; and
- other sources of bias.

We will rate each of these factors as ‘low risk’, ‘high risk’ or ‘unclear risk’ of bias. After we have assessed risk of bias at study level, we will then use the CINeMA (Confidence in Network Meta-Analysis) web tool to calculate the percentage contribution of each direct contrast to each network estimate (CINeMA 2017).

Measures of treatment effect

We will calculate the risk ratio (RR) for dichotomous outcomes. We will report time-to-response data as hazard ratios (HR). However, where studies report mean response time, we will calculate mean difference (MD), provided that the studies indicate that all participants responded to treatment during the trial period. If the studies assess health-related quality-of-life data using different scales, we will estimate the treatment effect using the standardised mean difference (SMD). We will present SMDs as standard deviation units and interpret as follows: 0.2 represents a small effect, 0.5 a moderate effect and 0.8 a large effect (Cohen 1988). We will report these measures of treatment effects alongside associated 95% confidence intervals (CI).

Unit of analysis issues

If we include cross-over trials, we will extract data from the first phase of the study for analysis (i.e. before the cross over occurred). We will conduct separate analyses for comparisons between iron intervention versus placebo, and irons versus active comparator (e.g. alternative iron intervention). If studies randomised participants to more than one iron treatment arm (e.g. with different doses), we will combine these for the primary analysis. Where outcomes are reported at several time points, we will undertake analyses at a single time point that is consistently reported by the studies and at the final point of follow-up. Where network meta-analyses are conducted, we will account for the effects of correlated effect estimates using appropriate methods (see Data synthesis).

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Dealing with missing data

We will contact the authors of included studies to supply any missing data. If data are needed to judge the risk of bias, we will make a judgement of unclear risk in the relevant category. Where 'response' outcome data are missing, we will use the intention-to-treat principle (ITT) on the assumption that all participants lost to follow-up were non-responders.

Assessment of heterogeneity

We will assess heterogeneity and inconsistency to ensure the validity of the analysis. Initially, we will assess heterogeneity through visual inspection of forest plots and the calculation of the Chi^2 and I^2 statistics (Borenstein 2009). For the network meta-analyses, we will use the between-study standard deviation to assess heterogeneity, with a threshold of 0.5 indicating heterogeneity. We will interpret I^2 statistics according to the guide below (Deeks 2019):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

We will assess consistency within the analysis through comparison of the estimates of treatment effect for each comparison from the direct and indirect pairwise meta-analyses for the closed loops within the NMA, using a node-splitting approach (Cooper 2009; Dias 2000). It is important that the direct and indirect evidence for the same comparisons agree, as joint analysis on an inconsistent network can be misleading. We will examine possible explanations for heterogeneity where sufficient data are available, including factors such as participant characteristics (e.g. age, sex), condition severity, treatment type and dose, healthcare system, and country.

Assessment of reporting biases

If there is an appropriate number of studies in a pooled analysis (i.e. more than 10 studies), we plan to investigate potential publication bias using funnel plots: trial effects versus trial size (Sterne 2017).

Data synthesis

We will synthesise studies through a narrative review with tabulation of results of included studies. Where possible, we will synthesise treatment effects for all comparisons and outcomes through meta-analyses, with the approach taken dependant on the outcome assessed and the data available (Borenstein 2009). We will conduct direct comparisons of treatment effects through pairwise meta-analyses. For the pairwise meta-analysis, we will analyse studies that are clinically homogeneous in terms of population, intervention, comparator and outcome. We will analyse studies that include ulcerative colitis, Crohn's disease or mixed populations together. However, we will analyse studies of different disease states (active, inactive) separately, and studies from paediatric population separately from adult data. We will use the fixed-effect model to carry out meta-analysis of primary and secondary outcome measures when we judge clinical and methodological heterogeneity to be appropriately low ($I^2 = 0\%$).

Second, where possible, we will assess the opportunity for estimating a network meta-analysis to compare different interventions through both direct and indirect evidence within connected networks of studies (Spiegelhalter 2004; Welton 2012). We will carry out network meta-analyses for the 'response' and 'withdrawal due to adverse events' outcomes. The use of direct and indirect evidence can strengthen inferences about the relative efficacy of the interventions being compared, whether due to a lack of, or sparse, evidence comparing the different interventions. Importantly, network meta-analyses allow for the comparison of multiple interventions simultaneously and for an estimation of the rank order based on efficacy (Welton 2012). We will present the network for the models graphically through network diagrams, allowing assessment of both the structure and extent of the evidence available for the different comparisons.

All network meta-analyses will take a Bayesian approach through Markov Chain Monte Carlo (MCMC) simulation (Chaimani 2019). The parameters that we will consider in the models will be the treatment effect of an intervention compared with other interventions, with the likelihood function dependent on the outcome used. We will assume study-specific log-odds ratios (ORs) to be from the normal distribution. We will use different prior distributions for the scale parameters (e.g. a uniform distribution for the base case and half-normal and inverse gamma distributions for sensitivity analyses). We will use vague priors for the treatment effects in the different models and we will estimate all models using three chains starting with different initial values. We will assess convergence through visual inspection of the Brooks-Gelman-Rubin diagnostic, with convergence assumed to have occurred when the ratio of between- and within-chain variability is stable around 1. We will use varying iterations and burn-in periods to ensure convergence, with burn-in periods discarded from the analysis. We will examine autocorrelation plots, with different rates of thinning applied to eliminate or reduce its effects where present. From each MCMC run, we will rank the treatments based on the magnitude of effect. We will then estimate the cumulative rank probabilities from the proportion of MCMC cycles in which each treatment has a certain rank. We will summarise the ranking in mean and range and display ranking in graphs. The closer the mean rank is to 1, the better the efficacy or safety.

We will assess adequacy of the fit of the models through a comparison of the residual deviance for the models with the number of unconstrained data points available, with an adequate fit when both closely match. Model selection and overall goodness of fit will be assessed through deviance information criteria (DIC), with a threshold of a difference of 3 to 5 points considered significant (lowest DIC = most appropriate fit; Spiegelhalter 2002, Welton 2012).

We will conduct pairwise meta-analyses of direct comparisons using Review Manager 5 (RevMan 5 (Review Manager 2014)), and Stata (Deeks 2019; Egger 2001), while we will estimate NMAs using the WinBUGS software.

Subgroup analysis and investigation of heterogeneity

As already noted, where heterogeneity is identified, we will investigate its possible causes through the inclusion of patient- and study-level characteristics as covariate within meta-regression analyses. The meta-regression will include factors such as length of follow-up, adopting the approach outlined by Achana and colleagues (Achana 2013). As the primary outcome (i.e. response) represents the number of events that occur within a patient population allocated to a particular treatment, we will assume a

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binomial distribution for the likelihood and we will use a clog-log link in the NMA for the linear predictor to take time into account. To carry out a statistical assessment of the disagreement between estimates within each pairwise comparison, we plan to use the I^2 statistic (Deeks 2019). We will also visually assess the overlap of the confidence intervals with the prediction interval and the variability in the point estimates. We will interpret I^2 statistic thresholds as follows:

- less than 50% will be regarded as low;
- 50% to 75% will be regarded as moderate; and
- more than 75% will be regarded as large.

Assessment of statistical inconsistency

We will also assess whether there is disagreement between direct and indirect estimates or between indirect estimates through different intermediate treatments in the network. We will do this for single loops of evidence within the network and for the network as a whole (Dias 2013; Salanti 2014). If sufficient data are available we will perform subgroup analysis to assess the impact of length of follow-up using methods described above

Sensitivity analysis

For the pairwise analysis of the primary outcome, we will conduct sensitivity analyses based on the following:

- random-effect versus fixed-effect modelling;
- excluding studies assessed as unclear or high risk of bias according to the Cochrane 'Risk of bias' tool;
- only including participants whose outcome is known (i.e. number of participants who completed the study used as a denominator).

Summary of findings and assessment of the certainty of the evidence

Assessment of evidence certainty generated from the network meta-analysis

We will assess the certainty of the evidence using GRADE (Chaimani 2019; Schünemann 2019a; Schünemann 2019b). We will apply this methodology to the network meta-analysis by focusing on the approach of Salanti 2014. This will be carried out using GRADEpro GDT and the CINeMA web tool (CINeMA 2017), where possible. We will assess evidence quality in two main ways, firstly, for each contrast and secondly, for the network as a whole, in order to assess the quality of the ranking order. We will assess individual GRADE factors as follows.

- Risk of bias: we will assess overall risk of bias for each contrast and also for the entire network.
- Indirectness: this relates to whether the population, intervention and outcome in the studies differ from those we have proposed (see Criteria for considering studies for this review) as well as intransitivity.
- Inconsistency: at the level of the contrast, we will take into consideration both heterogeneity in the direct evidence for that comparison and inconsistency related to different routes of analysis for the comparison (e.g. direct versus indirect evidence and two-arm versus three-arm trials). We will conduct the latter using a node-splitting approach (Dias 2013). As well as assessing the meta-analyses of the direct evidence for inconsistency, we will consider the network meta-analysis predictive intervals for that comparison in relation to GRADE 'default' minimum important differences, 0.75 and 1.25 (Guyatt 2011). We note that inconsistency can only be assessed where there is both direct and indirect evidence. We will assess GRADE inconsistency as serious limitations if there is heterogeneity in the direct estimate or inconsistency in the network with respect to that comparison. We will attribute very serious limitations to the comparison if there is severe heterogeneity or severe inconsistency or limitations with both heterogeneity and inconsistency. We will determine judgements on the magnitude of limitations by the reviewers through discussions. Rationales will be described transparently in the review report. At the level of the network, we will consider the global Wald test for inconsistency. Tests of this nature are typically underpowered, so a P value less than 0.1 will be considered significant. Additionally, if several contrasts show direct and indirect results that would have led to different clinical decisions, we will consider inconsistency to be present.
- Imprecision: at the level of the contrast, we will assess inconsistency for each pairwise comparison using the GRADE default minimally important difference values of 1.25 and 0.75 for the RR. We will also take into account the sample size for the direct evidence informing this contrast and consider it in relation to the optimal information size. At the level of the network, we will assess the overlap of the rankograms and the magnitude of the surface under the cumulative ranking (SUCRA) curve estimates.
- Publication bias: we will also assessed each pairwise comparison using standard GRADE for publication bias; we will use contour-enhanced funnel plots where appropriate (where there are 10 or more studies). We will use the contributions matrix to translate these judgements to the network as a whole.

The CINeMA web tool assesses network meta-analysis evidence based on the five GRADE domains listed above and downgrades pairwise, mixed and indirect evidence depending on whether there are major, some or no concerns.

'Summary of findings' table

For the top five interventions, we plan to present the main results on response and serious adverse events in 'Summary of findings' tables, reporting the results for a representative set of contrasts, with one row for each intervention versus the reference comparator. These tables will present key information concerning the certainty of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data (Schünemann 2019a). 'Summary of findings' tables also include an overall grading of the evidence using the GRADE approach and will follow the examples in Yepes-Nuñez 2019.

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APPENDICES

Appendix 1. Search strategy

Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid Evidence-Based Medicine Reviews Database (EBMR)

1. exp Inflammatory bowel diseases/
2. (Crohn* disease).tw.
3. (inflammatory bowel disease*).tw.
4. (regional enteritis or ileitis or colitis or proctosigmoiditis or rectocolitis or rectosigmoiditis or ulcerative proctocolitis or h?emorrhagic proctocolitis or proctitis).tw.
5. or/1-4
6. Anemia, Iron-Deficiency/
7. (anemia*or anaemia or anemic or anaemic).tw.
8. (iron deficien* or low iron or iron deplet* or hemoglobin or haemoglobin or red blood count or erythropoietin).tw.
9. or/6-8
10. exp Iron/
11. exp Iron Compounds/
12. (iron or ferrous* or ferric* or ferritin or ferumoxytol or sodium feredetate).tw.
13. or/10-12
14. 5 and 9 and 13

MEDLINE (Ovid SP)

1. exp Inflammatory bowel diseases/
2. (Crohn* disease).tw.
3. (inflammatory bowel disease*).tw.
4. (regional enteritis or ileitis or colitis or proctosigmoiditis or rectocolitis or rectosigmoiditis or ulcerative proctocolitis or h?emorrhagic proctocolitis or proctitis).tw.
5. or/1-4
6. Anemia, Iron-Deficiency/
7. (anemia*or anaemia or anemic or anaemic).tw.
8. (iron deficien* or low iron or iron deplet* or hemoglobin or haemoglobin or red blood count or erythropoietin).tw.
9. or/6-8
10. exp Iron/

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11. exp Iron Compounds/
12. (iron or ferrous* or ferric* or ferritin or ferumoxytol or sodium feredetate).tw.
13. or/10-12
14. 5 and 9 and 13
[15-25: Cochrane Handbook RCT filter - sensitivity max version]
15. randomized controlled trial.pt.
16. controlled clinical trial.pt.
17. randomi?ed.ab.
18. placebo.ab.
19. drug therapy.fs.
20. randomly.ab.
21. trial.ab.
22. groups.ab.
23. or/15-22
24. exp animals/ not humans/
25. 23 not 24
26. 14 and 25

CINAHL (EBSCO)

S1. MH "Inflammatory bowel diseases+"
S2. TI ("Crohn* disease" OR "inflammatory bowel disease" OR "regional enteritis" OR ileitis OR colitis OR proctosigmoiditis OR rectocolitis OR rectosigmoiditis OR "ulcerative proctocolitis" OR "h#emorrhagic proctocolitis" OR proctitis)
S3. AB ("Crohn* disease" OR "inflammatory bowel disease" OR "regional enteritis" OR ileitis OR colitis OR proctosigmoiditis OR rectocolitis OR rectosigmoiditis OR "ulcerative proctocolitis" OR "h#emorrhagic proctocolitis" OR proctitis)
S4. S1 OR S2 OR S3
S5. MH "Anemia, Iron-Deficiency"
S6. TI (anemia* OR anaemia OR anemic OR anaemic OR "iron deficien*" OR "low iron" OR "iron deplet*" OR hemoglobin OR haemoglobin OR "red blood count" OR erythropoietin)
S7. AB (anemia* OR anaemia OR anemic OR anaemic OR "iron deficien*" OR "low iron" OR "iron deplet*" OR hemoglobin OR haemoglobin OR "red blood count" OR erythropoietin)
S8. S5 OR S6 OR S7
S9. MH "Iron+"
S10. MH "Iron Compounds+"
S11. TI (iron OR ferrous* OR ferric* OR ferritin OR ferumoxytol OR sodium feredetate)
S12. S9 OR S10 OR S11
S13. S4 AND S8 AND S12
[S14: Wong 2006 "therapy studies" filter - SDSSGS version]
S14. MH "treatment outcomes+" OR MH "experimental studies+" or random*
S15. S13 AND S14

ClinicalTrials.gov (Expert search)

(inflammatory bowel disease OR Crohn OR Crohn ´s OR Crohns OR regional enteritis OR ileitis OR colitis OR proctosigmoiditis OR rectocolitis OR rectosigmoiditis OR proctocolitis OR proctitis) AND (iron OR ferric OR ferrous OR ferritin OR ferumoxytol OR sodium feredetate)

WHO ICTRP (Standard search)

inflammatory AND bowel AND disease AND iron OR
inflammatory AND bowel AND disease AND ferr* OR
inflammatory AND bowel AND disease AND ferumoxytol OR
inflammatory AND bowel AND disease AND feredetate OR
inflammatory AND bowel AND disease AND anemi* OR
inflammatory AND bowel AND disease AND anaemi* OR
crohn* AND iron OR
crohn* AND ferr* OR
crohn* AND ferumoxytol OR
crohn* AND feredetate OR
crohn* AND anemi* OR
crohn* AND anaemi*

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CONTRIBUTIONS OF AUTHORS

All review authors contributed equally.

DECLARATIONS OF INTEREST

Zipporah Iheozor-Ejiofor: none
Morris Gordon Since August 2016, I have received travel fees to attend international scientific and training meetings from Pharma companies. These grants included no honoraria, inducement, advisory role or any other relationship and were restricted to the travel and meeting related costs of attending such meetings. These include: DDW May 2017, World Congress of Gastroenterology October 2017, DDW May 2018, Advances in IBD December 2018, DDW May 2019.
The companies include: Biogaia (2017-19), Ferring (2018), Allergan (2017), synergy (bankrupt - 2018) and Tillots (2017-19).None of these companies have had any involvement in any works completed by me and I have never had any payments for any other activites for them, as confirmed below. From these date onwards, I have made a personal undertaking to take no further funds from any pharmaceutical or formula company in any form for travel or other related activities. This is to lift the limitations such funding has on my ability to act as a first and corresponding author on reviews, in line with the Cochrane policies on such matters and is reported in line with these policies. These current declarations will expire over the next 3 years and this statement updated regularly to reflect this.
Tariq Iqbal: I have been involved in basic iron research, iron treatment guidelines and studies involving iron and have received support and provided expertise to the three main iron manufacturers equally. I have received consulting fees or honorarium from Pharmacosmos (advisory board), Vifor (advisory board), Shield therapeutics (presentation), support to attend ECCO from both Pharmacosmos and Vifor, lecture fees from Pharmacosmos, Vifor and Shield Therapeutics, Ferring, Falk and Roche.
Patrick B Allen: none
Sami Hoque: none
Vasiliki Sinopoulou: none
Jaina Engineer: I hold the employed position of Publications and Information Manager at the charity Crohn's & Colitis UK. The charity funds research and produces information about all aspects of Crohn's and Colitis.
Anthony K Akobeng: none

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