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Interventions for maintenance of surgically-induced remission in Crohn's disease: a network meta-analysis (Protocol)

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TABLE OF CONTENTS

[Intervention Protocol]

Interventions for maintenance of surgically-induced remission in Crohn's disease: a network meta-analysis

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ABSTRACT

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

To assess the effects and harms of interventions for the maintenance of surgically-induced remission in Crohn's disease and to rank treatments in order of effectiveness.

BACKGROUND

Description of the condition

Crohn's disease is a chronic inflammatory disorder that can involve any part of the gastrointestinal tract. There is no cure for the disease, so management strategies are instead focused on induction and maintenance of remission, as well as supporting the many other symptoms that impact patients affected by the condition.

Approximately 75% of patients with Crohn's disease will eventually undergo surgical resection (Bernell 2000), with recent studies suggesting a rate of 3.8 operations per 100 person years (Ma 2017), and this can induce remission. However endoscopic recurrence of disease has been reported to be as high as 73% at one year post surgery (Rutgeerts 1990), and clinical relapse rates have been reported to range from 20 to 86% at five years post surgery (Gklavas 2017; Rutgeerts 2002).

Given these high relapse rates, there have been many studies to identify potential methods of prolonging postoperative remission, but there is no standard therapy for the prevention of postoperative recurrence in Crohn's disease (Hanuaer 2001; NICE 2016). A number of agents have been studied, but considerable uncertainty remains as to the efficacy of such treatments.

Description of the intervention

Corticosteroids, the mainstay of treatment of acute exacerbations, are not effective for maintenance of remission in Crohn's disease (Steinhart 2003), and chronic use is limited by numerous adverse events.

Probiotics and budesonide do not appear to provide any benefit for maintenance of surgically-induced remission (Doherty 2009). Nitroimidazole antibiotics may reduce relapse after surgery, although this benefit did not remain significant on sensitivity analysis and the antibiotics were not well tolerated and associated with a higher

risk of serious adverse events (Doherty 2009).

5-aminosalicylates are a group of compounds that have long been used in inflammatory bowel disease. The first 5-aminosalicylate agent used in clinical practice was sulphasalazine, which is composed of sulphapyridine linked by an azo bond to 5-aminosalicylic acid (5-ASA). Sulphasalazine was first used in the 1940s as a treatment for arthritis (Svartz 1942). Improvement in gastrointestinal symptoms was noted in patients who had concurrent ulcerative colitis leading to further use of this agent in inflammatory bowel disease. 5-Aminosalicylic acid agents have been shown to be safe and may be effective for maintenance of post-surgical remission when compared with placebo (Gordon 2011).

Purine analogues, such as azathioprine and 6-mercaptopurine, have also been shown to be effective when compared with placebo (Gordon 2014). However, on review the majority of studies compared these agents with 5-ASA and failed to demonstrate superiority, with more issues leading to withdrawal of therapy noted (Gordon 2014). These reviews led to the National Institute for Health and Care Excellence in the UK to change their guidance for maintenance of post-surgical remission in Crohn's disease to include the option of 5-ASA agents (NICE 2016).

Tumour necrosis factor-alpha (TNF-α) antagonists may provide a benefit in post-operative Crohn's disease (Doherty 2009; Gordon 2011), but issues of cost and safety exist (Di Sario 2016)

How the intervention might work

Corticosteroids, budesonide and 5-ASA agents all act as anti-inflammatory agents.

Azathioprine is a prodrug which is non-enzymatically degraded to 6-mercaptopurine which in turn is metabolised to the active component, 6-thioguanine nucleotide (6-TGN). 6-TGN is thought to work by inhibiting the proliferation of T and B lymphocytes and reducing the numbers of cytotoxic T cells and plasma cells. There are some trial data which suggest that neutrophil count is a predictor of induction and maintenance of remission in Crohn's disease (Colonna 1994), which may suggest the mechanism of action, although this is not well understood. The major limiting factor for the long term use of azathioprine has been the occurrence of adverse events leading to withdrawal of therapy in approximately 10% of patients (Hafraoui 2002), with dose-dependent and idiosyncratic adverse events occurring.

TNF-α antagonists are monoclonal antibodies directed towards TNF-α. Although TNF-α antagonists have been the benchmark biologic therapies for more than a decade, the exact mechanism of action is still incompletely understood (Levin 2016).

The mechanism by which probiotics and antibiotics may act is poorly understood. Due to the role that dysbiosis plays in IBD, it has been hypothesised that there is benefit in trying to restore the indigenous flora. Several observations, both in humans and animal models, emphasized the importance of bacterial flora in IBD pathogenesis, justifying the current interest in antibiotic and probiotic therapies aimed at the manipulation of enteric flora (Cui 2004).

Why it is important to do this review

Given the impact of surgical resection on Crohn's disease patients, clear evidence regarding management strategies to maintain a disease free state post-surgically is vital for both patients and clinicians. Many researchers have argued that the state of the gut post-surgery is massively different from a histological and clinical standpoint (Gordon 2017), and previous reviews have found that some standard treatments work in this setting and some do not (Gordon 2011; Gordon 2014). With a wide range of strategies available and no clear hierarchy regarding the efficacy of these treatments, evidence-based decision making is currently not possible. Additionally, given the variability in adverse event profiles and tolerability of the agents being considered, clarification of these issues is needed.

Comparative efficacy and safety data are best achieved by head-to-head trials. However, multiple trials of this sort will be needed and attracting funding to complete these trials may be difficult and take significant time, if these trials are conducted at all. Thus far, there are limited active head-to-head trials comparing treatments for maintaining post-surgical remission in Crohn's disease. An alternative strategy for obtaining comparative data is to conduct a network meta-analysis (NMA) in which multiple treatments are compared using both direct comparisons of interventions within randomised controlled trials (RCTs) and indirect comparisons across trials based on a common comparator (i.e. placebo). In other words, if compound A is compared with compound B in one trial, and the same compound B is compared with compound C in another trial, indirect information can be obtained for the comparison of compound A to compound C using this technique.

OBJECTIVES

To assess the effects and harms of interventions for the maintenance of surgically-induced remission in Crohn's disease and to rank treatments in order of effectiveness.

METHODS

Criteria for considering studies for this review

Types of studies

We will include published and unpublished RCTs irrespective of language or year of publication. We will exclude studies which use quasi-random methods of allocation (e.g. date of birth).

Types of participants

Trials enrolling participants of any age with Crohn's disease as defined by conventional clinical, radiological or endoscopic criteria will be considered for inclusion.

Patients must be in remission as defined by a recognized Crohn's disease activity index or endoscopy following surgery on recruitment, or who had undergone a surgical resection (as defined by the authors of the primary studies) no more than six months prior to starting maintenance treatment. We will only include studies with a mixed population (both medically and surgically-induced remission) provided outcome data for participants with surgically-induced remission are reported separately.

Types of interventions

We will consider trials comparing oral or topical corticosteroids, 5-ASA agents, purine analogues, TNF-α antagonists, other classes of biologic agents, probiotics, antibiotics or any other pharmaceutical intervention with no treatment, placebo or another active treatment for inclusion. Studies where participants received concomitant treatments which are not routinely administered for the purpose of maintaining remission (such as antidiarrhoeal medication, antibiotics or tapered steroids) will be included. Dose optimisation studies will not be included. Given the scope of overlapping and ongoing reviews, we will not consider trials assessing enteral diet, diet manipulation, herbal medicine or nutritional supplementation.

Types of outcome measures

Primary outcomes

The primary outcome will be clinical relapse. We will regard the following as providing the most relevant measures of outcome for the analyses:

- proportion of patients who fail to maintain clinical remission, as defined by the original studies

- time to relapse (survival data: study-level data reported as a hazard ratio (HR) with standard error (SE)).

We will accept the authors' definitions of what constitutes a clinical relapse.

Secondary outcomes

The secondary outcome measures will include the proportion of patients who:

1) Experience endoscopic relapse, as defined by the original studies;
2) Experience histologic relapse, as defined by the original studies;
3) Experience adverse events (as defined by FDA 2018. We will also note where studies fail to provide sufficient information and simply report outcome as 'adverse event');
4) Experience serious adverse events (as defined by FDA 2018. We will also note where studies fail to provide sufficient information and simply report outcome as 'serious adverse event'); and
5) Withdraw due to adverse events.

We will report outcome measures at the last time point available (assumed to be at the end of follow-up if not specified) and the time point specified in the methods as being of primary interest (if this was different from the latest time point available). However, we will also indicate when studies report outcomes at other time points.

Search methods for identification of studies

A. Electronic searching

We will search the following electronic databases from inception to present date, for relevant studies:

1. MEDLINE;
2. Embase;
3. CENTRAL;
4. Cochrane IBD Group Specialized Register;
5. Clinical trials.gov; and
6. The World Health Organization International Clinical Trials Registry Platform (ICTRP).

The search strategy will not be limited by language (see Appendix 1).

B. Reference searching

The references of all identified studies and relevant systematic reviews will be inspected for more trials.

C. Abstracts of major gastroenterology meetings

A manual search of abstracts submitted to major gastroenterology meetings (2015 to 2018) will be performed for the following journals to identify more trials that may have not been published in full at the time of the review:

1. Gastroenterology (American Gastroenterological Association);
2. Gut (British Society of Gastroenterology);
3. American Journal of Gastroenterology (American College of Gastroenterology);
4. Canadian Journal of Gastroenterology (Canadian Association of Gastroenterology);
5. Journal of Pediatric Gastroenterology and Nutrition (European Society of Paediatric Gastroenterology, Hepatology and Nutrition); and
6. Journal of Pediatric Gastroenterology and Nutrition (North American Society of Paediatric Gastroenterology, Hepatology and

Nutrition).

D. Personal contacts

Leaders in the field will be contacted to try to identify other studies.

E. Drug companies

The manufacturers of relevant agents will be contacted for additional data.

Data collection and analysis

Selection of studies

Papers (or abstracts) that appear to be potentially relevant will be identified by two authors. The authors, after reading the full texts, will independently assess the eligibility of all trials identified using the inclusion criteria above. Disagreement among authors will be resolved by discussion and consensus. If disagreements cannot be resolved, we will employ a third author for resolution.

Data extraction and management

A data extraction form will be developed and used to extract information on relevant features and results of included studies. Two authors will independently extract and record data on the predefined checklist. Extracted data will include the following items:

a. Characteristics of patients: age, sex, disease distribution, disease duration, disease activity index;

b. Total number of patients originally assigned to each treatment group;

c. Intervention: type and dose of agent;

d. Control: placebo, other drugs;

e. Concurrent medications; and

f. Outcomes: time of assessment, length of follow up, type of Crohn's disease activity index used, definitions of remission and relapse, site of surgery, relapse rates, adverse events.

Assessment of risk of bias in included studies

Two authors will independently assess bias using the Cochrane risk of bias tool (Higgins 2011). The study features to be assessed include:

a. Random sequence generation;

b. Allocation concealment;

c. Blinding of participants and personnel;

d. Blinding of outcome assessment;

e. Completeness of outcome data;

f. Selective reporting; and

g. Other sources of bias.

We will rate each of these factors as 'low risk', 'high risk' or 'unclear risk' of bias. After risk of bias assessment has been carried out at study level, we will then use the CINeMA 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) and corresponding 95% confidence interval (95% CI) for dichotomous outcomes using a random-effects model. We will calculate the mean difference (MD) and corresponding 95% CI for continuous outcomes measured using the same units. We plan to calculate the standardised mean difference (SMD) and corresponding 95% CI for continuous outcomes where different scales were used to evaluate the same outcome. The treatment effects will be summarized in terms of the RR estimates and associated two-sided 95% confidence intervals (CI).

Unit of analysis issues

Given the nature of the interventions, it is thought that only simple parallel group design trials will have been conducted, with no cluster randomised trials. If cluster randomised trials are identified, these will be included and, if unit of analysis issues are identified (e.g. randomisation and analysis at different units), the sample sizes or standard errors will be adjusted appropriately (Higgins 2011). Where cross-over trials are identified, these will be included and the effect estimates from the first period prior to cross-over included in the meta-analysis. Where outcomes are reported at several time points, analyses will be undertaken at single time point that is consistently reported by the trials and at the longest point of follow-up. Where network meta-analyses are conducted, the effects of correlated effect estimates will be accounted for using appropriate methods (see Data synthesis).

Dealing with missing data

Where dichotomous outcome data are missing, we will use an intention-to-treat principle (ITT). The ITT principle will be applied on the assumption that all patients lost to follow-up were treatment failures.

Assessment of heterogeneity

Heterogeneity and inconsistency will be assessed to ensure the validity of the analysis. Initially heterogeneity will be assessed through visual inspection of forest plots and the calculation of the Chi^2 and I^2 statistics (Borenstein 2009). For the network meta-analyses, the between study standard deviation will be used to assess heterogeneity, with a threshold of 0.5 indicating heterogeneity. Consistency within the analysis will be assessed 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 2010). It is important that the direct and indirect evidence for the same comparisons agree, as joint analysis on an inconsistent network can be misleading. Possible explanations for heterogeneity will be examined 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. Where appropriate, these factors will be investigated further through sub-group analyses and meta-regression (Borenstein 2009). Sensitivity analyses will explore possible causes of methodological heterogeneity, where sufficient data are available (Sutton 2000). This would include assessing the effects of studies that may be affected by factors such as risk of bias associated with allocation concealment, high loss to follow-up or lack of blinding in assessment of outcomes.

Assessment of reporting biases

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

Data synthesis

Studies will be synthesised through a narrative review with tabulation of results of included studies. Where possible, treatment effects for all comparisons and outcomes will be synthesized through meta-analyses, with the approach taken dependant on the outcome assessed and the data available (Borenstein 2009). Where the outcomes represent time-to-event data (e.g. time to relapse), the (log) hazard ratio (HR) with 95% CI (or CrI) will be used as the summary measure, adopting the approaches suggested by Sutton et al. given the available data (Egger 2001; Parmar 1998; Sutton 2000).

Different approaches will be taken for the meta-analysis. First, direct comparisons of treatment effects will be conducted through pairwise meta-analyses. Second, the opportunity for estimating a network meta-analysis (NMA) will be assessed to compare different interventions through both direct and indirect evidence within connected networks of trials (Spiegelhalter 2004; Welton 2012). 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, NMAs allow for the comparison of multiple interventions simultaneously and for an estimation of the rank order based on efficacy (Welton 2012). The network for the models will be presented graphically through network diagrams, allowing assessment of both the structure and extent of the evidence available for the different comparisons. As already noted, where heterogeneity is identified its possible causes will be investigated through the inclusion of patient and study level characteristics as covariate within meta-regression analyses. The meta-regression will include factors such as baseline risk (surrogate measure of patient characteristics) and length of follow-up (Gordon 2011; Gordon 2014), adopting the approach outlined by Achana et al (Achana 2013). Where multiple active treatment arms of the same class of drug or different doses of the same drug are included, comparisons may be correlated, influencing the outcome measure. Such correlations will be accounted for by assuming that the treatment effects from multi-arm studies are from a multivariate normal distribution, decomposing it into a series of conditional univariate distributions (Warren 2014). Some interventions have been considered to be sufficiently similar to have a 'class effect', with meta-analyses 'lumping' these interventions together. Aminosalicylates will be split into two separate interventions: sulfasalazine and 5-ASA (e.g. mesalazine, mesalamine, etc.). As pooling treatments that may be heterogeneous does not meet the consistency assumption, with the potential to cause conflict between the direct and indirect evidence, NMAs for the individual and the classes of interventions will be estimated where evidence allows and the estimates compared (Welton 2012). Where interventions routinely used for maintaining remission are administered as concomitant treatments, such studies will be excluded from the network.

All NMAs will take a Bayesian approach through Markov Chain Monte Carlo (MCMC) simulation. The parameters considered in the models will be the treatment effect of an intervention compared with other interventions, with the likelihood function dependent on the outcome used. As the primary outcome (i.e. clinical relapse) represents the number of events that occur within a patient population allocated to a particular treatment, a binomial distribution will be assumed for the likelihood. Trial specific log-odds ratios (ORs) will be assumed to be from the normal distribution. Different prior distributions will be used for the scale parameters (e.g. a uniform distribution for the base case and half-normal and inverse gamma distributions for sensitivity analyses). Vague priors will be used for the treatment effects in the different models. All models will be estimated using three chains starting with different initial values. Convergence will be assessed 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 one. Varying iterations and burn-in periods will be used to ensure convergence, with burn-in periods discarded from the analysis. Autocorrelation plots will be examined, with different rates of thinning applied to eliminate or reduce its effects where present.

Adequacy of the fit of the models will be assessed 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 three to five points considered significant (lowest DIC most appropriate fit) (Spiegelhalter 2002, Welton 2012). The adequacy of the approach used for the NMA will be assessed using a standard critical appraisal tool (Jansen 2014).

Pairwise meta-analyses of direct comparisons will be conducted

using RevMan (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.) and STATA v14.2 (version 14.2, StataCorp, Texas, USA) (Higgins 2011, Egger 2001), while NMAs will be estimated using the WinBUGS software (version 1.4.3) (MRC Biostatistics Unit, Cambridge, UK) (http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml).

Subgroup analysis and investigation of heterogeneity

Assessment of statistical heterogeneity

To carry out a statistical assessment of the disagreement between estimates within each pairwise comparison, we plan to use the I^2 statistic (Higgins 2011). We will also visually assess the overlap of the confidence intervals with the prediction interval and the variability in the point estimates. I^2 thresholds will be interpreted as follows:

- < 50% will be regarded as low;
- 50 to 75% will be regarded as moderate; and
- > 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. This will be done for single loops of evidence within the network and for the network as a whole (Dias 2013; Salanti 2014). Given that these tests are often underpowered, we will carry out the assessment using the 90% significance level.

Local approaches to evaluating inconsistency

The first stage involves separately synthesising the evidence for each pairwise contrast. This method tests the consistency assumption for each closed loop of the network separately then the magnitude of the inconsistency factors and their confidence intervals can be used for making inferences about the presence of inconsistency in each loop. We will present the results of this approach graphically in a forest plot using the 'ifplot' command in Stata 2017. This will be followed by the node splitting approach comparing direct and indirect relative treatment effects. For instance, a direct estimate of C versus B is compared with the indirect estimate from AB versus AC (Dias 2013). A test of the null hypothesis that there is no inconsistency is obtained using a Z-test. One test will be carried out for each treatment comparison. The ratio of odds ratios with confidence interval will be calculated each time. A confidence interval which excludes 1 indicates statistically significant inconsistency.

Global approaches to evaluating inconsistency

We will carry out a global assessment of inconsistency in the network using a Chi^2 test. This is useful in assessing whether the assumption of consistency holds for the entire network. Treatment comparisons that take ≥90% of the information from direct evidence are unlikely to have concerns for inconsistency. For comparisons with at least 10% of information derived from indirect evidence, a P value < 0.01, 0.01 to < 0.1 and > 0.1 will be interpreted as major, some and no concerns respectively

Investigation of heterogeneity and inconsistency

If sufficient studies are available, we will perform subgroup analyses assessing the effect of time since surgery (≤30 days versus >30 days), duration of follow-up (≤ 12 months versus > 12 months) and type of remission (clinical versus endoscopic) on the outcomes.

Sensitivity analysis

Methodological heterogeneity will be examined through sensitivity analysis, including components of risk of bias such as allocation concealment, loss to follow-up or blinding of outcome assessment. Data permitting, we will also exclude studies which are outliers in terms of dose of intervention, definition of outcome, direction or size of treatment effect or those identified as inconsistent by inconsistency testing.

Quality assessment of evidence generated from the network meta-analysis (NMA)

We will assess the certainty of the evidence using GRADE (Schünemann 2011a; Schünemann 2011b). 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 and the CINeMA webtool (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). The latter will be conducted using a node splitting approach (Dias 2013). As well as assessing the meta-analyses of the direct evidence for

inconsistency, we will consider the NMA 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. GRADE inconsistency will be assessed as serious limitations if there is heterogeneity in the direct estimate or inconsistency in the network with respect to that comparison. Very serious limitations will be attributed to the comparison if there is severe heterogeneity or severe inconsistency or limitations with both heterogeneity and inconsistency. Judgements on the magnitude of limitations will be determined 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: will also be assessed for each pairwise comparison using standard GRADE; 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 (Confidence in Network Meta-Analysis) webtool assesses NMA 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

We plan to present the main results on clinical relapse and withdrawal due to 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 2011a). 'Summary of findings' tables also include an overall grading of the evidence using the GRADE approach.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategies

Embase

1. random$.mp.
2. factorial$.mp.
3. (crossover$ or cross over$ or cross-over$).mp.
4. placebo$.mp.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl$ adj blind$).mp.
9. (double$ adj blind$).mp.
10. (tripl$ adj blind$).mp.
11. assign$.mp.
12. allocat$.mp.
13. crossover procedure/
14. double blind procedure/
15. single blind procedure/
16. triple blind procedure/
17. randomized controlled trial/
18. or/1-17
19. Exp Crohn disease/

20. Crohn*.mp.
21. IBD.mp.
22. Inflammatory bowel disease*.mp.
23. or/ 19-22
24. Exp Surgery/
25. Surgical*.mp.
26. Surgical resection.mp.
27. Colectomy.mp.
28. Resection*.mp.
29. or/24-28
30. Exp Post Operation/
31. Post-operative.mp.
32. Post opera*.mp.
33. Postopera*.mp.
33. or/ 30-33
34. Exp Corticosteroids/
35. (Corticosteroid* or Budesonide or Prednisone or Prednisolone or Hydrocortisone or Methylprednisolone).mp.
36. Exp 5-ASA/
37. (5- aminosalicylic acid or 5-aminosalicylates or Aminosalicylates or Mesalamine or Mesalazine or Sulfasalazine).mp.
39. Exp Purine analogues/
40. Tumor necrosis factor inhibitor*.mp.
41. TNF-antagonist.mp.
41. (Immunomodulator* or Azathioprine or Mercaptopurine or Infliximab or Adalimumab or Certolizumab or Methotrexate or Natalizumab or Vedolizumab or Ustekinumab).mp.
42. Exp Antibiotics/
43. (Antibiotic* or Ciprofloxacin or Metronidazole).mp.
44. (Probiotic* or Prebiotic*or Supplement* or Calcium or Acetaminophen or Ibuprofen or Fiber*).mp.
45. or/34-44
46. 18 and 23 and 29 and 33 and 45

MEDLINE

1. random$.tw.
2. factorial$.tw.
3. (crossover$ or cross over$ or cross-over$).tw.
4. placebo$.tw.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl$ adj blind$).tw.
9. (double$ adj blind$).tw.
10. (tripl$ adj blind$).tw.
11. assign$.tw.
12. allocat$.tw.
13. randomized controlled trial/
14. or/1-13
15. Exp Crohn disease/
16. Crohn*.mp.
17. IBD.mp.
18. Inflammatory bowel disease*.mp.
19. or/ 15-18
20. Exp Surgery/
21. Surgical*.mp.
22. Surgical resection.mp.
23. Colectomy.mp.

24. Resection*.mp.
25. or/20-24
26. Post operation.mp.
27. Post-operative.mp.
28. Post opera*.mp.
29. Postopera*.mp.
30. or/26-29
31. Exp Corticosteroids/
32. (Corticosteroid* or Budesonide or Prednisone or Prednisolone or Hydrocortisone or Methylprednisolone).mp.
33. Exp aminosalicylic acid/
34. (5- ASA or 5-aminosalicylates or Aminosalicylates or Mesalamine or Mesalazine or Sulfasalazine).mp.
35. Purine analogues.mp.
36. Tumor necrosis factor inhibitor*.mp.
37. TNF-antagonist.mp.
38. (Immunomodulator* or Azathioprine or Mercaptopurine or Infliximab or Adalimumab or Certolizumab or Methotrexate or Natalizumab or Vedolizumab or Ustekinumab).mp.
39. Exp Antibiotics/
40. (Antibiotic* or Ciprofloxacin or Metronidazole).mp.
41. (Probiotic* or Prebiotic*or Supplement* or Calcium or Acetaminophen or Ibuprofen or Fiber*).mp.
42. or/31-41
43. 14 and 19 and 25 and 30 and 42

Cochrane CENTRAL

#1 MeSH: [Inflammatory bowel disease] explode all trees
#2 Crohn Disease
#3 Crohn
#4 IBD
#5 #1 or #2 or #3 or #4
#6 MeSH: [Colectomy] explode all trees
#7 Surgery
#8 Surgical*
#9 Surgical resection
#10 Resection*
#11 #6 or #7 or #8 or #9 or #10
#12 Post operation
#13 Post-operative
#14 Post opera*
#15 Postopera*
#16 #12 or #13 or #14 or # 15
#17 Corticosteroid* or Budesonide or Prednisone or Prednisolone or Hydrocortisone or Methylprednisolone
#18 5- ASA or 5-aminosalicylates or Aminosalicylates or Mesalamine or Mesalazine or Sulfasalazine or Aminosalicylic acid
#19 Purine Analogues
#20 Tumor Necrosis Factor-alpha
#21 Tumor necrosis factor inhibitor*
#22 Immunomodulator* or Azathioprine or Mercaptopurine or Infliximab or Adalimumab or Certolizumab or Methotrexate or Natalizumab or Vedolizumab or Ustekinumab
#23 MeSH: [Anti-Bacterial Agents] explode all trees
#24 Antibiotic* or Ciprofloxacin or Metronidazole
#25 MeSH: [Probiotics] explode all trees
#26 Probiotic* or Prebiotic*or Supplement* or Calcium or Acetaminophen or Ibuprofen or Fiber*
#27 #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26
#28 #5 and #11 and #16 and #27

Clinicaltrials.gov/ ICTRP

1. Inflammatory bowel disease and surgery

2. Crohn's disease and surgery
3. Inflammatory bowel disease and resection
4. Crohn's disease and resection

CONTRIBUTIONS OF AUTHORS

All authors contributed to the writing of this protocol.

DECLARATIONS OF INTEREST

Andrew Clegg: None known.

Zipporah Iheozor-Ejiofor: None known.

Morris Gordon has received travel fees from Abbott, Nutricia, Biogaia, Ferring, Allergan, and Tillots to attend international scientific and training meeting such as DDW, Advances in IBD, ESPGHAN, BSPGHAN and Cochrane focused international events. None of these companies have had any involvement in any works completed by Morris Gordon me and he has never had any payments for any other activities.

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