Systematic review

1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

Efficacy of methotrexate in the management of inflammatory bowel disease: a systematic review and meta-analysis of randomized controlled trials

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.

30/10/2018

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

31/12/2018

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.
Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.
This field should be updated when any amendments are made to a published record and on completion and publication of the review. If this field was pre-populated from the initial screening questions then you are not able to edit it until the record is published.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Ole Haagen Nielsen

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Professor, Chief Physician Ole Haagen Nielsen

7. * Named contact email.

Give the electronic mail address of the named contact.

ole.haagen.nielsen@regionh.dk

8. Named contact address

Give the full postal address for the named contact.

Dept. of Gastroenterology D112

Herlev Hospital

University of Copenhagen

Herlev Ringvej 75

DK-2730 Herlev

Denmark

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

Phone +45 38 68 36 21 (Secretary)

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Dept. of Gastroenterology D112, University of Copenhagen, Herlev Hospital

Organisation web address:

https://www.herlevhospital.dk/

11. * Review team members and their organisational affiliations.

Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

Professor Ole Haagen Nielsen. Dept. of Gastroenterology D112, University of Copenhagen, Herlev and Gentofte Hospital
Dr Casper Steenholdt. Dept. of Gastroenterology D112, University of Copenhagen, Herlev and Gentofte Hospital
Assistant/Associate Professor Carsten Juhl. Dept. of Physiotherapy and Occupational Therapy, University of Copenhagen, Herlev and Gentofte Hospital
Professor Gerhard Rogler. University Hospital of Zürich, Switzerland

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

None

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members.

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

What is the effect of methotrexate in the management of inflammatory bowel disease based on renowned and validated disease activity scores?

16. * Searches.

Give details of the sources to be searched, search dates (from and to), and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

The following bibliographic databases will be searched without restriction on language and publication year.

MEDLINE via PubMed, Embase via Ovid and The Cochrane Central Register of Controlled Trials (CENTRAL), all from inception up to October 31st, 2018.

Furthermore, the reference lists of included studies and systematic reviews from the last five years on methotrexate therapy for management of inflammatory bowel disease will be scrutinized for relevant studies.

The following search strategy was performed in the respective databases: ("Inflammatory Bowel Diseases"[MeSH] OR Crohn*[TIAB] OR Ulcerative colitis*[TIAB] OR IBD [TIAB] OR Inflammatory bowel disease*[TIAB] OR proctocolitis*[TIAB] OR proctosigmoiditis*[TIAB] OR rectocolitis*[TIAB] OR rectosigmoiditis*[TIAB] OR proctitis*[TIAB]) AND ("Methotrexate"[MeSH] OR Methotrexate*[TIAB]) AND (randomized controlled trial [Publication Type] OR controlled clinical trial [Publication Type] OR randomized [TIAB] OR placebo [TIAB] OR drug therapy [Subheading] OR randomly [TIAB] OR trial [TIAB] OR groups [TIAB])

17. URL to search strategy.

Give a link to a published pdf/word document detailing either the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies), or upload your search strategy.Do NOT provide links to your search results.

https://www.crd.york.ac.uk/PROSPEROFILES/115047_STRATEGY_20181028.pdf

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Inflammatory bowel disease (i.e. ulcerative colitis and Crohn's disease).

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion criteria: Adults (18+ years) with inflammatory bowel disease, (i.e. ulcerative colitis and Crohn's disease).

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

Studies are eligible for the present project if they include (at least) one treatment group in which methotrexate is administered for inflammatory bowel disease.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Non-exposed control group

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

Randomized controlled trials.

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Primary outcome

Efficacy of methotrexate accessed via renown disease activity scores used in inflammatory bowel disease. For Crohn's disease the CDAI score (150 or below defined as remission; response ?70 (Response-70) or ?100 (Response-100)) followed by the HBI score (remission 0-4; mild 5-7; moderate 8-16, and severe ?17 (response ?3 reduction)). For ulcerative colitis the Mayo score (max 12 points): remission ?2 (with no item 1); mild 3-5; moderate 6-9, and severe ?10; response ?3) or partial score (i.e., without endoscopy (max 9 points): remission 0-1; mild 2-4; moderate 5-6, and severe 7-9; response ?2, followed by the SSCAI (max 15 points including extracolonic manifestations (1 point per manifestation)) (remission ?3; mild 4-6; moderate 7-9, and severe ?10; response ?4).

Secondary outcomes

Endoscopic disease activity scores for mucosal healing, defined as an absolute subscore for endoscopy of no more than 1 for the Endoscopic Mayo score (ulcerative colitis) or for Crohn's disease disease activity are assessed with the CDEIS followed by the SES-CD score (both these scores ?2). These endoscopic scores were followed by biomarkers (serum CRP normal ?10 mg/L or fecal calprotectin (remission ? 250 mg/kg) as well as radiology ("global assessment of radiologist(s)").

Timing and effect measures

Outcomes will be assessed immediately after finishing the intervention and at follow-up at 26 and 52 weeks.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

Additionally, any adverse event or serious adverse event (i.e. death, is life-threatening, requires inpatient

hospitalization, results in persistent or significant disability/incapacity, may have caused a congenital anomaly/birth defect, or requires intervention to prevent permanent impairment or damage) of methotrexate or comparator will also be registered.

Timing and effect measures

Outcomes will be assessed at follow-up at 52 weeks

26. * Data extraction (selection and coding).

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

Two members of the study team (OHN & CS) will independently access titles and abstracts for study eligibility. The full text will be obtained if studies are judged eligible by at least one reviewer. The same reviewers will also independently judge eligibility of the retrieved full-text studies. Consensus on inclusion will be reached by discussion including GR & CBJ.

A customized data-extraction form has been developed for each of the outcomes. Two authors (OHN & CS) will independently perform the data extraction.

The following data-extraction are considered mandatory: authors of the study, year of publication, design of trial, intervention characteristics, location of the trial (in case of multicentre studies, primary investigator affiliation will apply), number of patients allocated (to the methotrexate vs. control groups, respectively), the average patient age, average disease activity score and score applied, the endoscopy score and scoring system applied, number of females within the ITT population, the duration of study (presented in weeks) as well as reported biomarker changes and results of radiological exams (e.g. MRI). Authors will be contacted in case the data cannot be extracted from the published manuscript.

27. * Risk of bias (quality) assessment.

State whether and how risk of bias will be assessed (including the number of researchers involved and how discrepancies will be resolved), how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

Two reviewers (OHN & CS) will independently assess the methodological quality of the included studies using the Cochrane "Risk of bias tool": The reviewers will be judging the following domains as adequate (i.e. low risk of bias), unclear or inadequate: sequence generation, allocation concealment, blinding, incomplete outcome data assessed, selective outcome reporting or other biases. Disagreements in initial ratings of methodological quality assessment will be discussed between the two reviewers and GR until consensus is reached. The overall quality of evidence for the estimates will be evaluated by using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach and presented in a Summary of Findings table (SOF).

28. * Strategy for data synthesis.

Give the planned general approach to synthesis, e.g. whether aggregate or individual participant data will be used and whether a quantitative or narrative (descriptive) synthesis is planned. It is acceptable to state that a quantitative synthesis will be used if the included studies are sufficiently homogenous.

A meta-analysis will be applied using a random-effects model as heterogeneity is expected due to differences in interventions, outcome measures etc. The meta-analysis will be stratified on oral or parenteral (low or high) dosages of methotrexate applied if possible. Heterogeneity will be examined as between-study valuation and calculated as the I^2 statistic measuring the proportion of their variation (i.e., inconsistency) in the combined estimates due to between-study variance.

An I^2 value of 0% indicates that no inconsistency is seen between the results of individual trials, and an I^2 value of 100% indicates maximal inconsistency. Standardized mean differences (SMD) with 95% CIs will be calculated for outcome measures of continuous data and adjusted to Hedges g. The magnitude of the effect size of the pooled SMD will be interpreted as large if SMD 0.8; moderate if 0.5-0.8; weak if 0.2-0.5, and no effect determined if SMD is below0.2. For outcome measures where a meta-analysis is not possible a qualitative data synthesis of the results from individual studies will be performed.

29. * Analysis of subgroups or subsets.

Give details of any plans for the separate presentation, exploration or analysis of different types of participants (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or co-morbidities); different types of intervention (e.g. drug dose, presence or absence of particular components of intervention); different settings (e.g. country, acute or primary care sector, professional or family care); or different types of study (e.g. randomised or non-randomised).

A meta-regression analysis will be performed to explore the heterogeneity, if necessary. Relevant study-level covariates, defined as ones able to decrease inconsistencies measured as I^2 statistics (and thus the between-study variants Tau-square), will be investigated to estimate the effect of methotrexate therapy on inflammatory bowel disease dosage of methotrexate, co-morbidities, study quality and whether the study intervention was supervised or not.

30. * Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Meta-analysis
No

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
Yes

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is an English language summary.

32. Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

Denmark

33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

Give the link to the published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

The systematic review will be published in international a peer-reviewed scientific journal.

Do you intend to publish the review on completion?

No

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Methotrexate, Crohn's disease, ulcerative colitis, inflammatory bowel disease

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38. * Current review status.

Review status should be updated when the review is completed and when it is published. For newregistrations the review must be Ongoing.
Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

40. Details of final report/publication(s).

This field should be left empty until details of the completed review are available.

Give the link to the published review.