# Targeted Immune Modulators for Ulcerative Colitis: Effectiveness and Value

**Research Protocol**

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**Institute for Clinical and Economic Review**

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# Background, Objectives, and Research Questions

## Background

Ulcerative colitis (UC) is an autoimmune inflammatory bowel disease (IBD) that affects the mucosa, the innermost lining of the intestinal wall in the large bowel (i.e., the colon and rectum).[1] The disease causes long-lasting inflammation and ulcers in the digestive tract, and is typically marked by periods of remission and recurrence of symptoms. Symptoms may include frequent diarrhea, sometimes with blood or pus, abdominal and/or rectal pain, weight loss, and fatigue.[2] When the disease affects children, it can have a detrimental impact on growth, nutritional status, and psychosocial development.[3] It is estimated that approximately 900,000 individuals in the United States (US) have UC, 15-20% of whom are children.[4] Most individuals are diagnosed between the ages of 15 and 35.[5] The economic burden of UC is significant, ranging between an estimated $15-32 billion per year.[5]

UC is diagnosed based on the presence of symptoms with confirmation of disease via colonoscopy and biopsy. Other disease processes that may cause similar symptoms, such as infection and cancer, should be excluded. [6] The management of UC in adults is dependent on the severity of symptoms. In patients with mild disease, the use of rectal aminosalicylates may induce and maintain remission. Once symptoms have become moderate-to-severe, however, the use of budesonide or other corticosteroids as well as systemic immunomodulators such as azathioprine is warranted.[6] Those whose disease does not respond to or recurs despite systemic therapy are candidates for a number of targeted immune modulators (TIMs) to induce and/or maintain remission, including the tumor necrosis factor (TNF) inhibitors adalimumab (Humira®, AbbVie), golimumab (Simponi®, Janssen), and infliximab (Remicade®, Janssen), the $\alpha_4\beta_7$ integrin inhibitor vedolizumab (Entyvio®, Takeda), the Janus kinase (JAK) inhibitor tofacitinib (Xeljanz®, Pfizer), and the recently approved interleukin (IL)-12 and IL-23 inhibitor ustekinumab (Stelara®, Janssen). Elective colectomy (surgical removal of the colon) may be considered in patients whose disease does not respond to maximal medical management.[6] Recommended treatment options are more limited in children but do include most of the systemic therapies as well as infliximab.[4]

In addition to the above treatment approaches, vedolizumab, which is currently only available in intravenous (IV) form, is under review by the Food and Drug Administration (FDA) for subcutaneous use. How the clinical and economic effects of the currently approved and proposed medications for UC compare is of interest to patients, clinicians, and payers alike.

## Objectives

The scope of this project was previously available for public comment and has been revised upon further discussions and input from stakeholders. In accordance with the revised scope, this project will assess both the comparative clinical effectiveness and economic impacts of infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, and ustekinumab for the treatment of moderately-to-severely active UC. We will also review clinical and economic evidence for biosimilars infliximab-dyyb and infliximab-abda (Inflectra®, Pfizer and Renflexis®, Merck). The assessment aims to systematically evaluate the existing evidence. To that aim, the assessment is informed by two research components: a systematic review of the existing evidence and an economic evaluation. This document presents the protocol for the systematic review of existing evidence (i.e., the clinical review). The model analysis plan will include details on the proposed methodology and model structure that will be used for the economic evaluation (expected publication date February 3, 2020).

## Research Questions

To inform our review of the clinical evidence, we have developed the following research questions with input from clinical experts and patient organizations:

- In patients with moderately-to-severely active UC with inadequate response or intolerance to conventional therapy and no experience with biologics (i.e., biologic-naïve), what is the comparative efficacy, safety, and effectiveness of TIMs versus each other and ongoing conventional therapy (i.e., placebo arms in clinical trials) in terms of clinical remission, steroid-free remission, clinical response, mucosal healing, quality of life, adverse events, and other key outcomes during induction and maintenance?
- In patients with moderately-to-severely active UC with inadequate response or intolerance to conventional therapy and prior use of biologics (i.e., biologic-experienced), what is the comparative efficacy, safety, and effectiveness of TIMs versus each other and ongoing conventional therapy (i.e., placebo arms in clinical trials) in terms of clinical remission, steroid-free remission, clinical response, mucosal healing, quality of life, adverse events, and other key outcomes during induction and maintenance?

## PICOTS Criteria

In line with the above research questions, the following specific criteria have been defined utilizing PICOTS (Population, Interventions, Comparisons, Outcomes, Timing, Setting and Study Design) elements.

***Population***

The population of focus for the review is adults with moderately-to-severely active UC, whose disease has either inadequate response or intolerance to conventional therapy, such as corticosteroids, azathioprine, or mercaptopurine.

Additionally, based on the availability of data, we intend to include evidence on children ages six to 17 years old with moderately-to-severely active UC.

Data permitting, we intend to examine subpopulations including but not limited to:

1) Patients who are naïve to biologic therapy
2) Patients who have previously used biologic therapy.

Other subgroups of interest may include age (e.g., ≥65), presence of extraintestinal manifestations, or other comorbidities, data permitting.

***Interventions***

The interventions of interest developed with input from clinicians and patient organizations include:

- Vedolizumab (Entyvio, Takeda), subcutaneous and IV formulations
- Infliximab (Remicade, Janssen)*
- Infliximab-dyyb (Inflectra, Pfizer)*
- Infliximab-abda (Renflexis, Merck)*
- Adalimumab (Humira, AbbVie)
- Golimumab (Simponi, Janssen)
- Tofacitinib (Xeljanz, Pfizer)
- Ustekinumab (Stelara, Janssen)

*Given the labeled indication, we intend to review evidence on the use of infliximab and its biosimilars in children. Evidence on off-label use of any other interventions of interest in children may be included, if available.

We intend to include all FDA-approved biosimilars of reference products that are currently available on the US market. Importantly, our focus will be on patient-centric data for UC only; information limited to pharmacodynamics, pharmacokinetics, or other laboratory parameters will not be considered. We do not plan to include other FDA-approved biosimilars (e.g., biosimilars for adalimumab) as their entry to the US marketplace has been substantially delayed due to patent litigation.

***Comparators***

Based on data availability, we intend to compare the interventions of interest to ongoing background conventional therapy (i.e., placebo arms of clinical trials) and against each other.

***Outcomes***

The following outcomes of interest will be explored for evidence:

*Efficacy*

- Clinical remission
- Steroid-free remission
- Clinical response
- Mucosal healing
- Health-related quality of life
- Functional outcomes
- Other patient-reported outcomes
- Use of rescue medication
- UC-related hospitalization
- Surgery
- Mortality

*Safety*

- Serious adverse events
- Adverse events leading to discontinuation
- Treatment-emergent adverse events
    - Infections
    - Headache
    - Nausea
    - Fatigue
    - Pain
    - Pharyngitis
    - Respiratory
    - Autoimmune
    - Demyelinating disease
    - Injection reactions
    - Development of neutralizing antibodies

***Timing***

Evidence on intervention efficacy, safety, and effectiveness will be collected from studies testing treatments with at least six weeks exposure duration.

***Setting***

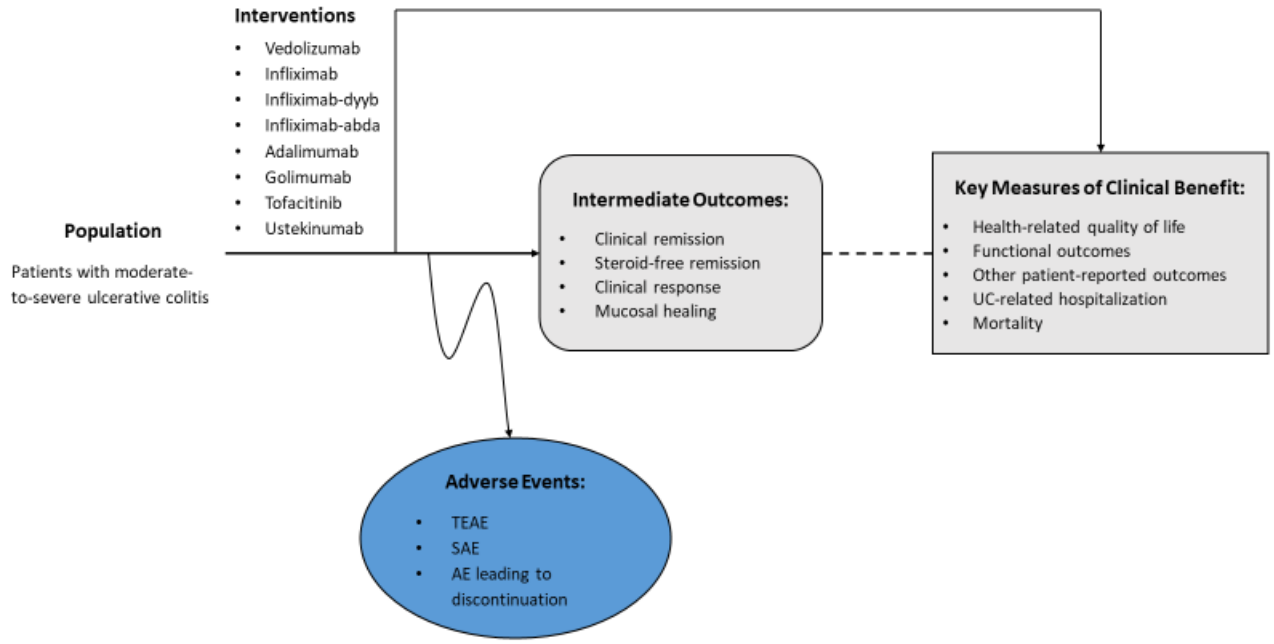
Evidence from all relevant settings will be considered, with a focus on outpatient settings as well as ambulatory and hospital-based settings.

***Study Design***

Randomized controlled trials with any sample size will be included. Higher quality comparative observational studies (sample size ≥500 for adults and ≥20 for children) will also be included.

## Analytic Framework

The proposed analytic framework for this project is depicted below.




AE: adverse event, SAE: serious adverse event, TEAE: treatment-emergent adverse event, UC: ulcerative colitis

The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific clinical or health outcomes. Outcomes are listed in the shaded boxes: those within the rounded boxes are intermediate outcomes (e.g., clinical remission), and those within the squared-off boxes are key measures of clinical benefit (e.g., health-related quality of life). The key measures of clinical benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of an action (typically treatment), which are listed within the blue ellipse.

# Evidence Review Methods

## Search Methods and Data Sources

Procedures for the systematic literature review assessing the evidence on TIMs for moderately-to-severely active UC will follow established best methods.[7,8] The review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[9] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

We will search MEDLINE and EMBASE for relevant studies. Each search will be limited to English language studies of human subjects and will exclude articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We will include abstracts from conference proceedings identified from the systematic literature search. All search strategies will be generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. We identified recent systematic reviews and a network meta-analysis (NMA) of the interventions of interest, which followed a similar scope. However, we will conduct a *de novo* search for the interventions of interest. The proposed search strategies include a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE) as well as free-text terms, and are presented in Tables 1 and 2 on the following pages.

To supplement the database searches, we will perform a manual check of the reference lists of included trials and reviews and invite key stakeholders to share references germane to the scope of this project. We will also supplement our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's Policy on Inclusion of Grey Literature in Evidence Reviews).

**Table 1. Search Strategy of MEDLINE***

| | Search Terms |
|---|---|
| 1. | colitis, ulcerative/ |
| 2. | ((ulcera* adj3 colitis) or inflammatory bowel disease* or IBD or UC).mp |
| 3. | (Infliximab or Infliximab-abda or Renflexis or Infliximab-dyyb or Inflectra or Remicade or CT P13).mp. |
| 4. | infliximab.af. |
| 5. | (Humira or Adalimumab ABTD2E7 or ABT D2E7).mp. |
| 6. | adalimumab.af. |
| 7. | (Entyvio or MLN0002 or Vedolizumab).mp. |
| 8. | vedolizumab.af. |
| 9. | (golimumab or simponi or CNTO 148).mp. |
| 10. | golimumab.af. |
| 11. | ustekinumab.af. |
| 12. | (ustekinumab or stelara or CNTO1275 or CNTO 1275).mp. |
| 13. | (tofacitinib or tofacitinib citrate or Xeljanz or CP 690?550).mp. |
| 14. | tofacitinib.af. |
| 15. | (abstract or addresses or autobiography or bibliography or biography or clinical trial, phase I or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or videoaudio media).pt. |
| 16. | (animals not (humans and animals)).sh. |
| 17. | exp cohort studies/ or comparative study.pt. or observational study.pt. or exp case-control studies/ or cohort.tw. or (observational adj2 stud*).tw or prospective.tw or retrospective.tw or longitudinal.tw. or compa*.tw OR groups.tw OR case control.tw OR multivariate.tw |
| 18. | control Groups/ or (control* adj2 (clinical or group* or trial* or study or studies or design* or arm*)).ti,ab. or ("clinical trial" or "clinical trial, phase ii" or "clinical trial, phase iii" or "clinical trial, phase iv" or "controlled clinical trial" or "multicenter study" or "randomized controlled trial").pt. or (randomi?ed adj6 (study or trial* or (clinical adj2 trial*))).ti,ab. or ((single or doubl*) adj2 blind*).ti,ab. |
| 19. | 1 or 2 |
| 20. | or/3-14 |
| 21. | 19 and 20 |
| 22. | 21 not 15 |
| 23. | 22 not 16 |
| 24. | 17 or 18 |
| 25. | 23 and 24 |
| 26. | limit 25 to english language |
| 27. | remove duplicates from 26 |

*Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present.

**Table 2. Search Strategy of EMBASE**

| | Search Terms |
|---|---|
| 1. | 'ulcerative colitis'/exp |
| 2. | ((ulcera* NEAR/3 colitis):ab,ti) OR 'inflammatory bowel disease*':ab,ti OR uc:ti,ab OR ibd:ti,ab |
| 3. | #1 OR #2 |
| 4. | 'infliximab'/exp OR infliximab:ab,ti OR 'remicade':ab,ti OR 'renflexis':ab,ti OR 'inflectra':ab,ti OR 'infliximab-abda' OR 'infliximab-dyyb':ab,ti OR 'ct p13':ab,ti |
| 5. | 'tofacitinib'/exp OR tofacitinib:ab,ti OR tasocitinib:ab,ti OR 'tofacitinib citrate':ab,ti OR xeljanz:ab,ti OR 'cp 690 550':ab,ti OR 'cp 690550':ab,ti |
| 6. | 'adalimumab'/exp OR adalimumab:ab,ti OR humira:ab,ti OR abtd2e7:ab,ti OR 'abt d2e7':ab,ti |
| 7. | 'golimumab'/exp OR 'golimumab':ab,ti OR 'simponi':ab,ti OR 'cnto 148':ab,ti |
| 8. | 'ustekinumab'/exp OR ustekinumab:ab,ti OR stelara:ab,ti OR cnto1275:ab,ti OR 'cnto 1275':ab,ti |
| 9. | 'vedolizumab'/exp OR vedolizumab:ab,ti OR entyvio:ab,ti OR mln0002:ab,ti |
| 10. | #4 OR #5 OR #6 OR #7 OR #8 OR #9 |
| 11. | #3 AND #10 |
| 12. | #11 NOT ('animal experiment'/de OR 'animal model'/de OR 'case report'/de OR 'human cell'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it) |
| 13. | #12 NOT [medline]/lim |
| 14. | #13 NOT (('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp) |
| 15. | #14 AND [english]/lim |
| 16. | clinical article'/exp OR 'controlled study'/exp OR 'major clinical study'/exp OR 'observational study'/exp OR 'prospective study'/exp OR 'retrospective study'/exp OR 'longitudinal study'/exp OR 'cohort analysis'/exp OR 'cohort':ti,ab OR 'compa*':ti,ab OR 'groups':ti,ab OR 'case control':ti,ab OR 'multivariate':ti,ab OR retrospective:ti,ab OR prospective:ti,ab OR longitudinal:ti,ab OR ((observational NEAR/2 stud*):ti,ab) |
| 17. | ('clinical':ti,ab AND 'trial':ti,ab) OR 'clinical trial'/exp OR 'randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR random*:ti,ab or control*:ti,ab OR 'control group'/exp OR 'drug therapy':lnk |
| 18. | #16 OR #17 |
| 19. | #15 AND #18 |

## Selection of Eligible Studies

Subsequent to the literature search and removal of duplicate citations using both online and local software tools, study selection will be accomplished through two levels of screening, at the abstract and full-text level. Two reviewers will independently screen the titles and abstracts of all publications identified using DistillerSR (Evidence Partners, Ottawa, Canada); a third reviewer will work with the initial two reviewers to resolve any issues of disagreement through consensus. No study will be excluded at abstract level screening due to insufficient information. For example, an abstract that does not report an outcome of interest in the abstract will be accepted for further review in full text.

Citations accepted during abstract-level screening will be retrieved in full text for review. Reasons for exclusion will be categorized according to the PICOTS elements during both title/abstract and full-text review.

## Data Extraction Strategy

Data will be extracted into evidence tables. The basic design and elements of the extraction forms will follow those used for other ICER reports. Elements include a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and quality assessment for each study.

The data extraction will be performed in the following steps:

1) One reviewer will extract information from the full articles, and a second reviewer will validate the extracted data.
2) Extracted data will be reviewed for logic, and a random proportion of data will be validated by a third investigator for additional quality assurance.

## Quality Assessment Criteria

We will use criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of clinical trials and cohort studies, using the categories "good," "fair," or "poor."[10]

*Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention paid to confounders in analysis. In addition, intention to treat analysis is used for randomized controlled trials (RCTs).*

*Fair: Any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all-important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

*Poor: Any of the following fatal flaws exist: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat or modified intention to treat (e.g., randomized and received at least one dose of study drug) analysis is lacking.*

## Publication Bias Assessment

Given the emerging nature of the evidence base for these newer treatments, we will scan the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include infliximab, Remicade, adalimumab, Humira, ABTD2E7, golimumab, Simponi, CNTO148, vedolizumab, Entyvio, MLN0002, tofacitinib, tasocitinib, Xeljanz, CP690550, ustekinumab, Stelara, CNTO1275, and infliximab biosimilars—infliximab-abda, Renflexis, infliximab-dyyb, and Inflectra, and CT-P13. We will select studies that would have met our inclusion criteria, and for which no findings have been published. We will provide qualitative analysis of the objectives and methods of these studies to ascertain whether there may be a biased representation of study results in the published literature.

## Evidence Synthesis

The purpose of the evidence synthesis is to estimate the clinical effectiveness of the interventions being compared. The analysis will be based on the data from all relevant studies identified from the systematic review. This section contains two components: 1) a summary of evidence base and, 2) a synthesis of results.

### *Summary of Evidence Base*

The studies will be summarized in the text and in evidence tables of the Evidence Report. This summary is key to understanding the evidence base pertaining to the topic. An evidence table shell is presented in Appendix B. Relevant data include those listed in the data extraction section. Any key differences between the studies in terms of the study design, patient characteristics, interventions (including dosing and frequency), outcomes (including definitions and methods of assessments), and study quality will be noted in the text of the report.

### *Synthesis of Results*

The results of the studies will be synthesized for each outcome and described narratively in the report. Analyses to be conducted will reflect the nature and quality of the evidence base (see below). Key considerations for interpreting the results will be specified and described in the Evidence Report.

All studies deemed sufficiently similar in terms of the key population, intervention, and outcome measures will be included in a quantitative synthesis. For this review, NMAs under a Bayesian framework will be conducted on outcomes including clinical remission and clinical response (measured via Mayo score). The outcomes will be analyzed separately for induction and maintenance phases. If data permit, we plan to conduct separate NMAs for patients who are biologic-naïve and patients who are biologic-experienced given the expected differences in the

efficacy of our interventions between these two subpopulations. We do not plan to conduct an NMA on the overall "mixed" population (i.e., including those who are biologic-naïve or biologic-experienced) for key clinical outcomes (e.g., clinical remission and clinical response); however, we would consider conducting analyses on the overall population if data are lacking for other outcomes.

An NMA extends pairwise meta-analyses by simultaneously combining both the direct estimates (i.e., estimates obtained from head-to-head comparisons) and indirect estimates (i.e., estimates obtained from common comparator[s]).[11,12] For continuous outcomes, the NMA model corresponds to a normal likelihood and an identity link. For binary outcomes, the NMA model corresponds to a binomial likelihood and a logit link. For ordered categorical outcomes, the NMA model corresponds to a multinomial likelihood and a probit link. We will include fixed or random effects on the treatment parameters depending on the study set in the networks.

Furthermore, for any network where there are "loops" in evidence, we will empirically compare the direct and indirect estimates to assess if the NMA consistency assumption is violated using a node-splitting approach.[13] If there is evidence of inconsistency, the results will be presented for the direct and indirect evidence separately. If there is no evidence of inconsistency, we will present the pooled results.

To explore heterogeneity across studies, we will examine if there are differences in the distribution of key characteristics across studies. For this project, key characteristics include mean Mayo score at baseline, duration of disease, background treatments, and prior experience with biologic therapy. If studies differ with respect to these characteristics, subgroup analyses or meta-regressions may be performed where sufficient data exist.

All NMAs will be conducted using R using JAGS software. Results for all pairwise comparisons will be presented in tabular fashion in terms of a point estimate and 95% credible intervals.

# References


1. American Society of Colon and Rectal Surgeons. Ulcerative Colitis. 2019; https://www.fascrs.org/patients/disease-condition/ulcerative-colitis. Accessed September 23, 2019.
2. Mayo Clinic. Ulcerative Colitis. 2019; https://www.mayoclinic.org/diseases-conditions/ulcerative-colitis/symptoms-causes/syc-20353326. Accessed September 23, 2019.
3. Bradley GM, Oliva-Hemker M. Pediatric ulcerative colitis: current treatment approaches including role of infliximab. *Biologics : targets & therapy.* 2012;6:125-134.
4. Turner D, Levine A, Escher JC, et al. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. *Journal of pediatric gastroenterology and nutrition.* 2012;55(3):340-361.
5. Crohn's & Colitis Foundation of America. The Facts About Inflammatory Bowel Diseases. 2014.
6. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG Clinical Guideline: Ulcerative Colitis in Adults. *American Journal of Gastroenterology.* 2019;114(3):384-413.
7. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med.* 1997;126(5):376-380.
8. Higgins JPT GSe. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011].* The Cochrane Collaboration. Available from http://handbook.cochrane.org.; 2011.
9. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg.* 2010;8(5):336-341.
10. Agency for Healthcare Research and Quality. U.S. Preventive Services Task Force Procedure Manual. 2008.
11. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ.* 2005;331(7521):897-900.
12. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med.* 2004;23(20):3105-3124.
13. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med.* 2010;29(7-8):932-944.
14. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ.* 2009;339:b2700.

# Appendix A. PRISMA Checklist

The checklist below is drawn from Moher et al. 2009.[9] An additional explanation of each item can be found in Liberati et al. 2009.[14]

| Section/Topic | # | Checklist Item | Reported on Page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12). | |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot. | |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers). | |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). | |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | |

doi:10.1371/journal.pmed.1000097.t001

# Appendix B. Data Extraction Summary Table Shell

| Author & Year of Publication (Trial) | Study Design | Interventions (n) & Dosing Schedule | Inclusion and Exclusion Criteria | Patient Characteristics | Outcomes |
|---|---|---|---|---|---|
| | | | | | |
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