Centers for Medicare and Medicaid Services: Vedolizumab (Entyvio®) Drug Price Negotiations

Effectiveness and Value

Research Protocol

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ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

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1. Background, Objectives, and Research Questions

1.1. Background

Ulcerative colitis (UC) and Crohn's disease (CD) are the two different types of autoimmune inflammatory bowel disease (IBD). UC primarily affects the mucosa, the innermost lining of the intestinal wall in the large bowel (i.e., the colon and rectum).[1] Crohn's disease, on the other hand, can affect the entire GI (gastrointestinal) tract from the mouth to the anus and can involve the full thickness, not just the mucosa. These diseases cause long-lasting inflammation and ulcers in the digestive tract, and are 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 2.4 to 3.1 million individuals in the United States (US) have IBD.[4] Most individuals are diagnosed between the ages of 15 and 35.[5] Among 25 million Medicare fee for service beneficiaries, there are approximately 100,000 people with CD (0.40%) and 160,000 people with UC (0.64%).[6] The economic burden of IBD is significant, with recent estimates of $50 billion per year in the United States.[7]

Both UC and CD are diagnosed based on symptoms of the disease and confirmed by colonoscopy with biopsy. Other disease processes that may cause similar symptoms, such as infection and cancer, need to be excluded.[8] The management of IBD 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 is indicated.[8] 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 interleukin (IL)-12 and IL-23 inhibitor ustekinumab (Stelara®, Janssen). In particular, vedolizumab has been highlighted by several commenters as a likely candidate for Medicare drug price negotiations for the 2028 price applicability year. Elective colectomy (surgical removal of the colon) may be considered in patients with UC whose disease does not respond to maximal medical management.[8] Colectomy is not routinely used for treatment in patients with CD.

1.2. Objectives

This project will assess both the comparative clinical effectiveness and economic impacts of vedolizumab for the treatment of UC and CD. The assessment aims to systematically evaluate the existing evidence, taking uncertainty into account. 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). See the model analysis plan (expected posting: 10/30/2025) for details on the proposed methodology and model structure that will be used for the economic evaluation.

1.3. Research Questions

To inform our review of the clinical evidence, we have developed the following research questions:

- What is the net health benefit of vedolizumab versus infliximab in the populations described below?
- What is the net health benefit of vedolizumab versus adalimumab in the populations described below?
- What is the net health benefit of vedolizumab versus ustekinumab in the populations described below?
- What is the net health benefit of vedolizumab versus conventional and/or systemic therapy in the populations described below?

1.4. 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.

PICOTS (Ulcerative Colitis)

Populations

The population of focus for the review is adults with moderate-to-severe UC, defined as a Mayo score of 6 to 12 with an endoscopic subscore ≥2, who no longer respond to at least one conventional and/or systemic therapy (i.e., corticosteroids, immunomodulators).

Subgroups of interest include those with disabilities, those with end-stage renal disease (ESRD), those with terminal illness, the Medicare-aged population (≥65 years), children (potentially from trials that included both adults and children or adolescents), presence of extraintestinal manifestations (e.g., arthritic symptoms, psychological effects), and treatment experience (TIM naïve vs. TIM experienced).

Intervention

- Vedolizumab (Entyvio®, Takeda)

Comparators

Data permitting, we intend to compare vedolizumab to drugs that are recommended by current guidelines and have Food and Drug Administration (FDA)-approved biosimilar versions available on the market, as well as to conventional systemic therapy.

FDA Approved Biologics	FDA Approved Biosimilars
• **Infliximab (Remicade®, Janssen)**	• Infliximab-abda (Renflexis®, Merck) • Infliximab-axxq (Avsola®, Amgen) • Infliximab-dyyb (Inflectra®, Celltrion) • Infliximab-qbtx (IXIFI®, Pfizer)
• **Adalimumab (Humira®, Abbvie)**	• Adalimumab-aacf (Idacio®, Fresenius Kabi) • Adalimumab-aaty (Yuflyma®, Celltrion) • Adalimumab-adaz (Hyrimoz®, Sandoz/Cordavis) • Adalimumab-adbm (Cyltezo®, Boehringer Ingelheim) • Adalimumab-afzb (Abrilada®, Pfizer) • Adalimumab-atto (Amjevita®, Amgen) • Adalimumab-aqvh (Yusimry®, Meitheal) • Adalimumab-bwwd (Hadlima®, Organon/Samsung Bioepis) • Adalimumab-fkjp (Hulio®, Biocon Biologics) • Adalimumab-ryvk (Simlandi®, Alvotech/Teva)
• **Ustekinumab (Stelara®, Janssen)**	• Ustekinumab-aauz (Otulfi®, Fresenius Kabi) • Ustekinumab-aekn (Selarsdi®, Alvotech) • Ustekinumab-auub (Wezlana, Amgen) • Ustekinumab-hmny (Starjezma®, Bio-Thera Solutions) • Ustekinumab-kfce (Yesintek®, Biocon) • Ustekinumab-srlf (Imuldosa®, Accord BioPharma) • Ustekinumab-stba (Steqeyma®, Celltrion) • Ustekinumab-ttwe (Pyzchiva®, Samsung Bioepis Co.)

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Clinical remission
    - Clinical response
    - Corticosteroid-free clinical remission
    - Health-related quality of life (HRQoL)
        - Inflammatory Bowel Disease Questionnaire (IBDQ)
        - SF-36
        - EQ-5D
        - Others as feasible
    - UC-related hospitalization
    - Colectomy
    - Adverse events (AEs) including
        - Serious AEs
        - AEs leading to discontinuation
- Other Outcomes
    - Normalization of C-Reactive Protein (CRP)/ Erythrocyte Sedimentation Rate (ESR)/calprotectin
    - Endoscopic healing
    - Endoscopic improvement
    - Histologic healing
    - Transmural histologic healing
    - Use of rescue medication
    - Functional outcomes
    - Adverse events including
        - Infections
        - Malignancies
        - Thrombotic events
        - Hepatic events

Timing

Evidence on intervention effectiveness and harms will be derived from studies of any duration.

Settings

All relevant settings will be considered, with a focus on all settings in the United States.

Study Design

Randomized controlled trials and non-randomized controlled trials with any sample size and duration will be included. High-quality comparative and single-arm observational studies (sample size >500) with at least 12 months of study duration will also be included for outcomes related to maintenance therapy.

PICOTS (Crohn's Disease)

Populations

The population of focus for the review is adults with moderate-to-severe CD, defined as a CD Activity Index (CDAI) score of 220 to 450, who no longer respond to at least one conventional and/or systemic therapy (i.e., corticosteroids, immunomodulators).

Subgroups of interest included those with disabilities, those with end-stage renal disease (ESRD), those with terminal illness, the Medicare-aged population (≥65 years), children (potentially from trials that included both adults and children or adolescents), presence of extraintestinal manifestations (e.g., arthritic symptoms, psychological effects), and treatment experience (TIM naïve vs. TIM experienced).

Interventions

The full list of interventions is as follows:

- Vedolizumab (Entyvio®, Takeda)

Comparators

Data permitting, we intend to compare vedolizumab to drugs that are recommended by current guidelines and have FDA-approved biosimilar versions available on the market, as well as to conventional systemic therapy.

FDA Approved Biologics	FDA Approved Biosimilars
• **Infliximab (Remicade®, Janssen)**	• Infliximab-abda (Renflexis®, Merck) • Infliximab-axxq (Avsola®, Amgen) • Infliximab-dyyb (Inflectra®, Celltrion) • Infliximab-qbtx (IXIFI®, Pfizer)
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• **Ustekinumab (Stelara®, Janssen)**	• Ustekinumab-aauz (Otulfi®, Fresenius Kabi) • Ustekinumab-aekn (Selarsdi®, Alvotech) • Ustekinumab-auub (Wezlana®, Amgen) • Ustekinumab-hmny (Starjezma®, Bio-Thera Solutions) • Ustekinumab-kfce (Yesintek®, Biocon) • Ustekinumab-srlf (Imuldosa®, Accord BioPharma) • Ustekinumab-stba (Steqeyma®, Celltrion) • Ustekinumab-ttwe (Pyzchiva®, Samsung Bioepis Co.)

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    - Health-related quality of life (HRQoL)
        - Inflammatory Bowel Disease Questionnaire (IBDQ)
        - SF-36
        - EQ-5D
        - Others as feasible
    - CD-related hospitalization
    - CD-related surgeries
    - Adverse events including
        - Serious AEs
        - AEs leading to discontinuation

- Other Outcomes
    - Normalization of CRP/ESR/calprotectin
    - Transmural healing
    - Histologic healing
    - Endoscopic healing
    - Endoscopic improvement
    - Mucosal healing
    - Use of rescue medication
    - Functional outcomes
    - Adverse events including
        - Infections
        - Malignancies
        - Thrombotic events
        - Hepatic events

Timing

Evidence on intervention effectiveness and harms will be derived from studies of any duration.

Settings

All relevant settings will be considered, with a focus on all settings in the United States.

Study Design

Randomized controlled trials and non-randomized controlled trials with any sample size and duration will be included. High-quality comparative and single-arm observational studies (sample size >500) with at least 12 months of study duration will also be included for outcomes related to maintenance therapy.

2. Evidence Review Methods

2.1. Search Methods and Data Sources

Procedures for the systematic literature review assessing the evidence on vedolizumab for UC and CD will follow established best methods.[9,10] The review will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11] The PRISMA guidelines include a list of 27 checklist items, which are described further in Appendix A.

For UC, we will begin our search by reviewing the clinical trials and observational studies included in ICER's 2020 review of targeted immunomodulators for UC.[12] We will also review other published systematic literature reviews (SLRs) and network meta-analyses (NMAs), including Attauabi et al 2023, Ananthakrishnan et al 2024, and Zhang et al 2025 to identify studies following our PICOTS.[13-15] Then, we will update our evidence base by searching MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for new, relevant studies published from July 2020 onwards (i.e., the end date of ICER's prior search).

For CD, we will begin our search by reviewing the clinical trials included in Versteegh et al 2025 and observational studies included in Ungaro et al 2020.[16,17] Then, we will update our evidence base by searching MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for both studies. As such, only clinical trials published since October 2023 and high-quality observational studies published since April 2019 will be eligible for inclusion.

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. 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 2.1. and 2.2. below.

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 grey literature policy).

Table 2.1. Search Strategy of Ovid MEDLINE(R) ALL, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews for Ulcerative Colitis

#	Search Term	Hits
1	colitis, ulcerative/	47508
2	((ulcera* adj3 colitis) or inflammatory bowel disease* or IBD or UC).mp	151265
3	1 or 2	151265
4	('entyvio' or 'vedolizumab' or "'mln 02 monoclonal antibody'" or 'MLN0002' or 'MLN-0002' or 'MLN-02' or 'MLN02').ti,ab.	2965
5	('Humira' or 'Amjevita' or 'Cyltezo' or 'D2E7 Antibody' or 'Antibody, D2E7' or 'Adalimumab-atto' or 'Adalimumab-adbm' or 'adalimumab-aacf' or 'idacio' or 'adalimumab-aaty' or 'yuflyma' or 'adalimumab-adaz' or 'hyrimoz' or 'adalimumab-fkjp' or 'hulio' or 'amjevita' or 'adalimumab-bwwd' or 'hadlima' or 'hulio' or 'hyrimoz' or 'idacio' or 'adalimumab-ryvk' or 'simlandi' or 'adalimumab-afzb' or 'abrilada' or 'adalimumab-aqvh' or 'yusimry').ti,ab.	878
6	('Monoclonal Antibody cA2' or 'Antibody cA2, Monoclonal' or 'cA2, Monoclonal Antibody' or 'MAb cA2' or 'Remicade' or 'Inflectra' or 'Renflexis' or 'Infliximab-dyyb' or 'Infliximab dyyb' or 'Infliximab-abda' or 'Infliximab abda' or 'infliximab' or 'inflectra' or 'renflexis' or 'avsola' or 'infliximab-axxq' or 'zymfentra' or 'IXIFI' or 'infliximab-qbtx').ti,ab.	18573
7	('CNTO 1275' or 'CNTO-1275' or 'Stelara' or 'Ustekinumab-aauz' or 'Otulfi' or 'Ustekinumab-aekn' or 'Selarsdi' or 'Ustekinumab-auub' or 'Wezlana' or 'Ustekinumab-kfce' or 'Yesintek' or 'Ustekinumab-srlf' or 'Imuldosa' or 'Ustekinumab-stba' or 'Steqeyma' or 'Ustekinumab-ttwe' or 'Pyzchiva' or 'ustekinumab-hmny').ti,ab.	204
8	4 or 5 or 6 or 7	21672
9	3 and 8	7223
10	9 not (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 video-audio media).pt.	5620
11	10 not (animals not (humans and animals)).sh.	5581
12	remove duplicates from 11	5350
13	Limit 12 to English language	5189
14	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.	3645466
15	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.	13684486
16	14 or 15	14557625
17	13 and 16	3820
18	limit 17 to yr="2020 - 2025"	1870

Table 2.2. Search Strategy of EMBASE for Ulcerative Colitis

#	Search Term	Hits
1	'ulcerative colitis'/exp	118003
2	((ulcera* NEAR/3 colitis):ab,ti) OR 'inflammatory bowel disease*':ab,ti OR uc:ti,ab OR ibd:ti,ab	215814
3	#1 OR #2	233730
4	'entyvio':ti,ab OR 'vedolizumab':ti,ab OR 'mln 02 monoclonal antibody':ti,ab OR 'mln0002':ti,ab OR 'mln-0002':ti,ab OR 'mln-02':ti,ab OR 'mln02':ti,ab	6944
5	'Humira':ti,ab OR 'Amjevita':ti,ab OR 'Cyltezo':ti,ab OR 'D2E7 Antibody':ti,ab OR 'Antibody, D2E7':ti,ab OR 'Adalimumab-atto':ti,ab OR 'Adalimumab-adbm':ti,ab OR 'adalimumab-aacf':ti,ab OR 'idacio':ti,ab OR 'adalimumab-aaty':ti,ab OR 'adalimumab-adaz':ti,ab OR 'hyrimoz':ti,ab OR 'adalimumab-fkjp':ti,ab OR 'hulio':ti,ab OR 'amjevita':ti,ab OR 'adalimumab-bwwd':ti,ab OR 'hadlima':ti,ab OR 'hyrimoz':ti,ab OR 'adalimumab-ryvk':ti,ab OR 'simlandi':ti,ab OR 'yuflyma':ti,ab OR 'adalimumab-afzb':ti,ab OR 'abrilada':ti,ab OR 'adalimumab-aqvh':ti,ab OR 'yusimry':ti,ab	1196
6	'Monoclonal Antibody cA2':ti,ab OR 'Antibody cA2, Monoclonal':ti,ab OR 'cA2, Monoclonal Antibody':ti,ab OR 'MAb cA2':ti,ab OR 'Remicade':ti,ab OR 'Inflectra':ti,ab OR 'Renflexis':ti,ab OR 'Infliximab-dyyb':ti,ab OR 'Infliximab dyyb':ti,ab OR 'Infliximab-abda':ti,ab OR 'Infliximab abda':ti,ab OR 'infliximab':ti,ab OR 'inflectra':ti,ab OR 'renflexis':ti,ab OR 'avsola':ti,ab OR 'infliximab-axxq':ti,ab OR 'zymfentra':ti,ab OR 'IXIFI':ti,ab OR 'infliximab-qbtx':ti,ab	35907
7	'CNTO 1275':ti,ab OR 'CNTO-1275':ti,ab OR 'Stelara':ti,ab OR 'Ustekinumab-aauz':ti,ab OR 'Otulfi':ti,ab OR 'Ustekinumab-aekn':ti,ab OR 'Selarsdi':ti,ab OR 'Ustekinumab-auub':ti,ab OR 'Wezlana':ti,ab OR 'Ustekinumab-kfce':ti,ab OR 'Yesintek':ti,ab OR 'Ustekinumab-srlf':ti,ab OR 'Imuldosa':ti,ab OR 'Ustekinumab-stba':ti,ab OR 'Steqeyma':ti,ab OR 'Ustekinumab-ttwe':ti,ab OR 'Pyzchiva':ti,ab OR 'ustekinumab-hmny':ti,ab	192
8	#4 OR #5 OR #6 OR #7	41450
9	#3 AND #8	16709
10	#9 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)	9905
11	#10 NOT [medline]/lim	7535
12	#11 NOT (('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp)	7523
13	#12 AND [english]/lim	7380
14	#13 NOT ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'short survey'/it OR 'erratum'/it OR 'note'/it)	7295
15	'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	13229276
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)	23636759
17	#15 OR #16	27856421
18	#14 AND #17	6734
19	#18 AND [2020-2025]/py	2527

Table 2.3. Search Strategy of Ovid MEDLINE(R) ALL, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews for Crohn's Disease (Clinical Trials Only)

#	Search Term	Hits
1	exp Crohn's Disease/	50148
2	('Crohn* disease' or 'Crohn* Enteritis' or 'Granulomatous Colitis' or 'cleron disease' or 'Inflammatory Bowel Disease 1' or 'Regional Ileiti*' or 'morbus crohn' or 'regional enter*' or 'Granulomatous Enteritis' or 'Ileocolitis').ti,ab.	66860
3	1 or 2	76138
4	('entyvio' or 'vedolizumab' or "'mln 02 monoclonal antibody'" or 'MLN0002' or 'MLN-0002' or 'MLN-02' or 'MLN02').ti,ab.	2965
5	('Humira' or 'Amjevita' or 'Cyltezo' or 'D2E7 Antibody' or 'Antibody, D2E7' or 'Adalimumab-atto' or 'Adalimumab-adbm' or 'adalimumab-aacf' or 'idacio' or 'adalimumab-aaty' or 'yuflyma' or 'adalimumab-adaz' or 'hyrimoz' or 'adalimumab-fkjp' or 'hulio' or 'adalimumab-atto' or 'amjevita' or 'adalimumab-bwwd' or 'hadlima' or 'adalimumab-fkjp' or 'hulio' or 'adalimumab-adaz' or 'hyrimoz' or 'adalimumab-aacf' or 'idacio' or 'adalimumab-ryvk' or 'simlandi' or 'adalimumab-aaty' or 'adalimumab-afzb' or 'abrilada' or 'adalimumab-aqvh' or 'yusimry').ti,ab.	878
6	('Monoclonal Antibody cA2' or 'Antibody cA2, Monoclonal' or 'cA2, Monoclonal Antibody' or 'MAb cA2' or 'Remicade' or 'Inflectra' or 'Renflexis' or 'Infliximab-dyyb' or 'Infliximab dyyb' or 'Infliximab-abda' or 'Infliximab abda' or 'infliximab' or 'inflectra' or 'infliximab-dyyb' or 'renflexis' or 'infliximab-abda' or 'avsola' or 'infliximab-axxq' or 'zymfentra' or 'infliximab-dyyb' or 'IXIFI' or 'infliximab-qbtx').ti,ab.	18573
7	('CNTO 1275' or 'CNTO-1275' or 'Stelara' or 'Ustekinumab-aauz' or 'Otulfi' or 'Ustekinumab-aekn' or 'Selarsdi' or 'Ustekinumab-auub' or 'Wezlana' or 'Ustekinumab-kfce' or 'Yesintek' or 'Ustekinumab-srlf' or 'Imuldosa' or 'Ustekinumab-stba' or 'Steqeyma' or 'Ustekinumab-ttwe' or 'Pyzchiva' or 'ustekinumab-hmny').ti,ab.	204
8	4 or 5 or 6 or 7	21672
9	3 and 8	6594
10	9 not (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 video-audio media).pt.	5151
11	10 not (animals not (humans and animals)).sh.	5135
12	remove duplicates from 11	4864
13	Limit 12 to English language	4661
14	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.	3645466
15	13 and 14	1357
16	limit 15 to yr="2023 - 2025"	209

Table 2.4. Search Strategy of EMBASE for Crohn's Disease (Clinical Trials Only)

#	Search Term	Hits
1	'crohns disease'/exp	132576
2	'crohn* disease':ti,ab OR 'crohn* enteritis':ti,ab OR 'granulomatous colitis':ti,ab OR 'cleron disease':ti,ab OR 'inflammatory bowel disease 1':ti,ab OR 'regional ileiti*':ti,ab OR 'morbus crohn':ti,ab OR 'regional enter*':ti,ab OR 'granulomatous enteritis':ti,ab OR 'ileocolitis':ti,ab	11788
3	#1 OR #2	233730
4	'entyvio':ti,ab OR 'vedolizumab':ti,ab OR 'mln 02 monoclonal antibody':ti,ab OR 'mln0002':ti,ab OR 'mln-0002':ti,ab OR 'mln-02':ti,ab OR 'mln02':ti,ab	6944
5	'Humira':ti,ab OR 'Amjevita':ti,ab OR 'Cyltezo':ti,ab OR 'D2E7 Antibody':ti,ab OR 'Antibody, D2E7':ti,ab OR 'Adalimumab-atto':ti,ab OR 'Adalimumab-adbm':ti,ab OR 'adalimumab-aacf':ti,ab OR 'idacio':ti,ab OR 'adalimumab-aaty':ti,ab OR 'adalimumab-adaz':ti,ab OR 'hyrimoz':ti,ab OR 'adalimumab-fkjp':ti,ab OR 'hulio':ti,ab OR 'amjevita':ti,ab OR 'adalimumab-bwwd':ti,ab OR 'hadlima':ti,ab OR 'hyrimoz':ti,ab OR 'adalimumab-ryvk':ti,ab OR 'simlandi':ti,ab OR 'yuflyma':ti,ab OR 'adalimumab-afzb':ti,ab OR 'abrilada':ti,ab OR 'adalimumab-aqvh':ti,ab OR 'yusimry':ti,ab	1196
6	'Monoclonal Antibody cA2':ti,ab OR 'Antibody cA2, Monoclonal':ti,ab OR 'cA2, Monoclonal Antibody':ti,ab OR 'MAb cA2':ti,ab OR 'Remicade':ti,ab OR 'Inflectra':ti,ab OR 'Renflexis':ti,ab OR 'Infliximab-dyyb':ti,ab OR 'Infliximab dyyb':ti,ab OR 'Infliximab-abda':ti,ab OR 'Infliximab abda':ti,ab OR 'infliximab':ti,ab OR 'inflectra':ti,ab OR 'renflexis':ti,ab OR 'avsola':ti,ab OR 'infliximab-axxq':ti,ab OR 'zymfentra':ti,ab OR 'IXIFI':ti,ab OR 'infliximab-qbtx':ti,ab	35907
7	'CNTO 1275':ti,ab OR 'CNTO-1275':ti,ab OR 'Stelara':ti,ab OR 'Ustekinumab-aauz':ti,ab OR 'Otulfi':ti,ab OR 'Ustekinumab-aekn':ti,ab OR 'Selarsdi':ti,ab OR 'Ustekinumab-auub':ti,ab OR 'Wezlana':ti,ab OR 'Ustekinumab-kfce':ti,ab OR 'Yesintek':ti,ab OR 'Ustekinumab-srlf':ti,ab OR 'Imuldosa':ti,ab OR 'Ustekinumab-stba':ti,ab OR 'Steqeyma':ti,ab OR 'Ustekinumab-ttwe':ti,ab OR 'Pyzchiva':ti,ab OR 'ustekinumab-hmny':ti,ab	192
8	#4 OR #5 OR #6 OR #7	41450
9	#3 AND #8	16709
10	#9 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)	9905
11	#10 NOT [medline]/lim	7535
12	#11 NOT (('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp)	7523
13	#12 AND [english]/lim	7380
14	#13 NOT ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'short survey'/it OR 'erratum'/it OR 'note'/it)	6088
15	'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	13229276
16	#14 AND #15	2894
17	#16 AND [2023-2025]/py	493

Table 2.5. Search Strategy of Ovid MEDLINE(R) ALL, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews for Crohn's Disease (Observational Studies Only)

#	Search Term	Hits
1	exp Crohn's Disease/	50148
2	('Crohn* disease' or 'Crohn* Enteritis' or 'Granulomatous Colitis' or 'cleron disease' or 'Inflammatory Bowel Disease 1' or 'Regional Ileiti*' or 'morbus crohn' or 'regional enter*' or 'Granulomatous Enteritis' or 'Ileocolitis').ti,ab.	66860
3	1 or 2	76138
4	('entyvio' or 'vedolizumab' or "'mln 02 monoclonal antibody'" or 'MLN0002' or 'MLN-0002' or 'MLN-02' or 'MLN02').ti,ab.	2965
5	('Humira' or 'Amjevita' or 'Cyltezo' or 'D2E7 Antibody' or 'Antibody, D2E7' or 'Adalimumab-atto' or 'Adalimumab-adbm' or 'adalimumab-aacf' or 'idacio' or 'adalimumab-aaty' or 'yuflyma' or 'adalimumab-adaz' or 'hyrimoz' or 'adalimumab-fkjp' or 'hulio' or 'adalimumab-atto' or 'amjevita' or 'adalimumab-bwwd' or 'hadlima' or 'adalimumab-fkjp' or 'hulio' or 'adalimumab-adaz' or 'hyrimoz' or 'adalimumab-aacf' or 'idacio' or 'adalimumab-ryvk' or 'simlandi' or 'adalimumab-aaty' or 'adalimumab-afzb' or 'abrilada' or 'adalimumab-aqvh' or 'yusimry'').ti,ab.	878
6	('Monoclonal Antibody cA2' or 'Antibody cA2, Monoclonal' or 'cA2, Monoclonal Antibody' or 'MAb cA2' or 'Remicade' or 'Inflectra' or 'Renflexis' or 'Infliximab-dyyb' or 'Infliximab dyyb' or 'Infliximab-abda' or 'Infliximab abda' or 'infliximab' or 'inflectra' or 'infliximab-dyyb' or 'renflexis' or 'infliximab-abda' or 'avsola' or 'infliximab-axxq' or 'zymfentra' or 'infliximab-dyyb' or 'IXIFI' or 'infliximab-qbtx').ti,ab.	18573
7	('CNTO 1275' or 'CNTO-1275' or 'Stelara' or 'Ustekinumab-aauz' or 'Otulfi' or 'Ustekinumab-aekn' or 'Selarsdi' or 'Ustekinumab-auub' or 'Wezlana' or 'Ustekinumab-kfce' or 'Yesintek' or 'Ustekinumab-srlf' or 'Imuldosa' or 'Ustekinumab-stba' or 'Steqeyma' or 'Ustekinumab-ttwe' or 'Pyzchiva' or 'ustekinumab-hmny').ti,ab.	204
8	4 or 5 or 6 or 7	21672
9	3 and 8	6594
10	9 not (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 video-audio media).pt.	5151
11	10 not (animals not (humans and animals)).sh.	5135
12	remove duplicates from 11	4864
13	Limit 12 to English language	4661
14	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.	13684486
15	13 and 14	3179
16	limit 15 to yr="2019 - 2025"	1457

Table 2.6. Search Strategy of EMBASE for Crohn's Disease (Observational Studies Only)

#	Search Term	Hits
1	'crohns disease'/exp	132576
2	'crohn* disease':ti,ab OR 'crohn* enteritis':ti,ab OR 'granulomatous colitis':ti,ab OR 'cleron disease':ti,ab OR 'inflammatory bowel disease 1':ti,ab OR 'regional ileiti*':ti,ab OR 'morbus crohn':ti,ab OR 'regional enter*':ti,ab OR 'granulomatous enteritis':ti,ab OR 'ileocolitis':ti,ab	11788
3	#1 OR #2	233730
4	'entyvio':ti,ab OR 'vedolizumab':ti,ab OR 'mln 02 monoclonal antibody':ti,ab OR 'mln0002':ti,ab OR 'mln-0002':ti,ab OR 'mln-02':ti,ab OR 'mln02':ti,ab	6944
5	'Humira':ti,ab OR 'Amjevita':ti,ab OR 'Cyltezo':ti,ab OR 'D2E7 Antibody':ti,ab OR 'Antibody, D2E7':ti,ab OR 'Adalimumab-atto':ti,ab OR 'Adalimumab-adbm':ti,ab OR 'adalimumab-aacf':ti,ab OR 'idacio':ti,ab OR 'adalimumab-aaty':ti,ab OR 'adalimumab-adaz':ti,ab OR 'hyrimoz':ti,ab OR 'adalimumab-fkjp':ti,ab OR 'hulio':ti,ab OR 'amjevita':ti,ab OR 'adalimumab-bwwd':ti,ab OR 'hadlima':ti,ab OR 'hyrimoz':ti,ab OR 'adalimumab-ryvk':ti,ab OR 'simlandi':ti,ab OR 'yuflyma':ti,ab OR 'adalimumab-afzb':ti,ab OR 'abrilada':ti,ab OR 'adalimumab-aqvh':ti,ab OR 'yusimry':ti,ab	1196
6	'Monoclonal Antibody cA2':ti,ab OR 'Antibody cA2, Monoclonal':ti,ab OR 'cA2, Monoclonal Antibody':ti,ab OR 'MAb cA2':ti,ab OR 'Remicade':ti,ab OR 'Inflectra':ti,ab OR 'Renflexis':ti,ab OR 'Infliximab-dyyb':ti,ab OR 'Infliximab dyyb':ti,ab OR 'Infliximab-abda':ti,ab OR 'Infliximab abda':ti,ab OR 'infliximab':ti,ab OR 'inflectra':ti,ab OR 'renflexis':ti,ab OR 'avsola':ti,ab OR 'infliximab-axxq':ti,ab OR 'zymfentra':ti,ab OR 'IXIFI':ti,ab OR 'infliximab-qbtx':ti,ab	35907
7	'CNTO 1275':ti,ab OR 'CNTO-1275':ti,ab OR 'Stelara':ti,ab OR 'Ustekinumab-aauz':ti,ab OR 'Otulfi':ti,ab OR 'Ustekinumab-aekn':ti,ab OR 'Selarsdi':ti,ab OR 'Ustekinumab-auub':ti,ab OR 'Wezlana':ti,ab OR 'Ustekinumab-kfce':ti,ab OR 'Yesintek':ti,ab OR 'Ustekinumab-srlf':ti,ab OR 'Imuldosa':ti,ab OR 'Ustekinumab-stba':ti,ab OR 'Steqeyma':ti,ab OR 'Ustekinumab-ttwe':ti,ab OR 'Pyzchiva':ti,ab OR 'ustekinumab-hmny':ti,ab	192
8	#4 OR #5 OR #6 OR #7	41450
9	#3 AND #8	16709
10	#9 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)	9905
11	#10 NOT [medline]/lim	7535
12	#11 NOT (('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp)	7523
13	#12 AND [english]/lim	7380
14	#13 NOT ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'short survey'/it OR 'erratum'/it OR 'note'/it)	6088
15	'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)	23636759
16	#14 AND #15	2894
17	#17 AND [2019-2025]/py	2217

2.2. Eligibility Criteria

Additional eligibility criteria:

- Biosimilar studies that do not focus on the outcomes of interest will be excluded.
- Observational studies that do not have full-text peer-reviewed publications will be excluded.

2.3. Study Selection Process

After 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 Nested Knowledge; 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 would 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.

2.4. Data Extraction Strategy

Data will be extracted into Microsoft Excel. 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 risk of bias 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.

2.5. Risk of Bias

We will examine the risk of bias for each randomized trial in this review using criteria published in the Cochrane Risk of Bias Assessment Tool Version 2.[18,19] Risk of bias will be assessed by study outcome for each of the following domains: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. We will use the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool for comparative observational studies.[20] Currently, there are no quality assessment tools developed by Cochrane for single-arm observational studies. In all cases, two reviewers will independently assess these tools. Any disagreements will be resolved through discussion or by consulting a third reviewer.

2.6. Subgroup Credibility

We will examine the credibility of subgroup analyses (aka effect modification analyses) determined to be clinically important for the review using criteria published in the Instrument for the Credibility of Effect Modification ANalyses (ICEMAN) tool (Version 1.1).[21] The credibility of each effect modifier will be assessed by outcome of interest, time point of interest, and effect measure. One reviewer will independently assess the credibility of the subgroup analyses and a second reviewer will validate the ratings.

2.7. Clinical Trial Diversity

We will evaluate the demographic diversity for each clinical trial in this review using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[22] Three demographic categories will be evaluated: race and ethnicity, sex, and age. Representation for each demographic category will be evaluated relative to the disease prevalence, using the metric "Participant to Disease-prevalence Representation Ratio" (PDRR). Each article will receive a rating of "Good", "Fair", or "Poor" for the three demographic categories. One reviewer will use the extracted and validated data from the trials to calculate the ratings. A second reviewer will validate the ratings.

2.8. Publication Bias

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 Entyvio, Vedolizumab, Humira, Adalimumab, Remicade, Infliximab, Stelara, Ustekinumab, Ulcerative Colitis, Crohn's Disease. We will select studies which 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.

2.9. 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 three components: (1) a summary of the evidence base, (2) synthesis of outcome results, and (3) heterogeneity and subgroups.

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.

We will also assess the feasibility of conducting a network meta-analysis (NMA) under a Bayesian framework. 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)).[23,24] For ordered categorical outcomes (e.g., clinical response and remission), the NMA model corresponds to a multinomial model with a probit link. For binary outcomes (e.g., endoscopic improvement), the NMA model corresponds to a generalized linear model with a logit link. For continuous outcomes (e.g., EQ-5D VAS scores), the NMA model corresponds to a generalized linear model with identity link. For all analyses, we will include random effects on the treatment parameters, and the amount of between-study variance (i.e., heterogeneity) will be assumed constant across all treatment comparisons. We will use noninformative prior distributions for all model parameters. We will initially discard the first 40,000 iterations as "burn-in" and base inferences on an additional 40,000 iterations using three chains. Convergence of chains will be assessed with the Gelman-Rubin statistic and visually using trace plots. If the chains do not converge, an additional 10,000 iterations will be run, sequentially, until convergence.

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.[25] 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.

All NMAs will be conducted using R. Results for all pairwise comparisons will be presented tabularly in terms of a point estimate and 95% credible intervals. We will also present results for each treatment versus conventional and/or systemic therapy graphically.

All data analysis will be validated by an independent member of the research team. The validator will review and confirm the data analysis methods, data format, and analysis code. The validator will re-run the analysis, validate the results, and confirm the appropriateness of reported data. If the results match within reasonable limits (e.g., small differences may occur due to random sampling variability or model convergence, package versions, etc.), the results are considered validated.

References

1. American Society of Colon and Rectal Surgeons. Ulcerative Colitis. Accessed September 23, 2019, https://www.fascrs.org/patients/disease-condition/ulcerative-colitis
2. Mayo Clinic. Ulcerative Colitis. Accessed September 23, 2019, https://www.mayoclinic.org/diseases-conditions/ulcerative-colitis/symptoms-causes/syc-20353326
3. Bradley GM, Oliva-Hemker M. Pediatric ulcerative colitis: current treatment approaches including role of infliximab. *Biologics : targets & therapy*. 2012;6:125-34. doi:10.2147/btt.s31833
4. (CDC) CfDCaP. Inflammatory bowel disease (IBD). Accessed September 11, 2025, https://www.cdc.gov/inflammatory-bowel-disease/php/facts-stats/index.html
5. Crohn's & Colitis Foundation of America. The Facts about Inflammatory Bowel Diseases. 2014;
6. Xu F, Carlson SA, Liu Y, Greenlund KJ. Prevalence of Inflammatory Bowel Disease Among Medicare Fee-For-Service Beneficiaries - United States, 2001-2018. *MMWR Morb Mortal Wkly Rep*. May 14 2021;70(19):698-701. doi:10.15585/mmwr.mm7019a2
7. Burisch J, Claytor J, Hernandez I, Hou JK, Kaplan GG. The Cost of Inflammatory Bowel Disease Care: How to Make it Sustainable. *Clin Gastroenterol Hepatol*. Feb 2025;23(3):386-395. doi:10.1016/j.cgh.2024.06.049
8. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG Clinical Guideline: Ulcerative Colitis in Adults. *The American journal of gastroenterology*. Mar 2019;114(3):384-413. doi:10.14309/ajg.0000000000000152
9. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med*. Mar 1 1997;126(5):376-80.
10. Higgins J, Thomas, J, Chandler, J, Cumpston, M, Li, T, Page, MJ, Welch, VA. Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). https://training.cochrane.org/handbook/current
11. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. Mar 29 2021;372:n71. doi:10.1136/bmj.n71
12. Review IfCaE. *Targeted Immune Modulators for Ulcerative Colitis: Effectiveness and Value*. 2020. https://icer.org/wp-content/uploads/2020/08/ICER_UC_Final_Evidence_Report_101620.pdf
13. Attauabi M, Dahl EK, Burisch J, Gubatan J, Nielsen OH, Seidelin JB. Comparative onset of effect of biologics and small molecules in moderate-to-severe ulcerative colitis: a systematic review and network meta-analysis. *EClinicalMedicine*. Mar 2023;57:101866. doi:10.1016/j.eclinm.2023.101866
14. Ananthakrishnan AN, Murad MH, Scott FI, et al. Comparative Efficacy of Advanced Therapies for Management of Moderate-to-Severe Ulcerative Colitis: 2024 American Gastroenterological Association Evidence Synthesis. *Gastroenterology*. 2024;167(7):1460-1482. doi:10.1053/j.gastro.2024.07.046
15. Zhang W, Zhao S, Li J, Sun Y, Wang X. Network meta-analysis of efficacy and safety of drugs for the treatment of moderate to severe ulcerative colitis. Systematic Review. *Frontiers in Pharmacology*. 2025-January-03 2025;Volume 15 - 2024doi:10.3389/fphar.2024.1481678

16. Versteegh M, Idema DL, Huygens S, et al. Comparative efficacy of all available pharmaceutical therapies for moderate to severe Crohn's disease: a systematic review and network meta-analysis. *Gastro Hep Advances*. 2025/08/12/ 2025:100764. doi:https://doi.org/10.1016/j.gastha.2025.100764
17. Ungaro RC, Aggarwal S, Topaloglu O, Lee WJ, Clark R, Colombel JF. Systematic review and meta-analysis: efficacy and safety of early biologic treatment in adult and paediatric patients with Crohn's disease. *Aliment Pharmacol Ther*. May 2020;51(9):831-842. doi:10.1111/apt.15685
18. Higgins JPT, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions. 2nd Edition.* Chichester (UK): John Wiley & Sons; 2019.
19. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. doi:10.1136/bmj.l4898
20. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *Bmj*. Oct 12 2016;355:i4919. doi:10.1136/bmj.i4919
21. Schandelmaier S, Briel M, Varadhan R, et al. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. *Cmaj*. 2020;192(32):E901-E906.
22. Agboola FW, AC. A Framework for Evaluating the Diversity of Clinical Trials. *Journal of Clinical Epidemiology*. 2024:111299.
23. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med*. Oct 30 2004;23(20):3105-24. doi:10.1002/sim.1875
24. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ*. Oct 15 2005;331(7521):897-900. doi:10.1136/bmj.331.7521.897
25. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med*. Mar 30 2010;29(7-8):932-44. doi:10.1002/sim.3767

Appendix A. PRISMA Checklist

The checklist below is drawn from Page et al. 2021.[11]

Section and Topic	Item #	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review.
ABSTRACT		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
METHODS		
Eligibility Criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information Sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.
Search Strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.
Selection Process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data Collection Process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data Items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study Risk of Bias Assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect Measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.
Synthesis Methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.

Section and Topic	Item #	Checklist Item
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting Bias Assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty Assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
RESULTS		
Study Selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study Characteristics	17	Cite each included study and present its characteristics.
Risk of Bias in Studies	18	Present assessments of risk of bias for each included study.
Results of Individual Studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.
Results of Syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.
Reporting Biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of Evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.
DISCUSSION		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.
OTHER INFORMATION		
Registration and Protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.

Section and Topic	Item #	Checklist Item
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing Interests	26	Declare any competing interests of review authors.
Availability of Data, Code, and Other Materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

Appendix B. Data Extraction Summary Table Shell

Author & Year of Publication	Study Design	Interventions & Dosing Schedule	Inclusion & Exclusion Criteria	Patient Characteristics	Outcomes