Evidence-based Practice Center Systematic Review Protocol

Project Title: Comparative Effectiveness of Pharmacologic Therapies for the Management of Crohn's Disease

I.   Background and Objectives for the Systematic Review

Background

Description of disease. Crohn's disease is characterized by chronic full thickness inflammation that can occur anywhere in the gastrointestinal tract, but most often affects small bowel and colon. Typical symptoms include abdominal pain, chronic diarrhea, gastrointestinal bleeding, associated extra-intestinal problems such as inflammatory arthritis, rashes, mouth ulcers, and increased risk of colon cancer. Crohn's disease affects between 400,000 and 600,000 North Americans.[1]

After the first year of diagnosis, at any one point in time, roughly 10-30% of Crohn's disease patients will have moderate to severe disease, 15-25% will have mild disease, and 55-65% will be in remission.[2, 3] However, this is not a static process. Over time, 73% of patients will have a relapsing and remitting course, while only 10% of patients will remain in remission over the course of many years.[4] The most common complications of Crohn's include fibrotic narrowings in the small bowel (strictures) which can lead to obstruction, collections of pus in the abdomen or around the rectum (abscesses), and spontaneous rupture of the bowel contents through the skin or other organs (fistulas).[5,6] Most of these complications require surgery. In fact, up to 60% of patients will require at least one surgical resection over their lifetime.[1,7] Thus, it is important to identify the patients with aggressive disease who are more likely to have early complications, with the need for multiple hospitalizations and surgeries; this is the group that requires more aggressive immune-based therapy.

Approximately 10% of those with Crohn's disease are children under the age of 17.[8] Children with Crohn's disease are at risk for growth retardation in the absence of adequately treated disease. Medication side-effects (which can include increased risk for infection as well as lymphoma) and the costs associated with the drugs used for the more severe forms of the disease are particularly concerning for children, who often have a lifetime of treatment ahead of them.

Treating Crohn's disease requires balancing the burden of inflammatory disease with the side-effects of the medications used. Most of the immunosuppressive drugs used for this disease have the potential for rare but significant side-effects, such as infection or lymphoma. Induction and maintenance of remission, improving quality of life, and avoiding complications such as hospitalization, surgeries, prolonged steroid exposure, growth retardation in children, fistulae, and side-effects of medications are the goals of current medical therapy. Medications include aminosalicylates, corticosteroids, immunomodulators, and biologics (Table 1). Physicians prescribe medications alone or in combination to eliminate the inflammation that causes both the troublesome symptoms (diarrhea, pain, bleeding) as well as the complications from the disease (strictures, abscesses and fistulas). Achieving disease remission reduces hospitalizations and surgeries, while improving quality of life and the ability to work.[9]

Interventions to treat Crohn's disease. Dr. Burrill Crohn's initial description of this disease suggested that it could be cured with wide surgical resection; this is now known to be untrue.[10,11] Medications are now used to treat the intestinal inflammation with the intent of altering the natural history of the disease. Sulfasalazine and corticosteroids have been used since the

middle of the last century to treat Crohn's disease with some success. Corticosteroids improve symptoms in many patients. However, in the year following the initiation of steroids, one third of patients become corticosteroid dependant, while another third require surgery.[12] Additionally, steroids induce mucosal healing or eliminate relapses.[13] Immunomodulators such as 6-mercaptopurine, azathioprine, and methotrexate are associated with mucosal healing, avoidance of steroid side-effects, and prevention of post-operative recurrences, but can be associated with potentially serious adverse events.[13] The first anti-tumor necrosis factor-α (anti-TNF) biologic, infliximab, was approved for Crohn's disease in 1998. The anti-TNF biologics now include adalimumab and certolizumab pegol. These drugs are associated with reductions in surgeries and hospitalizations and improved mucosal healing.[13] Even with these desirable properties, anti-TNF biologics are ineffective in one-third of patients, and fail within six months in another third; anti-TNF biologics are also expensive and serious side-effects have been reported.[14]

Current controversies in the treatment of Crohn's disease. There are many controversies in the field: (1) Is the use of combination therapy with a thiopurine agent in addition to a biologic agent more effective than either one alone? This was recently addressed in the Study of Biologic and Immunomodulator Naïve Patients in Crohn's disease [SONIC].[15] It found that combination therapy is more effective. However, this topic is still contested as combination therapy is associated with an increased risk for infection and lymphoma.[16] (2) Early use of immunomodulators and biologics ("top-down therapy"), have been recently advocated rather than after prolonged use of steroids ("step-up therapy"), with the expectation of better long-term outcomes.[17] The benefits of this early treatment approach need to be weighed against the risks of increased immunosuppression, including lymphoma,[16,18] and expense and harms of over-treating the 40% of patients who will not require an intestinal resection and 70% of patients who will not have aggressive, disabling disease.[1] (3) Finally, once initiated, can medications ever be successfully withdrawn without significantly increasing the risk of relapse? Initial data suggest it cannot be.[19] The major challenge and focus of current research is improving the natural history of disease while minimizing adverse events.[13]

Treatment guidelines and meta-analyses on the management of Crohn's disease. Treatment guidelines exist for the management of Crohn's disease, often combining evidence-based medicine with expert panel review when evidence-based research is sparse. In the United States, the American College of Gastroenterology, the American Gastroenterological Association, and the American Society of Colon and Rectal Surgeons publish management guidelines for Crohn's disease.[14,20-22] The treatment guidelines point to controversial areas in need of future research, including: treatments to achieve long-term remission; the benefits and harms of step-up versus top-down treatment strategies; and further evidence on optimizing the use of biologic agents given that many patients' disease can be managed with traditional treatments such as aminosalicylates, antibiotics, corticosteroids, and immunomodulators. How Crohn's disease medications should be combined is a subject of ongoing controversy and investigation. Our proposal will address these aims, as well as the safety and patient-reported outcomes representing quality of life associated with treatments alone and in combination.

Previous systematic reviews. Meta-analyses have examined individual medications compared to placebo but few have compared medications directly. Numerous high-quality meta-analyses have compared aminosalicylates, antibiotics, corticosteroids, immunomodulators, and biologics to placebo (there are 43 meta-analyses for Crohn's disease medications; 18 from the Cochrane Collaboration). A recent high-quality meta-analysis of randomized control trials (RCTs) published through February 2009 examined the efficacy of treatments after surgical resection, but did not report on the quality of life effects.[23] Few meta-analyses have examined quality of life, although this parameter remains a high priority topic for patients. The central question for patients and their caregivers is the comparison of medications (both within a class

and between classes) *to each other* at relevant time points in the natural history of disease. The proposed systematic review focuses on these important questions and includes comparisons of appropriate combinations of medications for this disease with attention to the timing of treatment initiation relative to the diagnosis of Crohn's disease.

Key Questions. We aim to compare the effectiveness, safety and patient-reported outcomes representing quality of life of individual and combined therapies for Crohn's disease including aminosalicylates, corticosteroids, immunomodulators, and biologics with regards to: (1) induction of Crohn's disease remission; (2) maintenance of Crohn's disease remission; (3) adverse effects; and (4) patient-reported outcomes representing quality of life after surgical resection.

Nomination history. This topic was nominated via AHRQ's website by a lay person with Crohn's disease who was frustrated by the lack of consensus among physicians about her treatment options after surgical resection. Her experience reflects the general lack of consensus about pharmacologic therapies for the management of Crohn's disease. In particular, our literature search revealed a lack of recent evidence-based guidelines on the management of Crohn's disease. Because of the recent high quality meta-analysis focused on treatment options after surgical resection, our key questions aim to compare treatment options at all points in the natural history of disease. We also aim to review the effects on patient quality of life as measured by patient-reported outcomes that have often been overlooked in the comparison of medications.

Expected use of report. The results of the proposed report will be of use to patients and their caregivers. Because the proposed systematic review aims to address controversial clinical issues identified by practice guidelines, we feel that the results of the report will be useful. The results will help provide an evidence base for future practice guidelines to influence patient management. The patient-reported outcomes will also help patients and caregivers to take into consideration the implications to the patient's daily life, not just the effectiveness of the treatment in clinical terms, when prescribing a medication.

Objectives

We aim to compare the effectiveness, safety and patient-reported measures of individual and combined therapies for Crohn's disease including aminosalicylates, corticosteroids, immunomodulators, and biologics with regards to: (1) induction of Crohn's disease remission; (2) maintenance of Crohn's disease remission; (3) adverse effects; and (4) patient-reported measures after surgical resection.

II. The Key Questions (KQ)

KQ1: What is the comparative effectiveness of therapies alone or in combination used to induce remission in adults and children with moderate-to-severe Crohn's disease?

KQ2: What is the comparative effectiveness of therapies alone or in combination used to maintain remission in adults and children with moderate-to-severe Crohn's disease?

KQ3: What is the comparative safety of therapies alone or in combination used in adults and children with moderate-to-severe Crohn's disease in terms of minimizing short- and long-term adverse effects?

KQ4: What is the comparative effectiveness of agents used to prevent post-operative recurrence in Crohn's disease as pertains to patient-reported outcomes?

Population

- For KQ1-2, the population is non-pregnant adults and children with moderate-to-severe Crohn's disease. Adults and children will be analyzed separately. A sensitivity analysis will include study populations with all levels of disease severity.
- For KQ3, the population is non-pregnant adults and children with moderate-to-severe Crohn's disease. Adults and children will be analyzed separately. Because we are looking for a safety signal and some studies may not have stratified their results by disease severity or type of inflammatory bowel disease, sensitivity analyses will include study populations with all levels of disease severity and study populations with inflammatory bowel disease not stratified by Crohn's disease and ulcerative colitis status.
- For KQ4, the population is non-pregnant adults and children with moderate-to-severe Crohn's disease who experienced at least one intestinal resection related to their disease. Adults and children will be analyzed separately. A sensitivity analysis will include study populations with all levels of disease severity.
- To the extent that we can, we will collect and analyze data by various subgroups, including disease location, disease behavior (inflammatory, stricturing or penetrating), duration of Crohn's disease, previous therapy, previous hospitalizations or surgeries and serologic biomarkers (e.g., C-reactive protein, a marker of inflammation).

Interventions

- The interventions in Table 1, either alone or in combination, will be included for KQ1-4. We plan to include studies that allow participants to be on concomitant medications (e.g., antibiotics).
- Dose, dose escalation, frequency and mode of administration and medication adherence/compliance information will be collected.

Comparators

- For KQ1-4, we will include head-to-head inter-class and intra-class comparisons in addition to comparisons made directly to placebo.

Outcomes

- For KQ1 and KQ2, induction and maintenance of remission will be measured in terms of response and remission (using the Crohn's Disease Activity Index [CDAI], the Pediatric Crohn's Disease Activity Index [PCDAI] or Harvey-Bradshaw index [HBI]), mucosal healing (i.e., Crohn's disease endoscopic index of severity [CDEIS], Simple Endoscopic Score for Crohn's disease [SES-CD], absence of ulcers), hospitalizations, surgeries, reduction of corticosteroids, and fistula response (i.e., complete closure, partial closure, and perianal disease activity index [PDAI]). For children, we will also measure growth. Patient-reported outcomes by remission and medication status will be measured by standard quality of life indices and specialty indices (Inflammatory Bowel Disease Questionnaire [IBD-Q], Short Inflammatory Bowel Disease Questionnaire [SIBDQ]) and will include other patient-reported outcomes such as days of work or school missed.
- For KQ3, harms of interest include mortality, lymphomas and other cancers, infections, infusion and injection-site reactions, bone fractures and other adverse events.

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- For KQ4, the outcome of interest is patient-reported outcomes measured with the same quality of life indices for KQ1 and KQ2, including days of work or school missed.

Timing

- Studies with all durations of follow-up will be included. Follow-up duration will be considered in the analyses.
- Because medications have different times to clinical response, we will consider these times in the analyses.

Setting

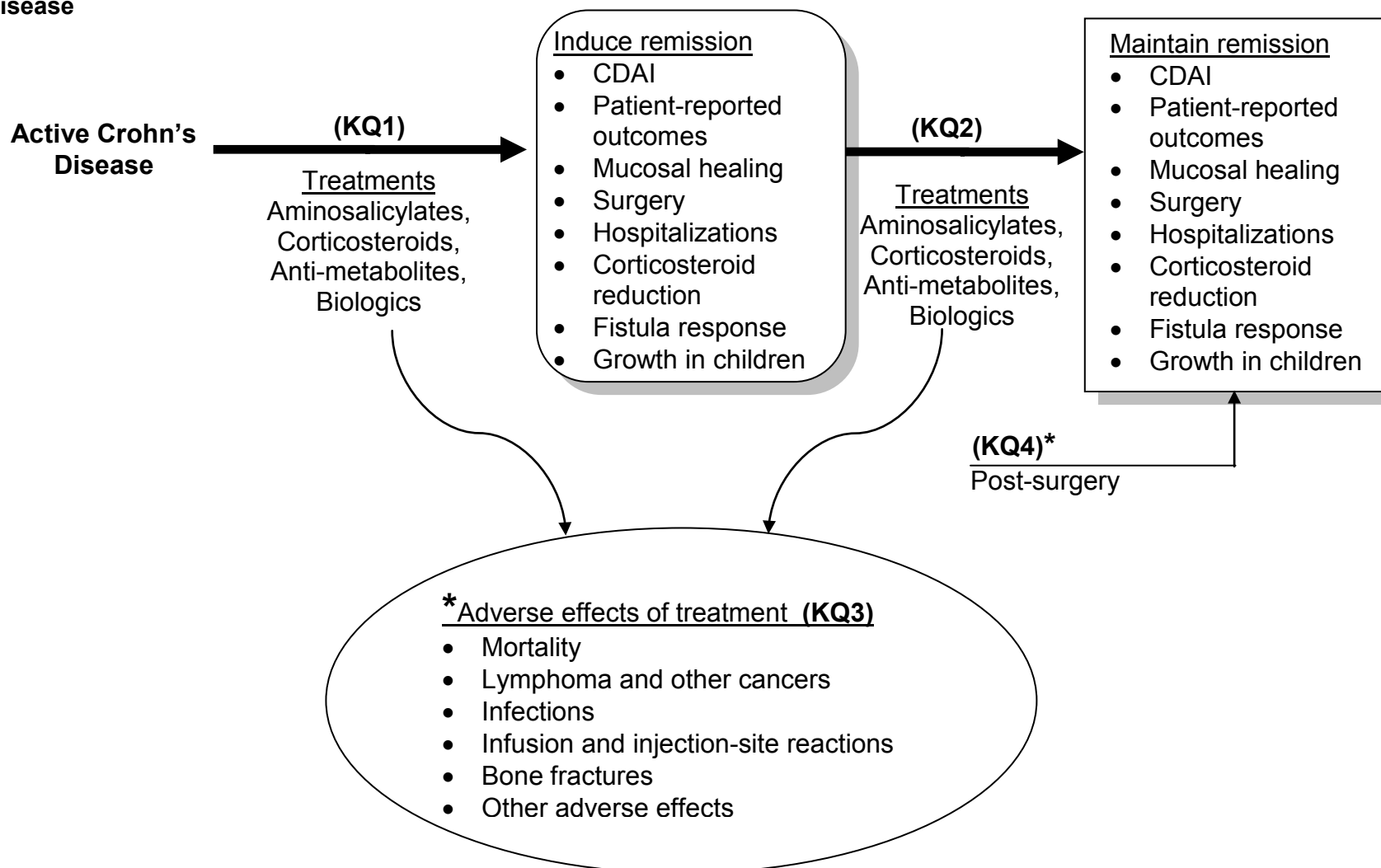- All study settings will be considered for inclusion.

Summary of Revisions to Key Questions

Based on the public comments, we made the following revisions to the Key Questions and protocol:

1) We have edited the Key Questions to be more explicit about the outcomes we are considering for this review.
2) For our population of interest, we have added a statement that we will analyze adults and children separately.
3) To address the question about serial therapy versus initial combination therapy, we will collect data regarding prior therapy and will consider analyzing those with and without prior therapy separately. We have added a statement describing this in our population of interest.
4) We specified in our population of interest that we will collect data on subgroups.
5) For our intervention of interest, we have added a statement that we will not exclude studies that allow participants to take antibiotics.
6) We will expand our quality of life measures to include other patient-reported outcomes that could reflect quality of life including days of work or school missed.
7) We will collect information on medication dose, dose escalation, frequency and mode of administration and medication adherence/compliance information.
8) We will take into account timing of clinical response in our comparisons as some medications do not have an immediate onset of action.
9) Because safety is an important issue and safety information may not always be reported by disease severity status or even by type of inflammatory bowel disease, we will perform sensitivity analyses for KQ3 including all levels of Crohn's disease severity and inflammatory bowel disease not specified. These sensitivity analyses will be compared to our analyses of moderate-to-severe Crohn's disease.
10) To frame KQ4, we will include a summary in our report of the previous Cochrane meta-analysis that addressed KQ1-3 for post-resection Crohn's. KQ4 will focus on patient-reported outcomes, including quality of life and days of work or school missed.
11) We will address our exclusion of pregnant women and non-pharmacologic therapies in our report. We feel that including these groups would greatly increase the already large workload. Because special situations apply to pregnant women and non-pharmacologic therapies, these topics should be considered for future reports of this kind.

III. Analytic Framework

Figure 1. Provisional analytic framework for pharmacologic therapies for the management of moderate to severe Crohn's Disease

Active Crohn's Disease

(KQ1)

Treatments
Aminosalicylates,
Corticosteroids,
Anti-metabolites,
Biologics

Induce remission
- CDAI
- Patient-reported outcomes
- Mucosal healing
- Surgery
- Hospitalizations
- Corticosteroid reduction
- Fistula response
- Growth in children

(KQ2)

Treatments
Aminosalicylates,
Corticosteroids,
Anti-metabolites,
Biologics

Maintain remission
- CDAI
- Patient-reported outcomes
- Mucosal healing
- Surgery
- Hospitalizations
- Corticosteroid reduction
- Fistula response
- Growth in children

(KQ4)*
Post-surgery

***Adverse effects of treatment (KQ3)**
- Mortality
- Lymphoma and other cancers
- Infections
- Infusion and injection-site reactions
- Bone fractures
- Other adverse effects

*For KQ4, the only examined endpoint will be patient-reported outcomes.

CDAI = Crohn's Disease Activity Index; KQ = Key Question

IV. Methods

We will conduct a systematic review of the comparative effectiveness and safety of individual and combined therapies for Crohn's disease including aminosalicylates, corticosteroids, immunomodulators, and biologics in terms of (1) induction of Crohn's disease remission, (2) maintenance of Crohn's disease remission, (3) adverse effects, and (4) patient-reported outcomes after surgical resection.

A. Criteria for Inclusion/Exclusion of Studies in the Review

Inclusion and exclusion criteria are provided in Table 2. For our study of medications to treat moderate to severe Crohn's disease, we will include randomized controlled trials (RCTs) of the medications of interest compared to each other or placebo (Table 1) for Key Questions 1 and 2, induction and maintenance of remission of Crohn's disease. For Key Questions 3 and 4 we will include RCTs in addition to non-randomized studies with at least two medication exposure groups (including placebo). For Key Question 3 about adverse effects of medications, because of the rarity and severity of hepatosplenic T-cell lymphoma and progressive multifocal leukoencephalopathy, we will include all study types (including case reports) for these outcomes.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions.

We will search the following databases for primary studies: MEDLINE®, EMBASE®, and the Cochrane Central Register of Controlled Trials. We will develop a search strategy for MEDLINE, accessed via PubMed, based on an analysis of the medical subject headings (MeSH) terms and text words of key articles identified a priori.

In addition, we will review the Scientific Information Packets provided by the pharmaceutical manufacturers. We will also review the reference lists of each included article, relevant review articles and related systematic reviews. We will also explore the use pharmaceutical medication registries.

Our search strategy for MEDLINE is:

("Crohn Disease"[mh] OR "Crohn's Disease"[tiab] OR "Crohn Disease"[tiab] OR "Crohns Disease"[tiab] OR (Crohn*[tiab] AND (ileitis[tiab] OR enteritis[tiab] OR ileocolitis[tiab] OR colitis[tiab])) OR "inflammatory bowel diseases"[mh] OR "inflammatory bowel disease"[tiab] OR "inflammatory bowel diseases"[tiab] OR IBD[tiab]) AND ("Aminosalicylic acids"[mh] OR "Anti-inflammatory agents, non-steroidal"[mh] OR mesalamine[mh] OR sulfasalazine[mh] OR "5-aminosalicylic acid"[tiab] OR "5-aminosalicylic acids"[tiab] OR "5-aminosalicylate"[tiab] OR "5-aminosalicylates"[tiab] OR "5-ASA"[tiab] OR aminosalicyl*[tiab] OR mesalamine*[tiab] OR mesalazine*[tiab] OR sulfasalazine*[tiab] OR sulphasalazine*[tiab] OR balsalazide[tiab] OR olsalazine[tiab] OR "immunosuppressive agents"[mh] OR azathioprine[mh] OR methotrexate[mh] OR "6-mercaptopurine"[mh] OR immunosuppression[tiab] OR immunosuppressive[tiab] OR immunosuppressives[tiab] OR immunomodulator*[tiab] OR immunomodulating[tiab] OR "anti-metabolite"[tiab] OR "anti-metabolites"[tiab] OR antimetabolit*[tiab] OR azathioprine[tiab] OR methotrexate[tiab] OR "6-mercaptopurine"[tiab] OR "antibodies, monoclonal/therapeutic use"[mh] OR "antibodies, monoclonal/administration and dosage"[mh] OR "antibodies, monoclonal/adverse effects"[mh] OR "anti-inflammatory agents"[mh] OR (("tumour necrosis factor"[tiab] OR "tumour necrosis factor-alpha"[tiab] OR "tumor necrosis factor"[tiab] OR "tumor necrosis factor-alpha"[tiab] OR TNF[tiab] OR TNF-alpha[tiab]) AND (antibod*[tiab] OR antagonist[tiab] OR antagonists[tiab] OR inhibitor*[tiab])

AND (agent*[tiab] OR treatment*[tiab] OR treated[tiab] OR therap*[tiab] OR drug[tiab] OR drugs[tiab] OR medication*[tiab])) OR "anti-tumour necrosis"[tiab] OR "anti-tumor necrosis"[tiab] OR anti-TNF*[tiab] OR biologic[tiab] OR biologics[tiab] OR adalimumab[tiab] OR infliximab[tiab] OR certolizumab[tiab] OR natalizumab[tiab] OR ustekinumab[tiab] OR budesonide[mh] OR glucocorticoids[mh] OR hydrocortisone[mh] OR methylprednisolone[mh] OR prednisolone[mh] OR prednisone[mh] OR "6-methylprednisolone"[tiab] OR budesonide[tiab] OR corticosteroid*[tiab] OR glucocorticosteroid*[tiab] OR prednisolone[tiab] OR prednisone[tiab]) NOT (animal[mh] NOT human [mh]) NOT (comment[pt] or editorial[pt]).

C. Data Abstraction and Data Management

Two independent reviewers will conduct title scans. For a title to be eliminated at this level, both reviewers will need to indicate that the study was ineligible. If the reviewers disagree, the article will be advanced to the next level, abstract review.

The abstract review phase was designed to identify studies reporting the effects of Crohn's disease medications on clinical outcomes, adverse events, and patient-reported outcomes. Abstracts will be reviewed independently by two investigators, and will be excluded if both investigators agree that the article meets one or more of the exclusion criteria (see inclusion and exclusion criteria listed in Table 2). Differences between investigators regarding abstract inclusion or exclusion will be tracked and resolved through consensus adjudication.

Articles promoted on the basis of abstract review will undergo another independent parallel review to determine if they should be included in the final qualitative and quantitative systematic review and meta-analysis. The differences regarding article inclusion will be tracked and resolved through consensus adjudication.

We will use a systematic approach for extracting data to minimize the risk of bias in this process. We will create standardized forms for data extraction, which will be pilot tested. By creating standardized forms for data extraction, we sought to maximize consistency in identifying all pertinent data available for synthesis.

Each article will undergo double review by study investigators for data abstraction. The second reviewer will confirm the first reviewer's data abstraction for completeness and accuracy. Reviewer pairs will be formed to include personnel with both clinical and methodological expertise. A third reviewer will audit a random sample of articles by the first two reviewers to ensure consistency in the data abstraction of the articles. Reviewers will not be masked to the articles' authors, institution, or journal.
For all articles, reviewers will extract information on general study characteristics (e.g., study design, study period, and followup), study participants (e.g., age, gender, race, duration of Crohn's disease, smoking status, disease severity, and disease location), eligibility criteria, interventions (e.g., route of administration and dosing), outcome measures and the method of ascertainment, and the results of each outcome, including measures of variability.

All information from the article review process will be entered into the DistillerSR database by the individual completing the review. Reviewers will enter comments into the system whenever applicable. The DistillerSR database will be used to maintain the data, as well as to create detailed evidence tables and summary tables.

D. Assessment of Methodological Quality of Individual Studies

Article quality will be assessed differently for RCTs and observational studies during the final qualitative and quantitative review. For RCTs, the dual, independent review of article quality will be based on the Cochrane Collaboration's Risk of Bias Tool.[24] For non-randomized observational studies, we will use the Newcastle Ottawa Scale.[25] Additionally, we plan to use

selected items from the McHarm Tool for assessing adverse events.[26] We will supplement these tools with additional quality assessment questions based on recommendations in the Guide for Conducting Comparative Effectiveness Reviews.[27] For both the RCTs and the non-randomized studies, the overall study quality will be assessed as:

- **Good (low risk of bias).** These studies had the least bias, and the results were considered valid. These studies adhered to the commonly held concepts of high quality, including the following: a clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
- **Fair.** These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.
- **Poor (high risk of bias).** These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

E. Data Synthesis

We will conduct meta-analyses when there are sufficient data (at least 3 studies) and studies are sufficiently homogenous with respect to key variables (population characteristics, study duration, and drug dose). We will then use these meta-analyses to conduct a network (also called mixed effects) meta-analysis (NMA).

We will attempt to conduct NMA to compare relative effects of different drug classes and of different agents within a drug class. We will not perform one comprehensive NMA considering each single agent because we consider such a treatment network to be too broad and at risk for considerable inconsistency. For all NMA we will conduct the following steps:

The first step in conducting the network meta-analysis is the creation of a network graph. For each outcome and treatment network (i.e. inter-class and within-class comparisons), we will construct a network graph that shows direct and indirect comparisons of the different interventions. Network graphs allow identifying all paths that contribute to the indirect comparisons and calculation of their effects estimates. This analysis will also generate the point estimates and measure of heterogeneity for each direct comparison and, thereby, allows a first appreciation of differences between direct and indirect evidence (known as inconsistency). This initial step for looking at inconsistency will, together with subsequent analyses, inform the decision whether a network meta-analysis should be conducted.

We will conduct a NMA following a Bayesian approach. We will estimate treatment effects relative to the reference treatment (basic parameters, i.e. comparisons with placebo) and derive comparisons between treatments regimens from the differences between basic parameters (functional parameters). The absolute effect (or efficacy) for each treatment will be estimated by adding the treatment specific effect (basic parameters) to the average effect of the overall baseline treatment effect. We will assume a normal likelihood and study effects (basic parameters) are treated as unrelated nuisance parameters with non-informative priors. We will analyze the data assuming both homogeneous variance and heterogeneous variance. If there is no evidence of inconsistency (i.e. if treatment effects derived from direct comparisons are consistent with those from indirect comparisons), we will assume a reference treatment group (e.g. placebo) as the overall baseline for every other treatment regimen. To assess

inconsistency, we will provide direct and indirect estimates for each comparison and compare them. To determine whether there is important inconsistency we will test differences between direct and indirect estimates not only statistically but also determine if they differ to a clinically important extent. For each outcome, a minimal important difference threshold will be set prior to performing the analysis. If the inconsistency exceeds this minimal important difference threshold we will investigate reasons for inconsistency that may include differences in patients, treatments, control interventions and outcome definitions across trials. If we identify such variables explaining inconsistency we will stratify the analyses accordingly. If we do not identify reasons for inconsistency we may decide not to conduct a NMA for the particular outcome. As statistical approaches to inconsistency, we will calculate global model fit statistics using the deviance information criterion and an inconsistency p value proposed by Lu et al.[28] We will use WinBUGS 1.4.3 (http://www.mrc-bsu.cam.ac.uk/bugs/) for these analyses.

F. Grading the Evidence for Each Key Question

At the completion of our review, we will grade the quantity, quality and consistency of the best available evidence addressing Key Questions 1 – 4 by adapting an evidence grading scheme recommended by the Guide for Conducting Comparative Effectiveness Reviews.[27] We will apply evidence grades to the bodies of evidence about each intervention comparison for each outcome. We will assess the strength of the study designs according to those which best control confounding, selection and information bias. We will assess the quality and consistency of the best available evidence, including assessment of limitations to individual study quality (using individual quality scores), consistency, directness, precision, and the magnitude of the effect.

We will classify evidence pertaining to Key Questions 1 – 4 into four basic categories: (1) "high" grade (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of the effect); (2) "moderate" grade (indicating moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of the effect and may change the estimate); (3) "low" grade (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and (4) "insufficient" grade (evidence is unavailable).

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VI. Definition of Terms

CD = Crohn's disease
CDAI = Crohn's disease activity index
FDA = Food and Drug Administration
IBD-Q = Inflammatory bowel disease questionnaire
KQ = Key question
NMA = network meta-analysis
RCT = randomized control trial
TNF = tumor necrosis factor
US = United States

NOTE: The following protocol elements are standard procedures for all protocols.

VIII. Review of Key Questions

For Comparative Effectiveness reviews (CERs) the key questions were posted for public comment and finalized after review of the comments. For other systematic reviews, key questions submitted by partners are reviewed and refined as needed by the EPC and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed.

IX. Technical Expert Panel (TEP)

A TEP panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. The TEP provides information to the EPC to identify literature search strategies, review the draft report and recommend approaches to specific issues as requested by the EPC. The TEP does not do analysis of any kind nor contribute to the writing of the report.

X. Peer Review

Approximately five experts in the field will be asked to peer review the draft report and provide comments. The peer reviewer may represent stakeholder groups such as professional or advocacy organizations with knowledge of the topic. On some specific reports such as reports requested by the Office of Medical Applications of Research, National Institutes of Health there may be other rules that apply regarding participation in the peer review process. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

It is our policy not to release the names of the Peer reviewers or TEP panel members until the report is published so that they can maintain their objectivity during the review process.

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Table 1. List of Disease-Modifying Drugs

Class	Generic name	US trade name	Route	Half-life	Mechanism of Action	FDA approved for CD in adults	FDA approved for CD in children
Aminosalicylate	Sulfasalazine	Azulfidine	Oral	5-10 hours	Unknown	No	No
Aminosalicylate	Mesalamine	Asacol, Canasa, Pentasa, Lialda, Rowasa	Oral, rectal	2-15 hours	Inhibits reactions involving inosinic acid	No	No
Anti-metabolite	Azathioprine	Azasan; Imuran	Oral, intravenous	5- hours	Purine synthesis Inhibitor	No	No
Anti-metabolite	Methotrexate	Methotrexate LPF	Intravenous, oral	3-15 hours	Works through adenosine receptor	No	No
Anti-metabolite	6-mercaptopurine	Purinethol	Oral	1-2 hours	Purine synthesis and metabolism Inhibitor	No	No
Biologic	Adalimumab	Humira	Subcutaneous	10-18 days	TNF inhibitor	Yes	No
Biologic	Infliximab	Remicade	Intravenous	9.8 days	TNF inhibitor	Yes	Yes
Biologic	Certolizumab Pegol	Cimzia	Subcutaneous	~14 days	TNF inhibitor	Yes	No
Biologic	Natalizumab	Tysabri	Intravenous	7-15 days	Prevents attachment of inflammatory immune cells to intestinal cell layers.	Yes	No
Biologic	Ustekinumab	Stelara	Subcutaneous	15-46 days	Interleukin-12 and interleukin-23 inhibitor	No	No
Corticosteroid	Prednisone Prednisolone 6-methylpredisolone Hydrocortisone Budesonide	All trade names	Oral, topical, intravenous	8-54 hours	Binds glucocorticoid receptors in cytoplasm where it upregulates anti-inflammatory genes	No	No

CD = Crohn's disease; FDA = Food and Drug Administration; TNF = tumor necrosis factor; US = United States

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Table 2. Inclusion and exclusion criteria

Population and condition of interest	☐ All studies will include human subjects exclusively.
	☐ We will include studies of patients of all ages who have moderate to severe Crohn's disease.
	☐ We will exclude studies if they included only pregnant women.
	☐ Sensitivity analyses for all Key Questions will include all levels of disease severity. Sensitivity analysis for KQ3 will include inflammatory bowel disease not specified.
Interventions	☐ All studies must have evaluated a Crohn's disease medication of interest (see Table 1) or combination of medications of interest compared to each other or to placebo.
Comparisons of interest	☐ For all but two outcomes, we will exclude all studies that do not have a comparison group, where the comparison is either a medication or combination of medications of interest or placebo. We will exclude studies that compared a medication of interest to a medication not of interest (such as antibiotics or fish oil supplements).
	☐ For two outcomes will include all levels of evidence (including case reports). All levels of evidence will be included for hepatosplenic T-cell lymphoma and progressive multifocal leukoencephalopathy because they are very rare and frequently fatal.
Outcomes	☐ We will exclude studies that do not apply to the key questions.
	☐ For Key Questions 1 and 2, induction and maintenance of remission, we will include the following outcomes: Crohn's disease activity index (CDAI), patient-reported outcomes representing quality of life, mucosal healing, surgery, hospitalizations, corticosteroid reduction, fistula response and growth in children.
	☐ For Key Question 3, harms of medication, we will include mortality, lymphomas and other cancers, infections, infusion and injection-site reactions, bone fractures and other adverse events.
	☐ For Key Question 4, patient-reported outcomes after intestinal resection, standard quality of life indices and specialty indices (IBD-Q) will be used in addition to patient-reported outcomes such as days of work or school missed.
Type of study	☐ We will exclude articles not written in English and articles with no original data (reviews, editorials, comments, letters). We will also exclude abstracts.
	☐ We will include studies with any sample size from any year that meet all other criteria.
	☐ For Key Questions 1 and 2, we will include only RCTs.
	☐ For Key Questions 3 and 4, we will include RCTs, non-RCTs, cohort studies with a comparison group, crossover studies and case-control studies. Because of the rarity and severity of hepatosplenic T-cell lymphoma and progressive multifocal leukoencephalopathy, we will include all study types (including case reports) for these outcomes.

RCT = randomized controlled trial