Effective Health Care Program

Future Research Needs Paper
Number 26

Pharmacological Management of Crohn's Disease: Future Research Needs

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Pharmacological Management of Crohn's Disease: Future Research Needs

Identification of Future Research Needs From Comparative Effectiveness Review No. 131

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Agency for Healthcare Research and Quality
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Prepared by:
Johns Hopkins University Evidence-based Practice Center
Baltimore, MD

Investigators:
Susan Hutfless, Ph.D.
Brandyn D. Lau, M.P.H., C.P.H.
Lisa M. Wilson, Sc.M.
Mark Lazarev, M.D.
Eric B. Bass, M.D., M.P.H.

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The information in this report is intended to help health care researchers and funders of research make well-informed decisions in designing and funding research and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of scientific judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical research and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances.

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None of the investigators have any affiliation or financial involvement that conflicts with the material presented in this report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

An important part of evidence reports is to not only synthesize the evidence, but also to identify the gaps in evidence that limited the ability to answer the systematic review questions. AHRQ supports EPCs to work with various stakeholders to identify and prioritize the future research that is needed by decisionmakers. This information is provided for researchers and funders of research in these Future Research Needs papers. These papers are made available for public comment and use and may be revised.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality. The evidence reports undergo public comment prior to their release as a final report.

We welcome comments on this Future Research Needs document. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

Richard G. Kronick, Ph.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director, EPC Program
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Christine Chang, M.D., M.P.H.
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

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Contributors

Melvin Heyman, M.D.
University of California, San Francisco
School of Medicine
San Francisco, CA

Sunanda V. Kane, M.D.
Mayo Clinic
Rochester, MN

Miguel Regueiro, M.D.
University of Pittsburgh School of Medicine
Pittsburgh, PA

David T. Rubin, M.D.
University of Chicago School of Medicine
Chicago, IL

Logan R. Thornton, M.P.H.
Patient Stakeholder

Thomas Ullman, M.D.
Mt. Sinai Hospital
New York, NY

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Executive Summary

Background

Crohn's disease is characterized by chronic inflammation that can occur anywhere in the gastrointestinal tract, but most often affects the small bowel and colon. Typical symptoms include abdominal pain, chronic diarrhea, and gastrointestinal bleeding. Crohn's disease affects between 400,000 and 600,000 North Americans.[1] Ten percent of Crohn's disease patients are children under the age of 17 years.[2]

The clinical management of Crohn's disease is complicated. Practice guidelines for Crohn's disease recommend that clinicians take into account the disease location, severity, complications, and extra-intestinal manifestations when choosing a treatment strategy. However, no universal treatment strategy exists.[3] The lack of consensus about the best treatment strategy can result in confusion and frustration for the Crohn's disease patient as well as practitioners who treat Crohn's disease patients.

Medications are the preferred treatment for Crohn's disease with surgical interventions reserved for complications of disease or evidence of dysplasia. Medical therapy in Crohn's disease targets intestinal inflammation with the intent of altering the natural history of the disease. Corticosteroids and aminosalicylates such as sulfasalazine have been used since the 1950s. Immunomodulators (6-mercaptopurine, azathioprine, and methotrexate) have been used for the treatment of Crohn's disease since the 1970s, although use of these medications was not routine until the 1990s.[4] The first biologic tumor necrosis factor (TNF)-alpha inhibitor, infliximab, was approved by the Food and Drug Administration (FDA) for the treatment of Crohn's disease in adults in 1998. The FDA-approved monoclonal antibodies against TNF-alpha inhibitor also include adalimumab and certolizumab pegol.[5] Another biologic agents used for the treatment of Crohn's disease include natalizumab, a monoclonal antibody against cellular adhesion molecule α4-integrin that is FDA-approved for Crohn's disease in adults.[5]

Our recent systematic review addressed several Key Questions in the management of Crohn's disease (see Table A). In that review, we identified several important gaps in the evidence, as shown in the analytic framework depicted in Figure A.[6] We used the population, intervention, comparison, outcome, timing, setting (PICOTS) framework to identify gaps from the evidence in relationship to the populations, interventions, comparisons, outcomes, timing, and settings relevant to treatments for Crohn's disease. Several gaps related to the target population (children, non-white, and risk stratification based on patient characteristics). Other gaps related to interventions and comparisons of interest (step up versus top down treatment and head to head comparisons within and between treatment classes), outcomes of interest (mucosal healing, and patient-reported symptoms), or a timing issue (remission beyond 2 years). The objective of this report is to identify and prioritize existing gaps in the synthesized literature pertaining to pharmacological induction and maintenance of remission for patients with Crohn's disease by engaging stakeholders using a modified Delphi method.

Methods

Stakeholder Identification

We solicited recommendations from the American College of Gastroenterology (ACG), the American Gastroenterological Association (AGA), and the Crohn's and Colitis Foundation of America (CCFA) for expert stakeholders representative of clinicians, researchers, private and federal agencies, and patients. Five academic physicians in the field of gastroenterology with a research interest in Crohn's disease management agreed to participate. We also included a patient who had served as a stakeholder for the original comparative effectiveness review. No stakeholder associated with a federal agency agreed to participate.

Stakeholder Engagement

Overview

We used a modified Delphi method to identify and prioritize existing gaps in the published literature on the pharmacologic management of Crohn's disease. The process had seven steps across four phases (Figure B). The Delphi method involved iterative rounds of responses by group members, providing aggregated feedback about all members' responses until consensus is reached. For each round, we used a Web-based assessment tool (SurveyMonkey™, Palo Alto, CA) that presented the list of the research gaps originally proposed by the authors based on the findings of the evidence review. Consensus among stakeholders was defined as agreement in responses of 50 percent or higher in three or more options for each category of research gaps. Gaps that did not achieve 50 percent or greater consensus among the stakeholders on three or more options were returned to the stakeholders, with their compiled feedback to reprioritize. Gaps achieving 50 percent or greater consensus in the following round were used to formulate specific research questions.

Phase 1: Identification of Research Gaps

We used the analytic framework (Figure A) to identify potential populations, medication comparisons, and outcomes gaps from the comparative effectiveness review. A Web-based assessment tool was populated with the identified research gaps specific to the induction of remission and, separately, the maintenance of remission. We queried the stakeholders on nine potential populations for whom future research may be a priority (Table B). We also asked the stakeholders about 13 medication comparisons (Table C) and 12 disease-related outcomes (Table D) that could be priorities for future research. For each question about prioritizing research gaps, optional free-text fields were provided for stakeholders to propose their own options.

Phase 2: Prioritization of Research Gaps

The stakeholders were given a copy of the executive summary of the evidence review and were asked to independently identify the three highest priority populations, medication comparisons, and outcomes for future research for both induction of remission and maintenance of remission using the Web-based system.

Phase 3: Consensus Building

Responses from the completed feedback forms were compiled and analyzed for agreement. Categories that did not achieve consensus as defined above on three or more options were sent back to the stakeholders in a revised form of the original Web-based assessment tool with the complied responses from the previous round in an attempt to build consensus.

Phase 4: Research Question Development

Research questions were developed based on feedback from stakeholders that achieved consensus during the second and third rounds. The stakeholders were presented with their compiled feedback from the second and third phases along with the research questions developed. They were asked to provide feedback on the clarity, utility, study design feasibility, ongoing studies addressing the questions, and priority of the research questions.

Identification of Ongoing Research

Clinical research repositories and research-related sites including ClinicalTrials.gov, NIH Reporter, the Canadian Institutes of Health Research, the World Health Organization Clinical Trials Registry, and the European Union Clinical Trials Register were searched to identify ongoing or recently completed studies related to the pharmacological management of Crohn's disease. Appendix Table A-1 details the search strategies used for each repository.

Results

The stakeholders' responses about the gaps in evidence concerning populations, medication comparisons, and outcomes varied for the induction of remission and the maintenance of remission of Crohn's disease. Therefore, results from the stakeholder prioritization are presented first as future research needs for the induction of remission and then for the maintenance of remission.

Induction of Remission

All stakeholders (100%) prioritized children as an important population for future research, while half of the stakeholders prioritized patients with severe disease and non-responders to biologics as important populations for future research (Table B). Among medication comparisons for induction of remission, only one medication comparison (One TNF-alpha inhibitor versus Another TNF-alpha inhibitor) achieved consensus among the stakeholders with 60 percent agreement during the first round of assessment. One stakeholder did not choose any of the proposed options and independently identified three medication comparisons using the free text option; however, no additional stakeholders rated these selections as a priority for future research.

In phase 3, all stakeholders (100%) prioritized one medication comparison (one TNF-alpha inhibitor versus another TNF-alpha inhibitor) as particularly important for future research, and half identified another medication comparison (a TNF-alpha inhibitor versus natalizumab) as important for future research on the induction of remission in Crohn's disease. Consensus was not achieved for other medication comparisons (Table C).

Maintenance of Remission

All stakeholders prioritized children as an important population for future research on the maintenance of Crohn's disease remission. Fifty percent of stakeholders agreed that non-responders to biologics, and patients with complications are important populations to study in future research (Table D).

Among medication comparisons for maintenance of remission, two medication comparisons, with variation only in the single-medication control arm (TNF-alpha inhibitor and thiopurine versus thiopurine only or TNF-alpha inhibitor only), achieved consensus during the first round (Table E). Compiled stakeholder responses regarding medication comparisons from the first consensus round were sent to the stakeholders with a request to evaluate and again prioritize the medication comparisons. During the second round, four stakeholders (60%) identified one medication comparison (TNF-alpha inhibitor and thiopurine versus TNF-alpha inhibitor) as a top priority for future research, while three stakeholders (50%) identified a previously low-ranked medication comparison (one TNF-alpha inhibitor versus another TNF-alpha inhibitor) as a top priority for future research on the induction of remission in Crohn's disease. The medication comparison originally agreed upon by 50 percent of stakeholders during the first round failed to achieve consensus during the second round, and was not included in our final list of research questions (Table E).

Final Prioritized Research Questions

Based on stakeholder feedback regarding populations, intervention comparisons, and outcomes, the following research questions were developed and prioritized by our stakeholders. They are listed in order from most to least important as ranked by the stakeholders:

1. For maintenance of remission in adults and children diagnosed with Crohn's disease, what is the comparative effectiveness of a TNF-alpha inhibitor and thiopurine versus a TNF-alpha inhibitor for the outcomes of steroid reduction, patient reported outcomes, Crohn's Disease Activity Index (CDAI), pediatric CDAI and mucosal healing?
2. For induction of remission in adults and children diagnosed with Crohn's disease, what is the comparative effectiveness of one TNF-alpha inhibitor versus another TNF-alpha inhibitor for the outcomes of mucosal healing, patient reported outcomes, steroid reduction, CDAI and pediatric CDAI?
3. For induction of remission in adults and children diagnosed with Crohn's disease, what is the comparative effectiveness of a TNF-alpha inhibitor versus natalizumab for the outcomes of mucosal healing, patient reported outcomes, steroid reduction, CDAI and pediatric CDAI?
4. For maintenance of remission in adults and children diagnosed with Crohn's disease, what is the comparative effectiveness of one TNF-alpha inhibitor versus another TNF-alpha inhibitor for the outcomes of steroid reduction, patient reported outcomes, CDAI, pediatric CDAI and mucosal healing?

For each of these research questions, the strongest and most appropriate study design is a randomized controlled trial with sufficient duration of follow-up to obtain reasonably precise estimates of the comparative effects on the outcomes of interest. Although studies of the induction of remission in Crohn's disease tend to have a shorter timeframe than studies of the maintenance of remission, even studies of remission need follow-up long enough to provide reliable estimates of the effects on the outcomes that matter most to patients, and clearly long-term remission is important to patients. Thus, long-term follow-up for at least 1 year and preferably for up to 5 years would be extremely valuable, especially for children who are at risk of having adverse effects on growth and development. Future randomized controlled trials that examine these questions about the treatment of Crohn's disease should give careful attention to the problems we found in our systematic review of previously published studies, including: (1) under-representation of non-white, pediatric, and newly diagnosed patients; (2) insufficient sample size to determine whether there are clinically important differences in adverse effects of medications; and (3) inconsistent attention to outcomes beyond measures of disease activity. Due to the difficulty and expense of performing large randomized controlled trials on the comparative effectiveness of medications that have already been approved for use by the Food and Drug Administration, observational studies will have a role to play in future research. However, observational studies of comparative effectiveness will need to incorporate sophisticated risk adjustment methods to account for the many different ways in which patients vary when they initiate treatment for Crohn's disease. In this regard, it would be helpful to distinguish between patients with moderate-to-severe disease and those with mild disease. Long-term follow-up also will be extremely important to capture adverse events that may not be manifest for years after the initiation of treatment.

Identification of Ongoing Research

We searched clinical research repositories and research-related sites including ClinicalTrials.gov, NIH Reporter, the Canadian Institutes of Health Research, the World Health Organization Clinical Trials Registry, and the European Union Clinical Trials Register to identify ongoing/recently completed studies related to the pharmacological management of Crohn's disease. Six potentially relevant studies were identified (Appendix Table A-2).

Discussion

All stakeholders indicated that future research was needed for the induction of remission using monotherapy of one TNF-alpha inhibitor against another TNF-alpha inhibitor. Equally so, this intervention was given second highest priority by the stakeholders among the research questions developed. Our stakeholders identified head-to-head comparison of combination therapy of TNF-alpha inhibitors and thiopurine against monotherapy of a TNF-alpha inhibitor for the maintenance of remission in Crohn's disease as a high priority for future research. Based on stakeholder feedback, it is clear that combination therapy consisting of a TNF-alpha inhibitor and thiopurine for maintenance of remission is extremely important for future research; however, there is some ambiguity regarding the best monotherapy comparison as thiopurine achieved our criterion for consensus in the first round (50%) but failed to do so in the second round (33%). However, this monotherapy intervention was the one given highest priority by our group of stakeholders.

Children were unanimously considered a high priority for all future research in the field of Crohn's disease. It was noted by one stakeholder that when assessing outcomes for children, the Pediatric CDAI should be used. It was agreed that the outcomes of highest priority are mucosal healing, patient reported outcomes, CDAI, and steroid reduction for studies of the induction and/or maintenance of remission of Crohn's disease.

In a recent report, Cheifetz and colleagues engaged gastroenterologists to prioritize future comparative effectiveness research topics in inflammatory bowel disease.[7] The authors reported that an "anti-TNF agent alone versus anti-TNF agent with thiopurine in patients with moderate to severe Crohn's disease failing thiopurine" was their sixth highest research priority among all inflammatory bowel disease related research questions. In addition, they reported that the "efficacy and safety of long-term immunomodulation versus anti-TNF therapy in Crohn's disease…" was their eighth highest research priority. Likewise, their findings reported the need to accept mucosal healing as a primary outcome.[7] These results support our findings about high priority interventions and outcomes for future research. However, our stakeholders unanimously agreed that children are the highest priority for future research while Cheifetz identified adults as a higher priority.

The American Recovery and Reinvestment Act of 2009 outlined several research priorities specific to the treatment of Crohn's disease[8] that have been endorsed by the AGA[9] including the introduction of biologics into the treatment algorithm for inflammatory diseases, including Crohn's disease. With respect to outcomes of interest, there are still conflicting opinions within the AGA regarding the utility of mucosal healing as a primary endpoint.[10,11] Despite these recent conflicts, it is suggested from our stakeholders and other recent reports,[7, 12, 13] that mucosal healing should be considered as a primary endpoint.

There were a few limitations to our research needs identification process. The investigators on the original systematic review were actively involved in the identification of research gaps in this study which allowed for potential investigator bias, such that internal experts developed both the Key Questions for the original comparative effectiveness review and identified potential gaps in the literature reviewed. This potential bias was mitigated by allowing stakeholders to independently identify other populations, medication comparisons, or outcomes for future research using a free-text option during each consensus round. A second limitation was that the complexity of the concepts in this topic may be a barrier for some patient stakeholders to contribute. To ensure that our information was accessible to a patient stakeholder, we identified a certified health educator, who possessed the requisite clinical knowledge to provide meaningful feedback from a patient's perspective. We also found that the responses from the patient stakeholder were consistent with those from the other expert stakeholders used in other surveys.

Conclusion

Children are a high priority for future research on the induction and maintenance of remission in patients diagnosed with Crohn's disease. Stakeholders identified substantial need for further research on the use of TNF-alpha inhibitors for induction and maintenance of remission of Crohn's disease. The stakeholders also identified an important need to report outcomes of mucosal healing, patient reported outcomes, CDAI and steroid reduction when conducting induction and maintenance of remission trials for Crohn's disease.

Tables

Table A. Listing of Key Questions

KQ 1	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?
KQ 2	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?
KQ 3	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?
KQ 4	What is the comparative effectiveness of agents used to prevent post-operative recurrence in Crohn's disease as pertains to patient-reported outcomes?

KQ = Key Question

Table B. Stakeholder identification and prioritization of populations of greatest importance for future research for the induction of remission in patients diagnosed with Crohn's disease

Phase 1: Identification of Evidence Gaps	Phase 2: Number of Stakeholders Indicating Item Was One of Top 3 Priorities	Phase 3: Stakeholder Prioritization Refinement	Phase 4: Inclusion in Final Research Questions
Children	6	*	‡
Severe disease	3	*	‡
Nonresponders to biologics	3	*	‡
Patients with complications (e.g. fistulizing disease)	2	*	
Women	1	*	
Non-Whites	1	*	
Mild disease	1	*	
Elderly	0	*	
Other	1	*	

* Consensus achieved in previous round, consensus-building round (phase 3) not required.
‡ Identified as a high priority research need.

Table C. Stakeholder identification and prioritization of medication comparisons of greatest importance for future research for the induction of remission in patients diagnosed with Crohn's disease

Phase 1: Identification of Evidence Gaps	Phase 2: Number of Stakeholders Rating Item as One of Top 3 Priorities	Phase 3: Number of Stakeholders Rating Item as One of Top 3 Priorities	Phase 4: Inclusion in Final Research Questions
One TNF-alpha inhibitor versus another TNF-alpha inhibitor	4	6	‡
TNF-alpha inhibitor + methotrexate versus steroid + methotrexate	2	0	
TNF-alpha inhibitor versus TNF-alpha inhibitor + methotrexate	2	1	
TNF-alpha inhibitor versus steroid + (6-mercaptopurine or azathioprine)	2	1	
TNF-alpha inhibitor versus natalizumab	2	3	‡
TNF-alpha inhibitor + azathioprine versus TNF-alpha inhibitor + methotrexate†	1	0	
TNF-alpha inhibitor versus steroid	1	2	
TNF-alpha inhibitor + (6-mercaptopurine or azathioprine) versus steroid + (6-mercaptopurine or azathioprine)	1	1	
Steroid + (6-mercaptopurine or azathioprine) versus steroid + methotrexate	1	1	
TNF-alpha inhibitor versus (6-mercaptopurine or azathioprine)	0	0	
TNF-alpha inhibitor versus methotrexate	0	2	
TNF-alpha inhibitor versus TNF-alpha inhibitor + (6-mercaptopurine or azathioprine)	0	0	
TNF-alpha inhibitor versus steroid + methotrexate	0	0	
Other: TNF-alpha inhibitor + azathioprine versus (natalizumab or vedolizumab)†	1	0	
Other: TNF-alpha inhibitor + azathioprine versus ustakinumab†	1	0	
Other: TNF-alpha inhibitor versus new treatment (e.g. Stelara)†	0	1	

TNF = tumor necrosis factor.

† Stakeholder provided comparison.

‡ Identified as a high priority research need.

Table D. Stakeholder identification and prioritization of populations of greatest importance for future research for the maintenance of remission in patients diagnosed with Crohn's disease

Phase 1: Identification of Evidence Gaps	Phase 2: Number of Stakeholders Rating Item as One of Top 3 Priorities	Phase 3: Stakeholder Prioritization Refinement	Phase 4: Inclusion in Final Research Questions
Children	6	*	‡
Nonresponders to biologics	3	*	‡
Patients with complications (e.g. fistulizing disease)	3	*	‡
Women	1	*	
Severe disease	1	*	
Mild disease	1	*	
Non-Whites	0	*	
Elderly	0	*	
Other	3	*	

* Consensus achieved in previous round, consensus-building round (phase 3) not required.
‡ Identified as a high priority research need.

Table E. Stakeholder identification and prioritization of medication comparisons of greatest importance for future research for the maintenance of remission in patients diagnosed with Crohn's disease

Phase 1: Identification of Evidence Gaps	Phase 2: Number of Stakeholders Rating Item as One of Top 3 Priorities	Phase 3: Number of Stakeholders Rating Item as One of Top 3 Priorities	Phase 4: Inclusion in Final Research Questions
TNF-alpha inhibitor + (6-mercaptopurine or azathioprine) versus TNF-alpha inhibitor	4	4	‡
TNF-alpha inhibitor + (6-mercaptopurine or azathioprine) versus (6-mercaptopurine or azathioprine)	3	2	
TNF-alpha inhibitor versus (6-mercaptopurine or azathioprine)	2	2	
TNF-alpha inhibitor versus methotrexate	2	2	
TNF-alpha inhibitor versus natalizumab	2	0	
(6-mercaptopurine or azathioprine) versus methotrexate	2	1	
One TNF-alpha inhibitor versus another TNF-alpha inhibitor	1	3	‡
TNF-alpha inhibitor + methotrexate versus TNF-alpha inhibitor	1	2	
TNF-alpha inhibitor + methotrexate versus methotrexate	1	1	
TNF-alpha inhibitor versus placebo	0	0	
(6-mercaptopurine or azathioprine) versus placebo	0	0	
Other: TNF-alpha inhibitor versus new treatment (that is safer)†	0	1	

TNF = tumor necrosis factor.

† Stakeholder provided comparison.

‡ Identified as a high priority research need.

Figures

Figure A. Analytic framework for identification of potential research gaps in phase 1

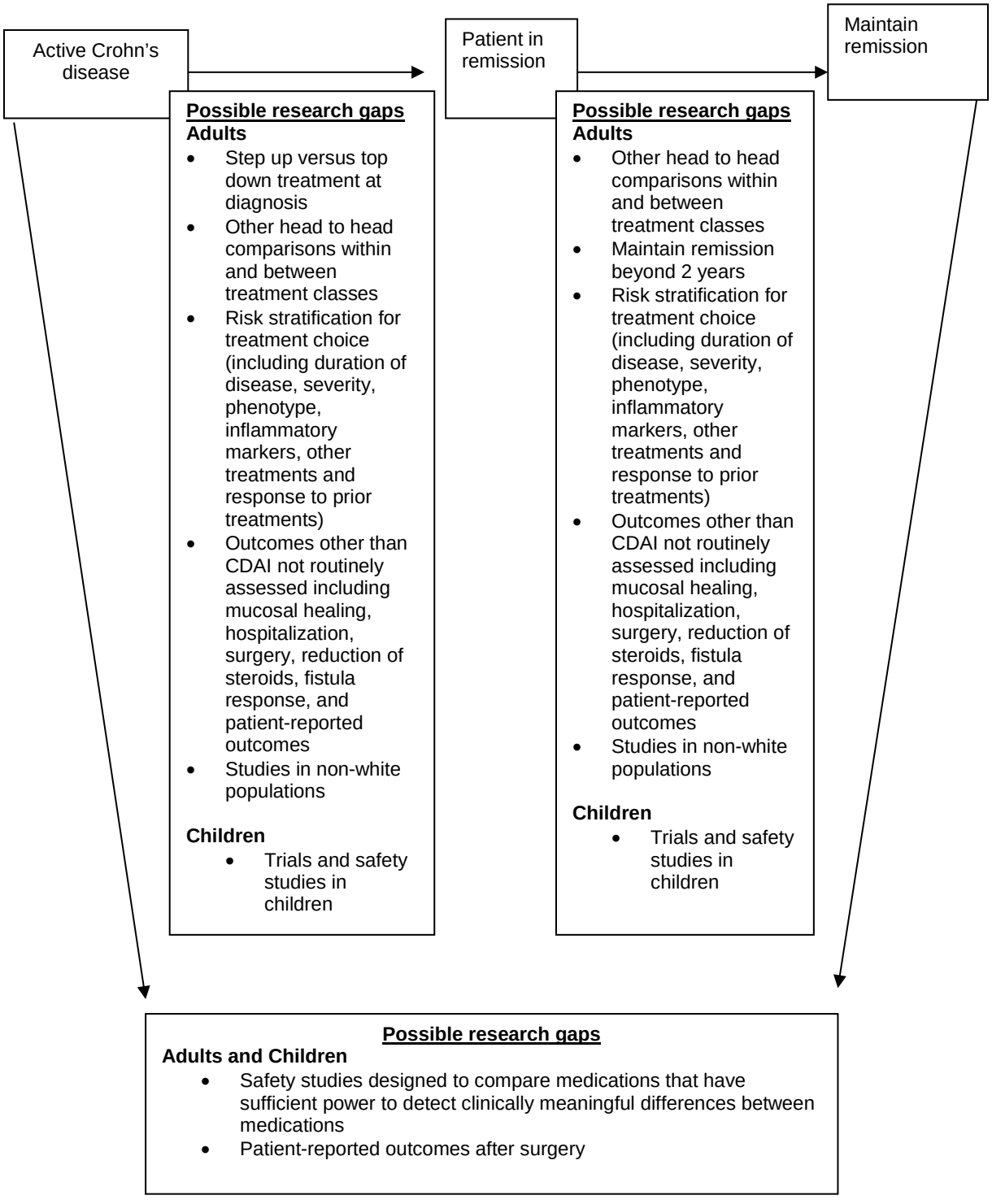
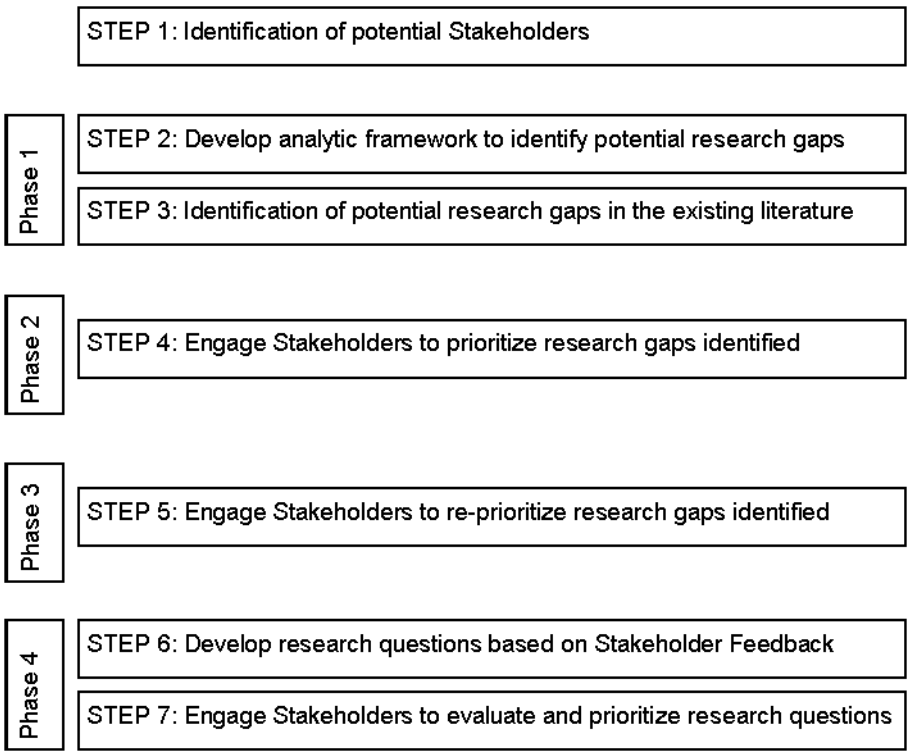


Figure B. Outline of steps for identification and prioritization of future research needs in Crohn's disease management



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Background

Context

Crohn's disease is characterized by chronic inflammation that can occur anywhere in the gastrointestinal tract, but most often affects the small bowel and colon. Typical symptoms include abdominal pain, chronic diarrhea, and gastrointestinal bleeding. Crohn's disease affects between 400,000 and 600,000 North Americans.[1] Ten percent of Crohn's disease patients are children under the age of 17 years.[2]

The clinical management of Crohn's disease is complicated. Clinical practice guidelines for Crohn's disease recommend that clinicians take into account the disease location, severity, complications, and extra-intestinal manifestations when choosing a treatment strategy. However, no universal treatment strategy exists for patients.[3] The lack of consensus about the best treatment strategy can result in confusion and frustration for the Crohn's disease patient as well as healthcare providers.

Medications are the healthcare providers' preferred treatment for Crohn's disease with surgical interventions reserved for refractory disease or evidence of dysplasia. Medical therapy in Crohn's disease targets intestinal inflammation with the intent of altering the natural history of the disease. Corticosteroids and aminosalicylates, such as sulfasalazine, have been used since the 1950s. Immunomodulators (6-mercaptopurine, azathioprine, and methotrexate) have been used for the treatment of Crohn's disease since the 1970s, although the use of these medications was not routine until the 1990s.[4] The first biologic tumor necrosis factor (TNF)-alpha inhibitor, infliximab, was approved by the Food and Drug Administration (FDA) for the treatment of Crohn's disease in adults in 1998. The FDA-approved monoclonal antibodies against TNF-alpha inhibitor also include adalimumab and certolizumab pegol.[5] Other biologic agents used for the treatment of Crohn's disease include natalizumab, a monoclonal antibody against cellular adhesion molecule α4-integrin that is FDA-approved for Crohn's disease in adults[5], and ustekinumab, a monoclonal antibody against interleukin 12 and interleukin 23 that is not currently FDA-approved for Crohn's disease.

Our recent systematic review addressed several Key Questions in the management of Crohn's disease.[6] In that review, we identified several important gaps in the evidence, as shown in the analytic framework depicted in Figure 1 and described in further detail below. The objective of this report is to identify and prioritize existing gaps in the synthesized literature pertaining to pharmacological induction and maintenance of remission for patients diagnosed with Crohn's disease by engaging expert stakeholders using a modified Delphi method.

Evidence Gaps

We used the PICOTS framework to identify gaps in how the evidence addressed the populations, interventions, comparisons, outcomes, timing, and setting of interest (see Figure 1). Several gaps related to the target population (children, non-white, and risk stratification based on patient characteristics). Other gaps related to interventions and comparisons of interest (step up versus top down treatment, and head to head comparisons within and between treatment classes), outcomes of interest (mucosal healing, and patient-reported symptoms), or a timing issue (i.e., remission beyond 2 years). These gaps served as the foundation to identify future research needs. In the following section, we elaborate further on the research gaps identified in the comparative effectiveness review.

Populations

Few pediatric studies were identified. Nine studies were identified that included exclusively pediatric patients. None of the adult studies that allowed participants under age 18 reported the results for children separately. Given the paucity of trials or observational studies that reported on safety, there is little evidence to guide the most effective and safe treatment for children. There is no existing evidence of quality of life or other patient-reported outcomes for these medications as reported by children or their parents.

Few studies included patients with complicated and severe disease. Many modern randomized controlled trials (RCTs) apply only to patients with uncomplicated, luminal Crohn's disease without stricture or abscess as these patients were excluded from the trials. Additionally, many RCTs excluded patients with very severe disease (Crohn's disease activity index [CDAI] > 450). Only two RCTs aimed to examine patients with fistula exclusively. The observational studies tended to include patients with all patterns of disease activity or behavior. Although the observational study findings are applicable to a wider range of patients, the majority of evidence was graded as low or insufficient. Because the risk-benefit ratio of medication use may depend on severity of disease, both effectiveness and safety should be assessed by disease severity.

Studies of recently diagnosed patients are needed because medication effectiveness may differ by disease duration. Most RCTs included patients with longer disease duration, often greater than ten years. Only a few studies randomized patients within three years of diagnosis. There are preliminary subgroup data that show patients with a short duration of disease have better response and remission rates.[14]

Additional future research needs include: (a) the inclusion of non-white patients in RCTs and safety studies; (b) performing head to head comparisons, especially for the biologics where no head-to-head study was identified; (c) performing head-to-head trials of biologics and immunomodulators that allow all thiopurine methyltransferase (TPMT) phenotypes, because the rate of TPMT metabolism rarely prohibits treatment in the clinical setting; (d) identifying treatments to induce and maintain remission in patients who do not respond to biologics, as these patients were excluded from many of the biologic maintenance trials; (e) specifying safety outcomes in advance and including them as primary or secondary outcomes in RCTs; (f) clarify whether safety outcomes associated with medication efficacy (such as disease flare and abscess) are safety outcomes or efficacy outcomes; (g) clearly accounting for the use of other medications in both RCTs and observational studies so that the independent effect of the medication of interest is more clear; (h) accounting for other confounders in observational studies and examining the reasons for the imbalance of potential confounders in the setting of RCTs; (i) conducting and reporting subgroup analyses appropriately in pre-specified groups and using interaction terms; (j) consistent reporting of outcomes in text and figures, especially for clinically relevant time points other than the primary outcome time point; and (k) for extremely rare safety outcomes that are likely to be reported in case reports, such as progressive multifocal leukoencephalopathy or hepatospenic T-cell lymphoma, synthesizing the data on a potential causal relationship would be more efficient if case reports emphasized criteria used to estimate these causal relationships such as the McMaster Quality Assessment Scale of Harms.[15]

Interventions

Comparative effectiveness studies of the step-up versus top-down approach are needed. The step-up versus top-down approach for treatment was one of the controversies that prompted this report. We also chose to organize our report according to the top-down approach to provide

relevance to this controversy. However, only one small open-label study directly tested step-up versus top-down treatment. Because patients were allowed to step-up throughout the study, by week 52, 20 percent of all patients were receiving infliximab, regardless of which group they were originally randomized, and by week 78 fewer than 10 percent of all patients were receiving prednisolone.[16] We had hoped to perform indirect comparisons in the absence of direct comparisons of step-up versus top-down treatment. However, we were not able to perform these indirect comparisons due to the heterogeneity of the study designs as described in the limitations.

Outcomes

RCTs did not routinely report on outcomes other than disease activity scales. Few studies reported on other indications of clinical remission such as hospitalizations, surgeries or mucosal healing. Controversy exists over the clinical relevance of the widely used CDAI as a measure of clinical disease activity and the CDAI is not considered an accurate measure of disease activity in stricturing or fistulizing disease.[17] The CDAI also does not correlate well with mucosal healing.[18] Additionally, disease activity indices are difficult to calculate and are not practical in the clinical setting,[17] limiting the applicability of the remission findings to clinical practice. Even though a representative from the FDA reported in 1995 that induction and maintenance of remission in Crohn's disease should include both absence of symptoms and endoscopic evidence of healing, few studies reported on mucosal healing.[19] There was information on the patient-reported Inflammatory Bowel Disease Questionnaire (IBDQ) outcome measure and occasionally the Medical Outcome Study Short Form (SF-36), but not days of work or school missed, which may be more meaningful and easier to communicate to Crohn's disease patients.

One study reported on a patient-reported outcome after surgical resection. Given that patient-reported outcomes may be even more relevant to patients who are not currently experiencing active clinical or endoscopic disease, these outcomes may be most relevant for treatment choice in these patients.

Timing

Evidence is lacking on the optimal treatment of Crohn's disease over a number of years. The short duration of the RCTs and observational studies limits the ability to assess one or more medications over a sizeable portion of a person's lifetime with disease. The duration of time that a treatment works, particularly for maintaining remission, is especially relevant for children who may not be fully developed and have a lifetime of disease and its treatment ahead of them.

Study Design

Observational studies may be too short in duration to observe some safety outcomes. The rare safety outcomes may take years to develop after exposure to the medication or may take years of medication use to develop. The majority of observational studies were shorter than five years,[20] which may not be sufficient to observe cases caused by the use of medication recorded during the study time period.

Methods

Identification of Evidence Gaps

Phase 1

We developed an analytic framework (Figure 1) to identify potential populations, medication comparisons and outcomes gaps from 2011 evidence report. We then searched the results and discussion sections of the evidence report, using the analytic framework, to identify potential research gaps. A Web-based assessment tool was populated with the identified research gaps specific to the induction of remission and the maintenance of remission. For each research gap category, an optional, free-text field was provided for stakeholders to identify gaps not listed in the assessment tool.

Phase 2

The stakeholders were provided with a copy of the executive summary of the 2011 evidence report and were asked to independently identify the three highest priority populations, medication comparisons, and outcomes for future research for both induction of remission and maintenance of remission.

Phase 3

Feedback from phase 2 was compiled and analyzed for agreement. Categories that did not achieve consensus on three or more options were sent back to the stakeholders in an attempt to build consensus. Compiled stakeholder responses regarding medication comparisons from phase 2 were sent to the stakeholders with a request to evaluate and prioritize the medication comparisons that did not achieve consensus.

Criteria for Prioritization

The stakeholders were provided with a copy of the executive summary of the 2012 evidence report and were asked to independently identify the highest priority populations, medications, medication comparisons, and outcomes for future research for individuals with Crohn's disease.

Engagement of Stakeholders, Researchers, and Funders

Stakeholder Identification

We solicited recommendations from the American College of Gastroenterology (ACG), the American Gastroenterological Association (AGA), and the Crohn's and Colitis Foundation of America (CCFA) for expert stakeholders representative of clinicians, researchers, private and federal agencies, and patients. Nine experts in the field of Crohn's disease were identified and invited to serve as a stakeholder. Five academic physicians in the field of gastroenterology with a research interest in Crohn's disease management and one patient agreed to serve as stakeholders for this project.

Stakeholder Engagement

We used a modified Delphi method to identify and prioritize existing gaps in the published literature as it pertains to the pharmacologic management of Crohn's disease, using seven steps across four phases (Figure 2). The Delphi method involves iterative rounds of responses by group members, providing aggregated feedback about other members' responses until consensus is reached. For each round, we used a Web-based assessment tool (SurveyMonkey™, Palo Alto, CA), with the list of the research gaps. Consensus among stakeholders was defined as agreement in responses of 50 percent or higher in three or more options for each category of future research needs. Categories that did not achieve 50 percent or greater consensus among the stakeholders on three or more options in phase 2 were returned for the stakeholders, with their compiled feedback from phase 2, to reprioritize.

Research Question Development and Research Design Considerations

Research questions were developed based on feedback from stakeholders that achieved consensus during the second and third rounds. The stakeholders were presented with their compiled feedback from the second and third phases along with the research questions developed. They were asked to provide feedback on the clarity, utility, study design feasibility, and priority of the research questions.

Results

Research Needs

In phase 1 of the process, the stakeholders identified gaps in evidence concerning populations, medication comparisons, and outcomes that varied for the induction of remission and the maintenance of remission of Crohn's disease. Results from the stakeholder prioritization are presented first as future research needs for the induction of remission and then for the maintenance of remission.

Induction of Remission

During phase 1 of this review, for the induction of remission in patients diagnosed with Crohn's disease, we identified nine potential populations for whom future research may be a priority (Table 1). We found 13 medication comparisons that are potential gaps in the literature (Table 2) pertaining to induction of remission for Crohn's disease, and 12 potential outcomes of interest (Table 3) for future research. All stakeholders (100%) prioritized children as an important while half prioritized patients with severe disease and non-responders to biologics as important populations for future research (Table 1). Among medication comparisons for induction of remission, only one medication comparison achieved consensus among the stakeholders with 60 percent agreement in phase 2. One stakeholder independently identified three medication comparisons for future research that were not included as part of this assessment.

In phase 3, all stakeholders (100%) prioritized one medication comparison (one TNF-alpha inhibitor versus another TNF-alpha inhibitor) as important for future research and half (50%) identified another medication comparison (a TNF-alpha inhibitor versus natalizumab) as important for future research for the induction of remission in Crohn's disease. Consensus was not achieved on a third medication comparison.

Maintenance of Remission

During phase 1, for the maintenance of remission in patients diagnosed with Crohn's disease, we identified nine potential populations for whom future research may be a priority (Table 4). We found 11 medication comparisons for which potential gaps in the literature exist (Table 5) pertaining to induction of remission for Crohn's disease and 13 potential outcomes of interest (Table 6) for future research.

All stakeholders again prioritized children as an important population for future research for the maintenance of remission of Crohn's disease. Fifty percent of stakeholders agreed that non-responders to biologics, and patients with complications are important populations to study in future research.

Among medication comparisons for maintenance of remission, two medication comparisons, with variation only in the single-medication control arm, achieved consensus in phase 2 (Table 5). Compiled stakeholder responses regarding medication comparisons from phase 2 were sent to the stakeholders with a request to evaluate and again prioritize the medication comparisons.

In phase 3, four stakeholders (60%) prioritized one medication comparison (TNF-alpha inhibitor and thiopurine versus TNF-alpha inhibitor) as important for future research while half (50%) identified a previously low-ranked medication comparison (one TNF-alpha inhibitor versus another TNF-alpha inhibitor) as important for future research for the induction of

remission in Crohn’s disease. The medication comparison originally agreed upon by 50 percent of stakeholders (TNF-alpha inhibitor and thiopurine versus thiopurine) failed to achieve consensus in phase 3, ergo this was not included in the final list of research questions.

Research Questions

Based on stakeholder feedback from phase 2 and phase 3 regarding populations, intervention comparisons, and outcomes, the following research questions were developed for future research and, in order, were prioritized by our stakeholders:

1. For maintenance of remission in adults and children diagnosed with Crohn's disease, what is the comparative effectiveness of a TNF-alpha inhibitor and thiopurine versus a TNF-alpha inhibitor for the outcomes of steroid reduction, patient reported outcomes, CDAI, pediatric CDAI and mucosal healing?
2. For induction of remission in adults and children diagnosed with Crohn's disease, what is the comparative effectiveness of one TNF-alpha inhibitor versus another TNF-alpha inhibitor for the outcomes of mucosal healing, patient reported outcomes, steroid reduction, CDAI and pediatric CDAI?
3. For induction of remission in adults and children diagnosed with Crohn's disease, what is the comparative effectiveness of a TNF-alpha inhibitor versus natalizumab for the outcomes of mucosal healing, patient reported outcomes, steroid reduction, CDAI and pediatric CDAI?
4. For maintenance of remission in adults and children diagnosed with Crohn's disease, what is the comparative effectiveness of one TNF-alpha inhibitor versus another TNF-alpha inhibitor for the outcomes of steroid reduction, patient reported outcomes, CDAI, pediatric CDAI and mucosal healing?

For each of these research questions, the strongest and most appropriate study design is a randomized controlled trial with sufficient duration of follow-up to obtain reasonably precise estimates of the comparative effects on the outcomes of interest. Although studies of the induction of remission in Crohn's disease tend to have a shorter timeframe than studies of the maintenance of remission, even studies of remission need follow-up long enough to provide reliable estimates of the effects on the outcomes that matter most to patients, and clearly long-term remission is important to patients. Thus, long-term follow-up for at least 1 year and preferably for up to 5 years would be extremely valuable, especially for children who are at risk of having adverse effects on growth and development. Future randomized controlled trials that examine these questions about the treatment of Crohn's disease should give careful attention to the problems we found in our systematic review of previously published studies, including: (1) under-representation of non-white, pediatric, and newly diagnosed patients; (2) insufficient sample size to determine whether there are clinically important differences in adverse effects of medications; and (3) inconsistent attention to outcomes beyond measures of disease activity. Due to the difficulty and expense of performing large randomized controlled trials on the comparative effectiveness of medications that have already been approved for use by the Food and Drug Administration, observational studies will have a role to play in future research. However, observational studies of comparative effectiveness will need to incorporate sophisticated risk adjustment methods to account for the many different ways in which patients vary when they initiate treatment for Crohn's disease. In this regard, it would be helpful to distinguish between patients with moderate-to-severe disease and those with mild disease. Long-term follow-up also will be extremely important to capture adverse events that may not be manifest for years after the initiation of treatment.

Identification of Ongoing Research

We searched clinical research repositories and research-related sites including ClinicalTrials.gov, NIH Reporter, the Canadian Institutes of Health Research, the World Health Organization Clinical Trials Registry, and the European Union Clinical Trials Register to identify ongoing/recently completed studies related to the pharmacological management of Crohn's disease. Appendix Table A-2 includes a summary of findings from these searches. Six potentially relevant studies were identified.

Discussion

The stakeholders identified future head-to-head research of combination therapy of TNF-alpha inhibitors and thiopurine against monotherapy of a TNF-alpha inhibitor for the maintenance of remission in Crohn's disease as a high priority. Based on stakeholder feedback, it is clear that combination therapy of a TNF-alpha inhibitor and thiopurine for maintenance of remission is extremely important for future research; however, there is some ambiguity regarding the monotherapy comparison as thiopurine did achieve our criterion for consensus in the first round (50%) but failed to do so in the second round (33%). However, this intervention was given highest priority by our group of stakeholders.

All stakeholders indicated that future research was needed for the induction of remission using monotherapy of one TNF-alpha inhibitor against another TNF-alpha inhibitor. Equally so, this intervention was given second highest priority by the stakeholders among the research questions developed.

Children were unanimously considered a high priority for all future research in the field of Crohn's disease. It was noted by one stakeholder that when assessing outcomes for children, the Pediatric CDAI should be used. It was agreed that the outcomes of highest priority are mucosal healing, patient reported outcomes, CDAI, and steroid reduction for bothinduction and maintenance of remission of Crohn's disease.

In a recent report, Cheifetz and colleagues engaged gastroenterologists to prioritize future comparative effectiveness research topics in inflammatory bowel disease. The authors reported that an "anti-TNF agent alone versus anti-TNF agent with thiopurine in patients with moderate to severe Crohn's disease failing thiopurine" was their sixth highest research priority among all inflammatory bowel disease related research questions. In addition, they reported that the "efficacy and safety of long-term immunomodulation versus anti-TNF therapy in Crohn's disease…" was their eighth highest research priority. Likewise, their findings reported the need to accept mucosal healing as a primary outcome.[7] These results support our findings of high priority interventions and outcomes for future research; however, our stakeholders unanimously agreed that children are the highest priority for future research while Cheifetz identified adults as a higher priority.

There were a few limitations to this study. The investigators on the original systematic review were actively involved in the identification of research gaps in this study which allowed for potential experimenter bias. This was mitigated by allowing stakeholders to independently identify other populations, medication comparisons or outcomes for future research during each phase. In addition, the complexity of the concepts in this topic may be a barrier for patient stakeholders to contribute however our patient stakeholder is a certified health educator for this topic and possessed the requisite clinical knowledge to provide meaningful feedback.

The American Recovery and Reinvestment Act of 2009 outlined several research priorities specific to the treatment of Crohn's disease[8] that have been endorsed by the AGA[9] including the introduction of biologics into the treatment algorithm for inflammatory diseases, including Crohn's disease. With respect to outcomes of interest, there are still conflicting opinions within AGA regarding the utility of mucosal healing as a primary endpoint.[10, 11] Despite these recent conflicts, it is clear from our findings and other recent reports,[7, 12, 13] that mucosal healing should be considered as a primary endpoint.

Conclusion

Children are a high priority for future research for the induction and maintenance of remission in patients diagnosed with Crohn's disease. Stakeholders identified a substantial need for further research on the use of TNF-alpha inhibitors for induction and maintenance of remission of Crohn's disease. The stakeholders also identified an important need to report outcomes of mucosal healing, patient reported outcomes, CDAI, and steroid reduction when conducting induction and maintenance of remission trials for Crohn's disease.

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Acronyms and Abbreviations

ACG	American College of Gastroenterology
AGA	American Gastroenterological Association
AHRQ	Agency for Healthcare Research and Quality
CCFA	Crohn's and Colitis Foundation of America
CDAI	Crohn's Disease Activity Index
EPC	Evidence-based Practice Center
FDA	Food and Drug Administration
PICOTS	Populations, interventions, comparisons, outcomes, timing, and setting of interest
RCT	Randomized controlled trial
TNF	Tumor necrosis factor
TPMT	Thiopurine methyltransferase

Tables

Table 1. Stakeholder identification and prioritization of populations of greatest importance for future research for the induction of remission in patients diagnosed with Crohn's disease

Phase 1: Identification of Evidence Gaps	Phase 2: Number of Stakeholders Indicating Item Was One of Top 3 Priorities	Phase 3: Stakeholder Prioritization Refinement	Phase 4: Inclusion in Final Research Questions
Children	6	*	‡
Severe disease	3	*	‡
Nonresponders to biologics	3	*	‡
Patients with complications (e.g. fistulizing disease)	2	*	
Women	1	*	
Non-Whites	1	*	
Mild disease	1	*	
Elderly	0	*	
Other	1	*	

* Consensus achieved in previous round, consensus-building round (phase 3) not required.

‡ Identified as a high priority research need

Table 2. Stakeholder identification and prioritization of medication comparisons of greatest importance for future research for the induction of remission in patients diagnosed with Crohn's disease

Phase 1: Identification of Evidence Gaps	Phase 2: Number of Stakeholders Rating Item as One of Top 3 Priorities	Phase 3: Number of Stakeholders Rating Item as One of Top 3 Priorities	Phase 4: Inclusion in Final Research Questions
One TNF-alpha inhibitor versus another TNF-alpha inhibitor	4	6	‡
TNF-alpha inhibitor + methotrexate versus steroid + methotrexate	2	0	
TNF-alpha inhibitor versus TNF-alpha inhibitor + methotrexate	2	1	
TNF-alpha inhibitor versus steroid + (6-mercaptopurine or azathioprine)	2	1	
TNF-alpha inhibitor versus natalizumab	2	3	‡
TNF-alpha inhibitor + azathioprine versus TNF-alpha inhibitor + methotrexate†	1	0	
TNF-alpha inhibitor versus steroid	1	2	
TNF-alpha inhibitor + (6-mercaptopurine or azathioprine) versus steroid + (6-mercaptopurine or azathioprine)	1	1	
Steroid + (6-mercaptopurine or azathioprine) versus steroid + methotrexate	1	1	
TNF-alpha inhibitor versus (6-mercaptopurine or azathioprine)	0	0	
TNF-alpha inhibitor versus methotrexate	0	2	
TNF-alpha inhibitor versus TNF-alpha inhibitor + (6-mercaptopurine or azathioprine)	0	0	
TNF-alpha inhibitor versus steroid + methotrexate	0	0	
Other: TNF-alpha inhibitor + azathioprine versus (natalizumab or vedolizumab)†	1	0	
Other: TNF-alpha inhibitor + azathioprine versus ustakinumab†	1	0	
Other: TNF-alpha inhibitor versus new treatment (e.g. Stelara)†	0	1	

TNF: Tumor necrosis factor.

† Stakeholder provided comparison.

‡ Identified as a high priority research need.

Table 3. Stakeholder identification and prioritization of outcomes of greatest importance for future research for the induction of remission in patients diagnosed with Crohn's disease

Phase 1: Identification of Evidence Gaps	Phase 2: Number of Stakeholders Rating Item as One of Top 3 Priorities	Phase 3: Stakeholder Prioritization Refinement	Phase 4: Inclusion in Final Research Questions
Mucosal healing	6	*	‡
Patient reported outcomes	5	*	‡
Crohn's Disease Activity Index	3	*	‡
Steroid reduction	3	*	‡
Surgery	1	*	
Hospitalization	0	*	
Mortality	0	*	
Progressive multifocal leukoencephalopathy	0	*	
Lymphoma and cancer	0	*	
Tuberculosis and other infections	0	*	
Infusion reactions	0	*	
Bone fractures	0	*	
Other	0	*	

* Consensus achieved in previous round, consensus-building round (phase 3) not required.

‡ Identified as a high priority research need.

Table 4. Stakeholder identification and prioritization of populations of greatest importance for future research for the maintenance of remission in patients diagnosed with Crohn's disease

Phase 1: Identification of Evidence Gaps	Phase 2: Number of Stakeholders Rating Item as One of Top 3 Priorities	Phase 3: Stakeholder Prioritization Refinement	Phase 4: Inclusion in Final Research Questions
Children	6	*	‡
Nonresponders to biologics	3	*	‡
Patients with complications (e.g. fistulizing disease)	3	*	‡
Women	1	*	
Severe disease	1	*	
Mild disease	1	*	
Non-Whites	0	*	
Elderly	0	*	
Other	3	*	

* Consensus achieved in previous round, consensus-building round (phase 3) not required.
‡ Identified as a high priority research need

Table 5. Stakeholder identification and prioritization of medication comparisons of greatest importance for future research for the maintenance of remission in patients diagnosed with Crohn's disease

Phase 1: Identification of Evidence Gaps	Phase 2: Number of Stakeholders Rating Item as One of Top 3 Priorities	Phase 3: Number of Stakeholders Rating Item as One of Top 3 Priorities	Phase 4: Inclusion in Final Research Questions
TNF-alpha inhibitor + (6-mercaptopurine or azathioprine) versus TNF-alpha inhibitor	4	4	‡
TNF-alpha inhibitor + (6-mercaptopurine or azathioprine) versus (6-mercaptopurine or azathioprine)	3	2	
TNF-alpha inhibitor versus (6-mercaptopurine or azathioprine)	2	2	
TNF-alpha inhibitor versus methotrexate	2	2	
TNF-alpha inhibitor versus natalizumab	2	0	
(6-mercaptopurine or azathioprine) versus methotrexate	2	1	
One TNF-alpha inhibitor versus another TNF-alpha inhibitor	1	3	‡
TNF-alpha inhibitor + methotrexate versus TNF-alpha inhibitor	1	2	
TNF-alpha inhibitor + methotrexate versus methotrexate	1	1	
TNF-alpha inhibitor versus placebo	0	0	
(6-mercaptopurine or azathioprine) versus placebo	0	0	
Other: TNF-alpha inhibitor versus new treatment (that is safer)†	0	1	

TNF = tumor necrosis factor.

† Stakeholder provided comparison.

‡ Identified as a high priority research need.

Table 6. Stakeholder identification and prioritization of outcomes of greatest importance for future research for the maintenance of remission in patients diagnosed with Crohn's disease

Phase 1: Identification of Evidence Gaps	Phase 2: Number of Stakeholders Rating Item as One of Top 3 Priorities	Phase 3: Stakeholder Prioritization Refinement	Phase 4: Inclusion in Final Research Questions
Steroid reduction	4	*	‡
Patient reported outcomes	4	*	‡
Crohn's Disease Activity Index	3	*	‡
Mucosal healing	3	*	‡
Surgery	2	*	
Lymphoma and cancer	2	*	
Hospitalization	0	*	
Mortality	0	*	
Progressive multifocal leukoencephalopathy	0	*	
Lymphoma and cancer	0	*	
Tuberculosis and other infections	0	*	
Infusion reactions	0	*	
Bone fractures	0	*	
Other	0	*	

* Consensus achieved in previous rounds, consensus-building round (phase 3) not required.

‡ Identified as a high priority research need.

Figures

Figure 1. Analytic framework for identification of potential research gaps in phase 1

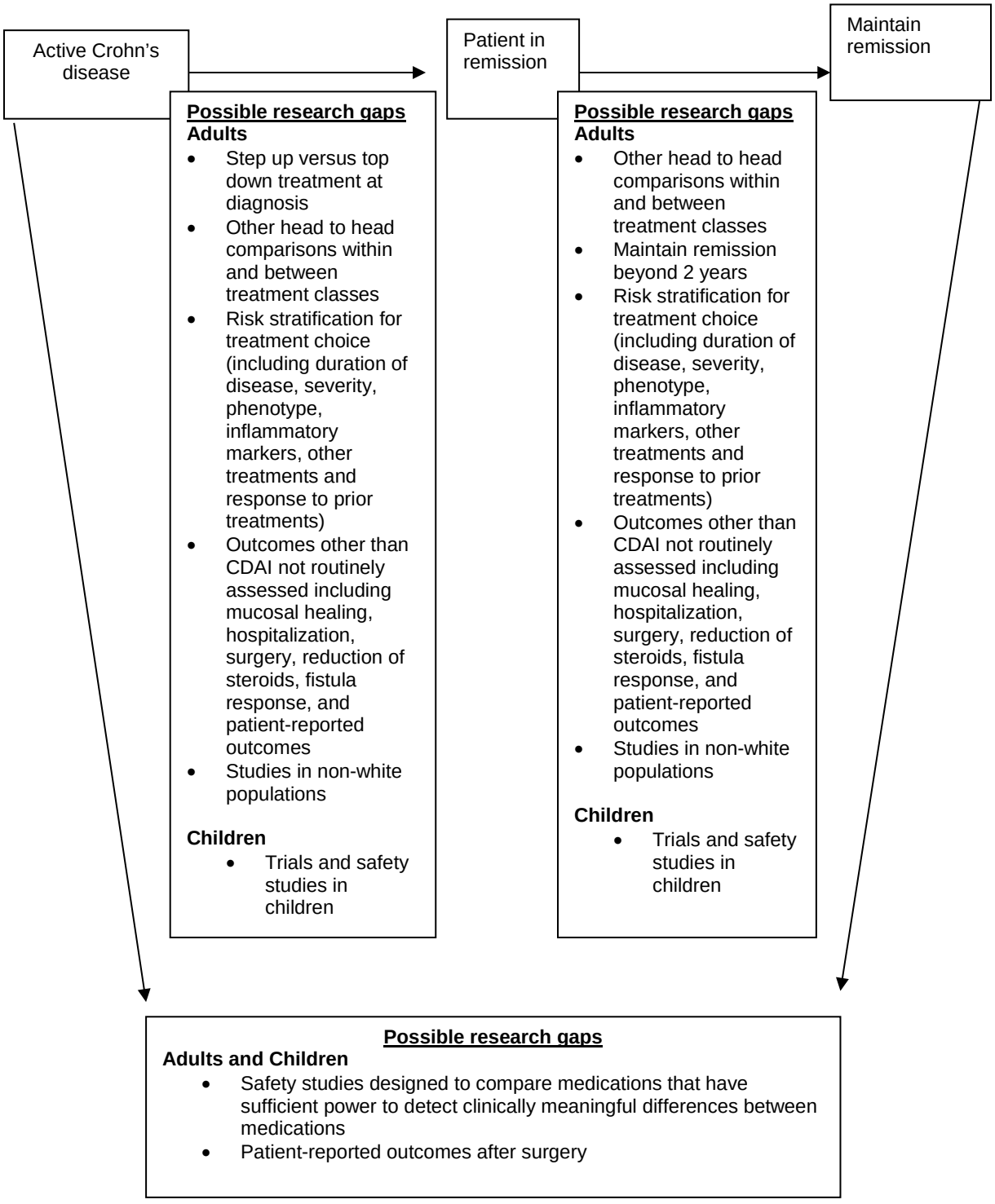
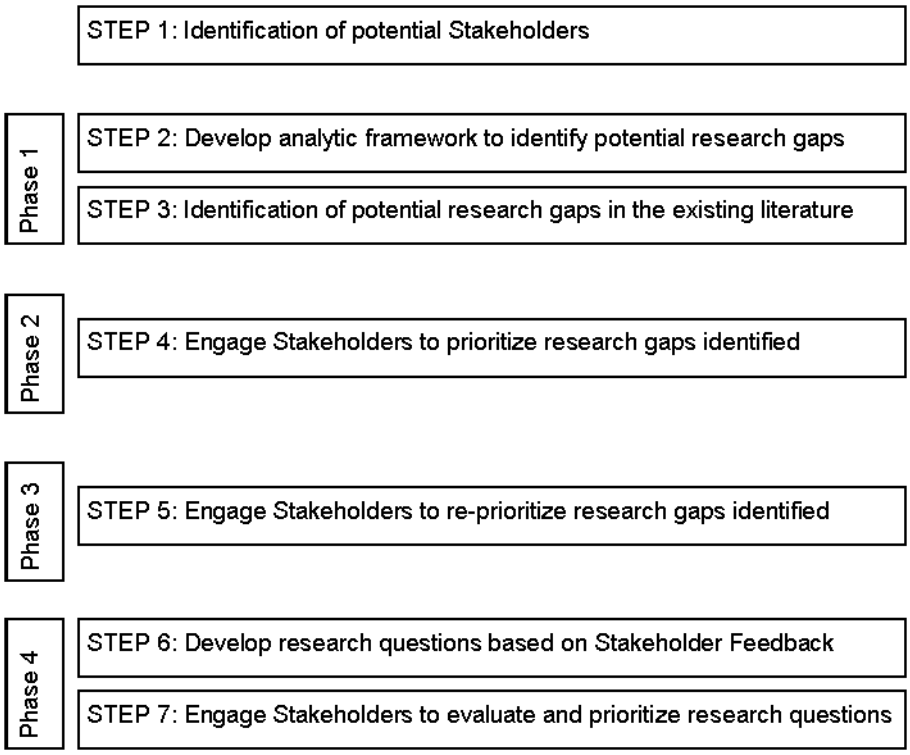


Figure 2. Outline of steps for identification and prioritization of future research needs in Crohn's disease management



Appendix A. Search Strategies and Potentially Relevant Ongoing/Recently Completed Studies

Table A-1. Search Strategies for potentially relevant ongoing studies for pharmacological management of Crohn's disease

Resource URL	Search Parameters	Search Terms/Strategy
ClinicalTrials.gov http://clinicaltrials.gov/	Advanced search, Conditions field used	Pharmacological Management of Crohn's Disease OR Treatment of Crohn's Disease
EU Clinical Trials Register https://www.clinicaltrialsregister.eu/	Not applicable	Crohn's Disease
NIH Reporter http://projectreporter.nih.gov/reporter.cfm	Projects field searched	Pharmacological Management of Crohn's Disease OR Treatment of Crohn's Disease
Canadian Institutes of Health Research http://www.cihr-irsc.gc.ca/	Funding Decisions Data field searched	Pharmacological Management of Crohn's Disease OR Treatment of Crohn's Disease
World Health Organization International Clinical Trials Registry Platform Search Portal http://apps.who.int/trialsearch/	Searched Condition field, Recruitment status = ALL	Pharmacological Management of Crohn's Disease OR Treatment of Crohn's Disease

Table A-2. Potentially relevant ongoing/recently completed studies

Title/ Identifier(s)	Study Dates	Description	Sponsor or Principal Investigator Collaborator(s)	Source
Title: Safety Study of Entocort for Children With Crohn's Disease **Identifier(s):** NCT01444092	**Start date:** November 2011 **Estimated study completion date:** January 2014 **Estimated primary completion date:** January 2014 (Final data collection date for primary outcome measure)	**Purpose:** A Safety Study using Entocort EC for children with mild to moderate Crohn's Disease **Study design:** Endpoint Classification: Safety Study Intervention Model: Single Group Assignment Masking: Open Label Primary Purpose: Treatment **Condition(s):** Crohn's Disease **Intervention(s):** Drug: Entocort **Estimated enrollment:** 110	**Sponsor OR PI and Collaborator(s):** AstraZeneca	ClinicalTrials.gov **Accessed at:** http://clinicaltrials.gov/ct2/show/NCT01444092
Title: Cimzia Versus Mesalamine for Crohn's Recurrence **Identifier(s):** NCT01696942	**Start date:** December 2012 **Estimated study completion date:** December 2015 **Estimated primary completion date:** December 2014 (Final data collection date for primary outcome measure)	**Purpose:** To evaluate the difference in clinical recurrence rates between certolizumab and mesalamine after 4 weeks, 3 months, 6 months, 9 months, and 12 months of use following ileocolectomy for Crohn's disease using the Crohn's Disease Activity Index (CDAI). **Study design:** Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Parallel Assignment Masking: Open Label Primary Purpose: Treatment **Condition(s):** Crohn's Disease **Intervention(s):** Drug: Cimzia Drug: Mesalamine **Estimated enrollment:** 24	**Sponsor OR PI and Collaborator(s):** Milton S. Hershey Medical Center UCB, Inc.	ClinicalTrials.gov **Accessed at:** http://clinicaltrials.gov/ct2/show/NCT01696942

Title: EUS Evaluation of Perianal and Peri-rectal Fistulizing Crohn's Disease With CERTOLIZUMAB Treatment **Identifier(s):** NCT01582568	**Start date:** June 2011 **Estimated study completion date:** December 2013 **Estimated primary completion date:** December 2013 (Final data collection date for primary outcome measure)	**Purpose:** To assess perianal and perirectal fistula healing (complete closure) based on endoscopic ultrasound (EUS) evaluation at 3 months and by PDAI (Pouchitis Disease Activity Index) and Fistula Drainage assessment by 6 months, showing no fistula (new or recurrence) in treatment of Crohn's' disease patient with Certolizumab (Cimzia). **Study design:** Endpoint Classification: Efficacy Study Intervention Model: Single Group Assignment Masking: Open Label Primary Purpose: Treatment **Condition(s):** Crohns Disease **Intervention(s):** Drug: Certolizumab **Estimated enrollment:** 20	**Sponsor OR PI and Collaborator(s):** Baylor College of Medicine UCB, Inc.	ClinicalTrials.gov **Accessed at:** http://clinicaltrials.gov/ct2/show/NCT01582568
Title: Efficacy and Safety of Two Treatment Models in Subjects With Moderate to Severe Crohn's Disease (CALM) **Identifier(s):** NCT01235689	**Start date:** February 2011 **Estimated study completion date:** June 2014 **Estimated primary completion date:** June 2014 (Final data collection date for primary outcome measure)	**Purpose:** To evaluate the Efficacy and Safety of two treatment models in subjects with moderate to severe Crohn's Disease **Study design:** Allocation: Randomized Endpoint Classification: Safety/Efficacy Study Intervention Model: Parallel Assignment Masking: Open Label Primary Purpose: Treatment **Condition(s):** Crohn's Disease **Intervention(s):** Biological: adalimumab Drug: prednisone Drug: azathioprine **Estimated enrollment:** 240	**Sponsor OR PI and Collaborator(s):** Abbott	ClinicalTrials.gov **Accessed at:** http://clinicaltrials.gov/ct2/show/NCT01235689

Title: Adalimumab for the Management of Post-operative Crohn's Disease (CD) (POPART) **Identifier(s):** NCT01629628	**Start date:** July 2012 **Estimated study completion date:** July 2016 **Estimated primary completion date:** July 2016 (Final data collection date for primary outcome measure)	**Purpose:** Comparing the efficacy of adalimumab with immunomodulator therapy (i.e. 6-mercaptopurine, 6-MP), in maintaining remission of post-operative CD patients, with a high risk of disease recurrence. **Study design:** Allocation: Randomized Endpoint Classification: Efficacy Study Intervention Model: Parallel Assignment Masking: Open Label Primary Purpose: Prevention **Condition(s):** Crohn Disease **Intervention(s):** Drug: Adalimumab Drug: 6 Mercaptopurine **Estimated enrollment:**	**Sponsor OR PI and Collaborator(s):** Tel-Aviv Sourasky Medical Center Abbott	ClinicalTrials.gov **Accessed at:** http://clinicaltrials.gov/ct2/show/NCT01629628
Title: Comparison of the human TNF-alpha antibody adalimumab with infliximab in induction and maintenance of steroid-free remission in patients with moderate to severe Crohn's disease **Identifier(s):** EudraCT Number: 2008-004926-18	**Start date:** 2008-10-30 **Estimated study completion date:** Ongoing	**Purpose:** To compare the human TNF-alpha antibody adalimumab with infliximab in respect to induction and maintenance of steroid-free remission in patients with moderate to severe Crohn's disease **Study design:** RCT **Condition(s):** Moderate to severe Crohn's disease **Intervention(s):** Adalimumab Infliximab **Estimated enrollment:** 100	**Sponsor OR PI and Collaborator(s):** IBD Center LMU Munich	EU Clinical Trials Register **Accessed at:** https://www.clinicaltrialsregister.eu/ctr-search/trial/2008-004926-18/DE