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Development of a core outcome set for clinical trials in inflammatory bowel disease: study protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey

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ABSTRACT

Introduction:

Crohn's disease (CD) and ulcerative colitis (UC), the main forms of inflammatory bowel disease (IBD), are chronic, progressive, and disabling disorders of the gastrointestinal tract. Although data from randomized controlled trials (RCTs) provide the foundation of evidence that validates medical therapy for IBD, considerable heterogeneity exists in the measured outcomes used in these studies. Furthermore, in recent years, there has been a paradigm shift in IBD treatment targets, moving from symptom-based scoring to improvement or normalization of objective measures of inflammation such as endoscopic appearance, inflammatory biomarkers, and histologic and radiographic endpoints. The abundance of new treatment options and evolving endpoints poses opportunities and challenges for all stakeholders involved in drug development. Accordingly, there exists a need to harmonize measures used in clinical trials through development of a core outcome set (COS).

Methods and Analysis:

The development of an IBD-specific COS includes four steps. First, a systematic literature review is performed to identify outcomes previously used in IBD RCTs. Second, semi-structured qualitative interviews are conducted with key stakeholders, including patients, clinicians, researchers, pharmaceutical industry representatives, health care payers, and regulators to identify additional outcomes of importance. Using the outcomes generated from literature review and stakeholder interviews, an international two-round Delphi survey is conducted to prioritize outcomes for inclusion in

the COS. Finally, a consensus meeting is held to ratify the COS and disseminate findings for application in future IBD trials.

Ethics and Dissemination:

Given that over 30 novel therapeutic compounds are in development for IBD treatment, the design of robust clinical trials measuring relevant and standardized outcomes is crucial. Standardizing outcomes through a COS will reduce heterogeneity in trial reporting, facilitate valid comparisons of new therapies, and improve clinical trial quality.

Keywords:

Inflammatory bowel disease, Crohn's disease, ulcerative colitis, core outcome set, systematic review, consensus methods, Delphi

STRENGTHS AND LIMITATIONS

- This protocol outlines the first international consensus effort to develop a core outcome set (COS) for use in IBD clinical trials. With over 30 novel therapeutic compounds in development for IBD treatment and rapidly evolving treatment targets, the need to harmonize clinical trial efficacy and safety outcomes in a COS is exigent.
- The multistep process to develop the COS is rigorous and involves a detailed systematic literature review, semi-structured interviews with key stakeholder groups, two-round Delphi survey to prioritize key outcomes, and a consensus meeting to ratify the COS.

- To develop the COS, we will seek input from multiple stakeholders, including patients, clinicians, researchers, pharmaceutical industry representatives, health care payers, and regulators. This will generate diverse viewpoints reflecting clinical practices from around the wolrd.

INTRODUCTION

The inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), are chronic, progressive, and often disabling disorders of the gastrointestinal tract with no cure. Worldwide, the incidence of IBD is increasing with the highest incidence in North America and Europe; however rapidly rising rates of disease in Asia[1] have recently been observed. Typical symptoms of these diseases, which include diarrhea, gastrointestinal bleeding, and abdominal pain, cause impaired quality of life, reduced work capacity, and social stigmatization.[2] Although the etiology of IBD is unknown, existing evidence implicates development of a dysregulated immune response in genetically susceptible individuals consequent to complex interactions between the intestinal microbiome and environmental exposures.[3] Both CD and UC are lifelong diseases without a cure that typically require continued medical therapy as well as surgery in a large proportion of patients. Additionally, the direct and indirect costs associated with IBD is estimated to exceed $30 billion annually in the United States alone.[4 5]

Treatment of CD and UC is focused on controlling inflammation with anti-inflammatory and immunosuppressive agents, with goals of induction and maintenance of remission. In particular, the adoption of biologic therapies over the past two decades has revolutionized IBD management, making sustained remission an achievable therapeutic target.[6] Approval of these new agents has relied upon data from robust randomized controlled trials (RCTs)[7-14] that in recent years have increased in size and sophistication. Advances in this field continue at an increasingly rapid pace with multiple

classes of agents in late phase development.[15 16] In parallel, a paradigm shift in treatment targets for IBD has occurred, with a move away from symptom-based scoring[17-19] to normalization of more objective measures of inflammation such as endoscopic appearance, inflammatory biomarkers, and histologic and radiographic endpoints. Furthermore, recognizing the need to accurately measure the patient experience with IBD, the US Food and Drug Administration (FDA) has advocated for measurement of patient-reported outcomes (PROs) in clinical trials.[20]

In addition to the shift in efficacy outcomes measured in IBD trials, the assessment of safety outcomes has also changed with the introduction of biologic and immunomodulator therapies, which are often used in combination. As novel treatments are developed to target different components of the immune response, short and long-term safety evaluations are essential. These include the risks of bacterial infections (including tuberculosis), viral infections (including hepatitis B or herpes zoster virus reactivation), malignancy, lymphoma, infusion and injection reactions, and development of anti-drug antibodies.[21]

These shifts in the research environment have led investigators and regulatory authorities to re-evaluate the key efficacy and safety outcomes measured in IBD clinical trials. The selection of appropriate outcomes is critical for several reasons. First, their operating properties determine trial efficiency and ultimately drive both our ability to accurately identify effective new therapies and the cost of dug development programs. Second, choice of outcomes can shape clinical practice if the selected endpoints are

perceived to be relevant to both patients and health care professionals. Third, identification of standardized outcomes has potential to facilitate and improve the quality of systematic reviews and meta-analyses. Finally, outcome measures are critical components of the analyses used by payers to determine the safety and relative cost-effectiveness of competing treatments and significantly influence regulatory and formulary policy.[22]

It is apparent that insufficient attention has been paid to the standardized assessment of outcome measures for IBD trials. Notably, no formalized consensus exists regarding what to measure, how to measure, and when to measure selected efficacy and safety outcomes in IBD trials.[23] Given the evolving landscape of IBD treatment endpoints and the rapid development of new therapies, an international consensus agreement on core outcomes for use in future IBD trials is of critical importance.

A core outcome set (COS) is a consensus derived minimum set of outcomes that should be measured and reported in all clinical trials of a given disease.[22] The expectation is that core outcomes will always be collected and reported, but the COS is not restrictive such that investigators are still encouraged to explore other outcomes in addition to the COS. COS have been developed and utilized effectively in several specialties, most prominently in rheumatology through the Outcome Measures in Rheumatology (OMERACT) initiative.[24] Protocols have been proposed for COS development in other areas of health research[25-31] and to facilitate this activity the Core Outcome Measures in Effectiveness Trials (COMET) initiative has begun.[32]

Implementation of a successful COS should reduce heterogeneity in outcome reporting, enhance the quality of evidence synthesis and systematic reviews, and increase the relevance of clinical research for multiple stakeholders.[33]

This protocol establishes the context and scope for COS development in IBD, outlines the methods to be adopted for each step of COS development, and increases awareness of this effort to encourage IBD researchers and other stakeholders from around the world to participate.

METHODS AND ANALYSIS

Our interest in developing this COS has been listed in the non-database list of the COMET initiative (www.comet-initiative .org). This project will use published recommendations[22] for the development of an international consensus IBD-specific COS in a multi-step process. Detailed methodology for each step of the process is provided in the relevant sections below.

1) Completion of a systematic review to identify efficacy and safety outcomes currently reported in IBD randomized controlled trials
2) Identification of additional outcomes important to key stakeholders, including IBD patients and patient advocacy groups, clinicians, researchers, pharmaceutical industry representatives, health care payers, regulators and policy makers through semi-structured stakeholder interviews
3) Prioritization of outcomes and generation of a consensus outcomes list using a two-round Delphi survey[34]
4) Ratification of the COS in a consensus meeting of global experts

Scope of the core outcome set

This COS is intended as the international standard for clinical trials examining the efficacy of treatments in adult patients (≥18 years) with IBD. Patients included within the scope of this COS include those with:

1) Crohn's disease – including both luminal and peri-anal fistulizing disease
2) Ulcerative colitis – including patients with pouchitis after colectomy

Health interventions included within the scope of this COS include trials of therapeutic compounds and treatment algorithms. Effectiveness of surgical interventions will not be evaluated in this COS.

Identifying existing knowledge

To our knowledge, two existing initiatives have potential conceptual overlaps with the development of a COS. However, both projects have differing aims and neither of these identified projects have the same scope as the COS:

1) The International Consortium for Health Outcomes Measurement (ICHOM) is developing a standardized outcome set for IBD.[35] The ICHOM initiative is centered on devising patient- and value-based health care outcomes, which is most relevant as a quality metric for healthcare payers, with a broader scope on healthcare provision rather than a specific focus on core outcomes for assessment in clinical trials.
2) The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) program was initiated by the International Organization for the Study of Inflammatory Bowel Diseases.[6] Their recommendations for clinical, endoscopic, histologic, imaging, biomarker, and patient-reported targets in CD and UC aim to guide clinical practice rather than drive endpoint selection for clinical trials and drug development.

Step 1: Systematic literature review

A literature review will be conducted to identify and compare outcomes reported in existing studies of interventions for adult IBD patients.

Types of studies, participants, and interventions

RCTs and systematic reviews of RCTs (with or without meta-analysis) will be included. Studies not describing IBD treatment outcomes, conference proceedings/abstracts without complete trial description, or studies for which full-text is not available in English will be excluded. Trial participants will include all adult IBD patients (≥18 years), including specific subgroups of patients with peri-anal fistulizing CD and UC patients developing pouchitis after restorative proctocolectomy. Interventions will include trials of therapeutic compounds (including systemic and topical corticosteroids, anti-inflammatories and mesalamine compounds, immune modulating agents, pre- and probiotic therapies, biologic and biosimilar therapies, fecal microbiota transplantation, and small molecule therapy) and trials of management algorithms applied to IBD patients. Both effectiveness and safety outcomes will be assessed. Surgical interventions will be excluded.

Search methods for identification of studies and study eligibility

Full terms of a comprehensive, electronic search strategy developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines are detailed in Supplemental File 1.[36] The search strategy will be applied to MEDLINE, PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL). ClinicalTrials.gov will be searched for relevant projects currently underway

and we will also screen abstracts from the American College of Gastroenterology Annual Scientific Meeting, Digestive Disease Week, United European Gastroenterology Week, and European Crohn's and Colitis Organization conference proceedings published from January 2007 through June 2016. The reference lists of relevant studies will be searched for additional studies not identified from the electronic database search. No language restrictions will be applied to the initial search strategy but studies without English-language full text will be excluded from the selection of relevant articles. Given the substantial changes in IBD trial design over the past two decades, we will restrict the search to studies published after 1998 to ensure selection of more contemporary and relevant outcomes. Two review authors (CM and CEP) will independently screen the abstracts returned from the search strategy and any studies not meeting inclusion criteria will be excluded. In cases of dispute, a third review author (VJ) will be consulted.

Assessment of methodologic quality

As the primary focus of the systematic review will be to generate a list of potential outcome measures, the methodologic quality of the reported outcomes in included studies will be assessed using four questions[37]:

1) Is the primary outcome clearly stated?
2) Is the primary outcome clearly defined so that another researcher would be able to reproduce its measurement (e.g. measurement tools, measurement timing)?
3) Are secondary outcomes clearly stated?
4) Are secondary outcomes clearly defined?

As the primary scope of this project evaluates outcome reporting, the overall methodological quality of the included studies from systematic reviews will not be evaluated.

Data extraction, analysis, and presentation

Independent data extraction will be performed by two review authors (CM and CEP) for the following: author details and affiliation, year and journal of publication, study design, study population (CD, UC, peri-anal fistulizing CD and pouchitis), intervention(s) under review, primary and secondary effectiveness and safety outcome(s) reported, outcome definition(s), and outcome measurement tool(s). Disagreement will be resolved through discussion and if resolution is not possible, a third reviewer (VJ) will be consulted. Original study authors will be contacted if there is unclear/unavailable data. The data will be synthesized and presented in a descriptive table, with all reported outcome measures and the quality of outcome reporting. Efficacy outcomes will be stratified by category: clinical, endoscopic, histologic, radiologic, laboratory, patient-reported, and composite scales of multiple outcome measures. Safety outcomes will be stratified by adverse event type (e.g. infections, cardiac adverse events, malignancies, lymphoma, infusion/injection reactions, immunologic adverse events) and by severity (hospitalization, intervention discontinuation, death). These outcomes will then be condensed into a preliminary list for consideration in semi-structured interviews and the Delphi survey.

Step 2: Stakeholder involvement

Outcomes measured in clinical trials must be meaningful to patients, health care providers, and health care systems who receive, deliver, and pay for care, respectively. Therefore, the input of multiple stakeholders affected by a COS for IBD trials will be sought. Semi-structured interviews will be conducted with the following aims:

1) Preliminary prioritization of the importance of efficacy and safety outcome measures generated through the systematic review
2) Augmentation of this list with additional items considered important to stakeholders but not captured in the literature

Stakeholder interview participants and recruitment

We will engage and conduct interviews with the following stakeholder groups: 1) patients with IBD; 2) specialists caring for patients with IBD, including gastroenterologists, surgeons, and specialist nurses; 3) representatives from patient advocacy groups; 4) representatives from the pharmaceutical industry and; (5) representatives from regulatory agencies (e.g. FDA, European Medicines Agency, Health Canada). Participants will be purposively sampled to obtain a comprehensive representation in demographics, patient clinical characteristics, treatment experiences, and professional expertise. Sample size will be estimated pragmatically to achieve saturation of views represented in the qualitative data. An initial sample size of 30 interviews is estimated, or at theme saturation.

Data collection and analysis

Qualitative semi-structured interviews will be conducted, allowing all participants to raise issues considered of greatest importance. A topic guide will be provided to ensure all interviews address critical topics pertaining to COS development, including: 1) patient experiences of living with IBD and the benefits and harms of IBD-related treatment; 2) outcomes believed to be relevant and important to include in IBD trials and why; 3) measurement tools for use in IBD clinical trials that are effective, reliable, and practical; and 4) relative importance of outcomes identified from the systematic review. Face-to-face or telephone interviews lasting 30-60 minutes will be conducted by experts in qualitative methods and all interviews will be recorded and transcribed verbatim. Recordings will be imported into qualitative analysis software and narrative data will then be indexed and mapped to a thematic framework, providing a summary of participants' key points and priorities.[38]

Step 3: Delphi survey

An international Delphi survey, informed by literature review and semi-structured stakeholder interviews, will then be performed to achieve consensus on the outcomes for inclusion in the COS. The Delphi method allows panel members to anonymously derive consensus through multiple rounds of sequential questionnaires. After each round, the group responses are provided to panelists who can then reconsider their position in light of other viewpoints. The anonymity of the Delphi method avoids the opinions of prominent personalities from dominating the consensus and also facilitates wide international participation.[34] The Delphi process will consist of two rounds of

electronic-based questionnaire, response, and feedback. All electronic questionnaires will be pilot tested prior to distribution to ensure clarity.

Selection of panel members

For this study, the Delphi panel will include a minimum target sample size of 50 respondents. We aim to recruit a diverse participant pool, with involvement from each major stakeholder group, including patients, clinicians, researchers, and representatives from patient advocacy groups, industry, and research funding organizations. Selected participants will reflect a broad range of clinical experiences and geographical expertise, with representation from Canada, the United States, the United Kingdom, continental Europe, Asia, and Australia.

Researchers with extensive experience in IBD will be sought for the Delphi survey. During the systematic review, a list of authors with at least 25 publications in the field of IBD over the past 10 years (2006-2016), including at least two clinical trials or one systematic review of clinical trials on IBD will be compiled and invited to participate. Clinicians experienced in managing IBD will be recruited through convenience sampling. Patients will be eligible for inclusion in the Delphi survey if they have a confirmed history of CD or UC, attendance of healthcare for IBD, and fluent understanding of written English. Patients will be identified through national and international patient advocacy groups and authors connections and collaboration of the authors to ensure multi-national representation.

All potential participants will be emailed an invitation letter outlining the aims and details of the study and the rationale and importance of completing the entire Delphi process. Respondents who agree to take part will be assigned a unique identification number. For each round of the process, participants will have three weeks to complete the survey with generic email reminders sent at the one and two week marks. All data will be stored against the unique identifier only; participants will be blinded to the other respondents in the study. Only the lead author (CM) and primary investigator (VJ) will have access to the complete list of Delphi survey panelists. For each round of the Delphi survey, response and attrition rates will be calculated.

Delphi round one

In the first round, participants will be asked to identify the stakeholder group to which they belong, and complete questions about their professional background and experience with clinical research relevant to IBD. They will then be presented with the complete list of efficacy and safety outcomes generated from the literature review and stakeholder interviews. Outcome order will be randomly assigned to mitigate the influence of display order on scoring. Participants will be asked to rank each outcome on a scale from 1 to 9, based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group definitions.[39] Scores of 1-3 indicate an outcome that is not important for inclusion, scores of 4-6 indicate an outcome important but not critical for inclusion, and scores of 7-9 indicate an outcome felt critical for inclusion in the COS. An option to select “Unsure of significance” will also be available. Participants will be asked to focus on ranking the most important

outcomes for inclusion highly and excluding outcomes felt to be of lesser importance; regardless of score, all outcomes will be carried to the second round. Finally, through free text entry, participants will have the option to clarify compelling arguments for and against inclusion of outcomes and to identify additional outcomes not included in the first round questionnaire.

Responses from round one will be analyzed and collated into a feedback report. Descriptive statistics will be used to summarize the number of participants scoring each outcome and the distribution of scores. Responses to open-ended questions will be reviewed by the authorship team to evaluate for substantial arguments and additional suggestions will be reviewed for uncaptured outcomes in the first round questionnaire. Subgroup analysis will be conducted, stratifying scores by stakeholder group to evaluate for differences from other panelist responses. Panelists who do not complete the first round survey will not be invited to participate in round two.

Delphi round two

In round two, each participant will be provided with the number of respondents and distribution of scores for each efficacy and safety outcome from the first round, stratified by stakeholder group. They will then be shown their own score from round one and asked to rescore each outcome, with consideration based on insights from the group. Each outcome will be rescored on a scale from 1-9 as previously described and participants will be specifically asked whether each outcome should be included in the COS. Changes in score from round-to-round will be documented.

Responses from round two will be analyzed with descriptive statistics. Outcomes for which ≥70% of panelists scored it 7 to 9 and fewer than 15% of panelists scored it 1 to 3 were decided *a priori* to have met consensus for inclusion.[22] Conversely, outcomes for which ≥70% of panelists scored it 1 to 3, and fewer than 15% of panelists scored it 7 to 9 were defined to have met consensus for exclusion. Outcomes not meeting these definitions were classified as lack of consensus. While these definitions are subjective, they have been recommended by previous COS authors [22] and avoid *post-hoc* definitions of consensus that may bias the results.

Step 4: Consensus meeting

A face-to-face consensus meeting with key stakeholders will be held after completion of the Delphi process. The meeting will be chaired by an independent facilitator with the objective of finalizing the outcomes for inclusion in the COS. Participants will be purposively sampled from panelists completing both rounds of the Delphi study; approximately 30 participants from diverse stakeholder groups will be invited to participate. The results from each round of the Delphi survey will be reviewed and participants will ratify the efficacy and safety outcomes that meet consensus criteria for inclusion and exclusion. Participants will then discuss the outcomes for which there was lack of agreement; based on the discussion, participants will then anonymously vote for each outcome for inclusion and exclusion in the finalized COS using a format similar to that of the Delphi survey.

ETHICS AND DISSEMINATION

Ethical Considerations

As with previous COS development projects, this project is considered a service evaluation not directly influencing patient care or safety.[25 40] All participants involved will be asked for their consent before participating in either stakeholder interviews or the Delphi survey, and all procedures will be conducted according to the Declaration of Helsinki.

Dissemination

With over 30 novel therapeutic compounds in various stages of clinical development[41], the adoption of an international consensus COS will be critical in ensuring future clinical trials report valid, meaningful, and standardized outcomes. This need is particularly exigent, commensurate with the transition from traditional symptom-based outcomes such as the Crohn's Disease Activity Index and Mayo Clinic score, to a diverse array of endoscopic, histologic, radiographic, safety, and patient-reported endpoints. Through this COS, we intend to reduce outcome reporting bias, reduce reporting heterogeneity, improve clinical trial quality in IBD, and facilitate more robust data synthesis of treatment interventions.

A finalized COS reporting guideline and explanatory document will be drafted, including all efficacy and safety outcomes and measurements as determined by the Delphi rounds and consensus meeting. These documents will be disseminated by high impact publication.

DECLARATIONS

Authorship Contributions

CM and VJ were involved in study conception and manuscript drafting and editing. RP, RNF, BGF, WJS and CEP were involved in study conception and manuscript editing. RK and BGL were involved in manuscript editing for important intellectual content.

Data Sharing Statement

All data from the project will be available upon request from the corresponding author.

Competing interests

Christopher Ma has no conflicts of interest to declare

Remo Panaccione has received scientific advisory board fees from Abbott/AbbVie, Amgen, Janssen, Merck, Pfizer, Prometheus Laboratories, Salix Pharma, Shire, Takeda, Warner Chilcott; consulting fees from Abbott/AbbVie, Amgen, Aptalis, Astra Zeneca, Baxter, BMS, Centocor, Elan/Biogen, Eisai, Ferring, GSK, Janssen, Merck, Millennium, Pfizer, Proctor & Gamble, Prometheus Therapeutics and Diagnostics, Schering-Plough, Shire, Takeda, UCB Pharma, Warner Chilcott; research grants from Abbott/AbbVie, Amgen, Aptalis, Astra Zeneca, Baxter, BMS, Centocor, Eisai, Elan/Biogen, Ferring, GSK, Janssen, Merck, Millennium, Pfizer, Proctor & Gamble, Prometheus, Shire, Schering-Plough, Takeda, UCB Pharma, Warner Chilcott; and speaker's bureau fees from Abbott/AbbVie, Amgen, Aptalis, Astra Zeneca, Baxter, BMS, Centocor, Eisai, Elan/Biogen, Ferring, GSK, Janssen, Merck, Millennium, Pfizer, Proctor & Gamble, Prometheus, Schering-Plough, Shire, Takeda, UCB Pharma, Warner Chilcott

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Abbreviations

CD (Crohn's disease); CDAI (Crohn's Disease Activity Index); CENTRAL (Cochrane Central Register of Controlled Trials); COMET (Core Outcome Measures in Effectiveness Trials); COS (core outcome set); GRADE (Grading of Recommendations Assessment, Development, and Evaluation); IBD (inflammatory bowel disease); ICHOM (International Consortium for Health Outcomes Measurement); OMERACT (Outcome Measures in Rheumatology); PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses); PRO (patient reported outcome); RCT (randomized controlled trial); UC (ulcerative colitis); STRIDE (Selecting Therapeutic Targets in Inflammatory Bowel Disease)

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SUPPLEMENTAL FILE 1

Systematic review search strategies

MEDLINE

1. Inflammatory bowel disease.mp or exp Inflammatory Bowel Diseases/
2. Crohn's disease.mp or exp Crohn Disease/
3. ulcerative colitis.mp or exp Colitis, Ulcerative/
4. 1 or 2 or 3
5. limit #4 to yr="1998-Current"
6. trial.mp. or exp Clinical Trial, Phase I/ or exp Controlled Clinical Trial/ or exp Clinical Trial/ or exp Clinical Trial, Phase II/ or exp Clinical Trial, Phase III/ or exp Randomized Controlled Trial/
7. 5 and 6

PUBMED

1. "Inflammatory Bowel Diseases" [Majr MeSH]
2. "Crohn Disease" [Majr MeSH]
3. "Colitis, Ulcerative" [Majr MeSH]
4. 1 or 2 or 3
5. "Clinical Trial" [Publication Type]
6. 4 and 6
7. Filter Publication date 1998/01/01 to Current

EMBASE

1. exp inflammatory bowel disease/ or exp ulcerative colitis/ or exp Crohn disease
2. limit 1 to yr="1998-Current"
3. exp "phase 2 clinical trial (topic)"/ or exp "phase 4 clinical trial (topic)"/ or exp "clinical trial (topic)"/ or exp "phase 3 clinical trial (topic)"/ or exp "randomized controlled trial (topic)"/ or exp controlled clinical trial/ or exp "phase 1 clinical trial (topic)"/
4. 2 and 3

CENTRAL

1. inflammatory bowel disease:ti,ab,kw (Word variations have been searched)
2. Crohn's disease:ti,ab,kw (Word variations have been searched)
3. Crohn disease:ti,ab,kw (Word variations have been searched)
4. Ulcerative colitis:ti,ab,kw (Word variations have been searched)
5. #1 OR #2 OR #3 OR #4
6. Publication Year from 1998 to 2016

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Development of a core outcome set for clinical trials in inflammatory bowel disease: study protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey

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Development of a core outcome set for clinical trials in inflammatory bowel disease: study protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey

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ABSTRACT

Introduction:

Crohn's disease (CD) and ulcerative colitis (UC), the main forms of inflammatory bowel disease (IBD), are chronic, progressive, and disabling disorders of the gastrointestinal tract. Although data from randomized controlled trials (RCTs) provide the foundation of evidence that validates medical therapy for IBD, considerable heterogeneity exists in the measured outcomes used in these studies. Furthermore, in recent years, there has been a paradigm shift in IBD treatment targets, moving from symptom-based scoring to improvement or normalization of objective measures of inflammation such as endoscopic appearance, inflammatory biomarkers, and histologic and radiographic endpoints. The abundance of new treatment options and evolving endpoints poses opportunities and challenges for all stakeholders involved in drug development. Accordingly, there exists a need to harmonize measures used in clinical trials through development of a core outcome set (COS).

Methods and Analysis:

The development of an IBD-specific COS includes four steps. First, a systematic literature review is performed to identify outcomes previously used in IBD RCTs. Second, semi-structured qualitative interviews are conducted with key stakeholders, including patients, clinicians, researchers, pharmaceutical industry representatives, health care payers, and regulators to identify additional outcomes of importance. Using the outcomes generated from literature review and stakeholder interviews, an international two-round Delphi survey is conducted to prioritize outcomes for inclusion in

the COS. Finally, a consensus meeting is held to ratify the COS and disseminate findings for application in future IBD trials.

Ethics and Dissemination:

Given that over 30 novel therapeutic compounds are in development for IBD treatment, the design of robust clinical trials measuring relevant and standardized outcomes is crucial. Standardizing outcomes through a COS will reduce heterogeneity in trial reporting, facilitate valid comparisons of new therapies, and improve clinical trial quality.

Keywords:

Inflammatory bowel disease, Crohn's disease, ulcerative colitis, core outcome set, systematic review, consensus methods, Delphi

STRENGTHS AND LIMITATIONS

- This protocol outlines the first international consensus effort to develop a core outcome set (COS) for use in IBD clinical trials. With over 30 novel therapeutic compounds in development for IBD treatment and rapidly evolving treatment targets, the need to harmonize clinical trial efficacy and safety outcomes in a COS is exigent.
- The multistep process to develop the COS is rigorous and involves a detailed systematic literature review, semi-structured interviews with key stakeholder groups, two-round Delphi survey to prioritize key outcomes, and a consensus meeting to ratify the COS.

- To develop the COS, we will seek input from multiple stakeholders, including patients, clinicians, researchers, pharmaceutical industry representatives, health care payers, and regulators. This will generate diverse viewpoints reflecting clinical practices from around the world.
- Although the scope of this COS will be focused towards use in prospective clinical trials in IBD, the selected outcomes may not be relevant for open-label or retrospective studies of IBD treatment

INTRODUCTION

The inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), are chronic, progressive, and often disabling disorders of the gastrointestinal tract with no cure. Worldwide, the incidence of IBD is increasing with the highest incidence in North America and Europe; however rapidly rising rates of disease in Asia[1] have recently been observed. Typical symptoms of these diseases, which include diarrhea, gastrointestinal bleeding, and abdominal pain, cause impaired quality of life, reduced work capacity, and social stigmatization.[2] Although the etiology of IBD is unknown, existing evidence implicates development of a dysregulated immune response in genetically susceptible individuals consequent to complex interactions between the intestinal microbiome and environmental exposures.[3] Both CD and UC are lifelong diseases without a cure that typically require continued medical therapy as well as surgery in a large proportion of patients. Additionally, the direct and indirect costs associated with IBD is estimated to exceed $30 billion annually in the United States alone.[4 5]

Treatment of CD and UC is focused on controlling inflammation with anti-inflammatory and immunosuppressive agents, with goals of induction and maintenance of remission. In particular, the adoption of biologic therapies over the past two decades has revolutionized IBD management, making sustained remission an achievable therapeutic target.[6] Approval of these new agents has relied upon data from robust randomized controlled trials (RCTs)[7-14] that in recent years have increased in size and sophistication. Advances in this field continue at an increasingly rapid pace with multiple

classes of agents in late phase development.[15 16] In parallel, a paradigm shift in treatment targets for IBD has occurred, with a move away from symptom-based scoring[17-19] to normalization of more objective measures of inflammation such as endoscopic appearance, inflammatory biomarkers, and histologic and radiographic endpoints.

Furthermore, recognizing the need to accurately measure the patient experience with IBD, the US Food and Drug Administration (FDA) has advocated for measurement of patient-reported outcomes (PROs) in clinical trials.[20] The utilization of PROs as a treatment endpoint in IBD trials poses unique challenges: importantly, symptom scoring is likely to remain a central component of IBD PROs, despite poor sensitivity and specificity for predicting mucosal inflammation.[21] Symptom scoring may also be confounded by psychological comorbidity and perceived stress,[22] resulting in disparities between PROs and objectively assessed endoscopic, radiographic, and histologic disease activity, especially in Crohn's disease. Thus, the adoption of PROs as a primary therapeutic target in clinical trials would require careful evaluation.

In addition to the shift in efficacy outcomes measured in IBD trials, the assessment of safety outcomes has also changed with the introduction of biologic and immunomodulator therapies, which are often used in combination. As novel treatments are developed to target different components of the immune response, short- and long-term safety evaluations are essential. These include the risks of bacterial infections (including tuberculosis), viral infections (including hepatitis B or herpes zoster virus

reactivation), malignancy, lymphoma, infusion and injection reactions, and development of anti-drug antibodies.[23]

These shifts in the research environment have led investigators and regulatory authorities to re-evaluate the key efficacy and safety outcomes measured in IBD clinical trials. The selection of appropriate outcomes is critical for several reasons. First, their operating properties determine trial efficiency and ultimately drive both our ability to accurately identify effective new therapies and the cost of dug development programs. Second, choice of outcomes can shape clinical practice if the selected endpoints are perceived to be relevant to both patients and health care professionals. Third, identification of standardized outcomes has potential to facilitate and improve the quality of systematic reviews and meta-analyses. Finally, outcome measures are critical components of the analyses used by payers to determine the safety and relative cost-effectiveness of competing treatments and significantly influence regulatory and formulary policy.[24]

It is apparent that insufficient attention has been paid to the standardized assessment of outcome measures for IBD trials. Notably, no formalized consensus exists regarding what to measure, how to measure, and when to measure selected efficacy and safety outcomes in IBD trials.[25] Given the evolving landscape of IBD treatment endpoints and the rapid development of new therapies, an international consensus agreement on core outcomes for use in future IBD trials is of critical importance.

A core outcome set (COS) is a consensus derived minimum set of outcomes that should be measured and reported in all clinical trials of a given disease.[24] The expectation is that core outcomes will always be collected and reported, but the COS is not restrictive such that investigators are still encouraged to explore other outcomes in addition to the COS. COS have been developed and utilized effectively in several specialties, most prominently in rheumatology through the Outcome Measures in Rheumatology (OMERACT) initiative.[26] Protocols have been proposed for COS development in other areas of health research[27-33] and to facilitate this activity the Core Outcome Measures in Effectiveness Trials (COMET) initiative has begun.[34] Implementation of a successful COS should reduce heterogeneity in outcome reporting, enhance the quality of evidence synthesis and systematic reviews, and increase the relevance of clinical research for multiple stakeholders.[35]

This protocol establishes the context and scope for COS development in IBD, outlines the methods to be adopted for each step of COS development, and increases awareness of this effort to encourage IBD researchers and other stakeholders from around the world to participate.

METHODS AND ANALYSIS

Our interest in developing this COS has been listed in the non-database list of the COMET initiative (www.comet-initiative.org). This project will use published recommendations[24] for the development of an international consensus IBD-specific COS in a multi-step process. Detailed methodology for each step of the process is provided in the relevant sections below.

1) Completion of a systematic review to identify efficacy and safety outcomes currently reported in IBD randomized controlled trials
2) Identification of additional outcomes important to key stakeholders, including IBD patients and patient advocacy groups, clinicians, researchers, pharmaceutical industry representatives, health care payers, regulators and policy makers through semi-structured stakeholder interviews
3) Prioritization of outcomes and generation of a consensus outcomes list using a two-round Delphi survey[36]
4) Ratification of the COS in a consensus meeting of global experts

Scope of the core outcome set

This COS is intended as the international standard for clinical trials examining the efficacy of treatments in adult patients (≥18 years) with IBD. Patients included within the scope of this COS include those with:

1) Crohn's disease – including both luminal and peri-anal fistulizing disease
2) Ulcerative colitis – including patients with pouchitis after colectomy

Health interventions included within the scope of this COS include trials of therapeutic compounds and treatment algorithms. Effectiveness of surgical interventions will not be evaluated in this COS.

Identifying existing knowledge

To our knowledge, two existing initiatives have potential conceptual overlaps with the development of a COS. However, both projects have differing aims and neither of these identified projects have the same scope as the COS:

1) The International Consortium for Health Outcomes Measurement (ICHOM) is developing a standardized outcome set for IBD.[37] The ICHOM initiative is centered on devising patient- and value-based health care outcomes, which is most relevant as a quality metric for healthcare payers, with a broader scope on healthcare provision rather than a specific focus on core outcomes for assessment in clinical trials.
2) The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) program was initiated by the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD).[6] Their recommendations for clinical, endoscopic, histologic, imaging, biomarker, and patient-reported targets in CD and UC aim to guide clinical practice rather than drive endpoint selection for clinical trials and drug development.

Step 1: Systematic literature review

A literature review will be conducted to identify and compare outcomes reported in existing studies of interventions for adult IBD patients. No sources of financial support will be used for the systematic review.

Types of studies, participants, and interventions

RCTs and systematic reviews of RCTs (with or without meta-analysis) will be included. Studies not describing IBD treatment outcomes, conference proceedings/abstracts without complete trial description, or studies for which full-text is not available in English will be excluded. Trial participants will include all adult IBD patients (≥18 years), including specific subgroups of patients with peri-anal fistulizing CD and UC patients developing pouchitis after restorative proctocolectomy. Interventions will include trials of therapeutic compounds (including systemic and topical corticosteroids, anti-inflammatories and mesalamine compounds, immune modulating agents, pre- and probiotic therapies, biologic and biosimilar therapies, fecal microbiota transplantation, and small molecule therapy) and trials of management algorithms applied to IBD patients. Both effectiveness and safety outcomes will be assessed. Surgical interventions will be excluded.

Search methods for identification of studies and study eligibility

Full terms of a comprehensive, electronic search strategy developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines are detailed in Supplemental Files 1 and 2.[38] The search strategy will be applied to MEDLINE, PubMed, EMBASE, and the Cochrane Central Register of

Controlled Trials (CENTRAL). ClinicalTrials.gov will be searched for relevant projects currently underway and we will also screen abstracts from the American College of Gastroenterology Annual Scientific Meeting, Digestive Disease Week, United European Gastroenterology Week, and European Crohn's and Colitis Organization conference proceedings published from January 2007 through June 2016. The reference lists of relevant studies will be searched for additional studies not identified from the electronic database search. No language restrictions will be applied to the initial search strategy but studies without English-language full text will be excluded from the selection of relevant articles. Given the substantial changes in IBD trial design over the past two decades, we will restrict the search to studies published after 1998 to ensure selection of more contemporary and relevant outcomes. Two review authors (CM and CEP) will independently screen the abstracts returned from the search strategy and any studies not meeting inclusion criteria will be excluded. In cases of dispute, a third review author (VJ) will be consulted.

Assessment of methodologic quality

As the primary focus of the systematic review will be to generate a list of potential outcome measures, the methodologic quality of the reported outcomes in included studies will be assessed using four questions[39]:

1) Is the primary outcome clearly stated?
2) Is the primary outcome clearly defined so that another researcher would be able to reproduce its measurement (e.g. measurement tools, measurement timing)?
3) Are secondary outcomes clearly stated?

4) Are secondary outcomes clearly defined?

As the primary scope of this project evaluates outcome reporting, the overall methodological quality of the included studies from systematic reviews will not be evaluated.

Data extraction, analysis, and presentation

Independent data extraction will be performed by two review authors (CM and CEP) using a standardized extraction form for the following: author details and affiliation, year and journal of publication, study design, study population (CD, UC, peri-anal fistulizing CD and pouchitis), intervention(s) under review, primary and secondary effectiveness and safety outcome(s) reported, outcome definition(s), and outcome measurement tool(s). Disagreement will be resolved through discussion and if resolution is not possible, a third reviewer (VJ) will be consulted. Original study authors will be contacted if there is unclear/unavailable data. The data will be synthesized and presented in a descriptive table, with all reported outcome measures and the quality of outcome reporting. Efficacy outcomes will be stratified by category: clinical, endoscopic, histologic, radiologic, laboratory, patient-reported, and composite scales of multiple outcome measures. Safety outcomes will be stratified by adverse event type (e.g. infections, cardiac adverse events, malignancies, lymphoma, infusion/injection reactions, immunologic adverse events) and by severity (hospitalization, intervention discontinuation, death). These outcomes will then be condensed into a preliminary list for consideration in semi-structured interviews and the Delphi survey.

Records will be managed in EndNote™ reference software (Clarivate Analytics, Boston, MA).

Step 2: Stakeholder involvement

Outcomes measured in clinical trials must be meaningful to patients, health care providers, and health care systems who receive, deliver, and pay for care, respectively. Therefore, the input of multiple stakeholders affected by a COS for IBD trials will be sought. Semi-structured interviews will be conducted with the following aims:

1) Preliminary prioritization of the importance of efficacy and safety outcome measures generated through the systematic review
2) Augmentation of this list with additional items considered important to stakeholders but not captured in the literature

Stakeholder interview participants and recruitment

We will engage and conduct interviews with the following stakeholder groups: 1) patients with IBD; 2) specialists caring for patients with IBD, including gastroenterologists, surgeons, and specialist nurses; 3) representatives from patient advocacy groups; 4) representatives from the pharmaceutical industry and; (5) representatives from regulatory agencies (e.g. FDA, European Medicines Agency, Health Canada). Participants will be purposively sampled to obtain a comprehensive representation in demographics, patient clinical characteristics, treatment experiences, and professional expertise. Sample size will be estimated pragmatically to achieve

saturation of views represented in the qualitative data. An initial sample size of 30 interviews is estimated, or at theme saturation.

Data collection and analysis

Qualitative semi-structured interviews will be conducted, allowing all participants to raise issues considered of greatest importance. A topic guide will be provided to ensure all interviews address critical topics pertaining to COS development, including: 1) patient experiences of living with IBD and the benefits and harms of IBD-related treatment; 2) outcomes believed to be relevant and important to include in IBD trials and why; 3) measurement tools for use in IBD clinical trials that are effective, reliable, and practical; and 4) relative importance of outcomes identified from the systematic review. Face-to-face or telephone interviews lasting 30-60 minutes will be conducted by experts in qualitative methods and all interviews will be recorded and transcribed verbatim. Recordings will be imported into qualitative analysis software and narrative data will then be indexed and mapped to a thematic framework, providing a summary of participants' key points and priorities.[40]

Step 3: Delphi survey

An international Delphi survey, informed by literature review and semi-structured stakeholder interviews, will then be performed to achieve consensus on the outcomes for inclusion in the COS. The Delphi method allows panel members to anonymously derive consensus through multiple rounds of sequential questionnaires. After each round, the group responses are provided to panelists who can then reconsider their

position in light of other viewpoints. The anonymity of the Delphi method avoids the opinions of prominent personalities from dominating the consensus and also facilitates wide international participation.[36] The Delphi process will consist of two rounds of electronic-based questionnaire, response, and feedback. All electronic questionnaires will be pilot tested prior to distribution to ensure clarity.

Selection of panel members

For this study, the Delphi panel will include a minimum target sample size of 50 respondents. We aim to recruit a diverse participant pool, with involvement from each major stakeholder group, including patients, clinicians, researchers, and representatives from patient advocacy groups, industry, and research funding organizations. Selected participants will reflect a broad range of clinical experiences and geographical expertise, with representation from Canada, the United States, the United Kingdom, continental Europe, and the Asia-Pacific.

Researchers with extensive experience in IBD will be sought for the Delphi survey. During the systematic review, a list of authors with at least 25 publications in the field of IBD over the past 10 years (2006-2016), including at least two clinical trials or one systematic review of clinical trials on IBD will be compiled and invited to participate. The lead and corresponding authors of clinical trials or systematic reviews will be preferentially invited to participate. Clinicians experienced in managing IBD will be recruited through convenience sampling. Specifically, clinical medical and surgical leads of dedicated IBD centers from North America, Europe, and the Asia-Pacific will be

identified and recruited; this recruitment strategy has been previously used by other COS developers.[28 29]

Patients will be eligible for inclusion in the Delphi survey if they have a confirmed history of CD or UC, attendance of healthcare for IBD, and fluent understanding of written English. Patients will be identified through national and international patient advocacy groups and authors' connections. Strong collaborative partnerships between the authorship team and IBD centers in Europe and the Asia-Pacific will aim to incorporate multi-national patient representation. Representatives from the pharmaceutical industry will also be invited to participate; this group will comprise approximately 10% of Delphi survey participants.

All potential participants will be emailed an invitation letter outlining the aims and details of the study and the rationale and importance of completing the entire Delphi process. Respondents who agree to take part will be assigned a unique identification number. For each round of the process, participants will have three weeks to complete the survey with generic email reminders sent at the one and two week marks. All data will be stored against the unique identifier only; participants will be blinded to the other respondents in the study. Only the lead author (CM) and primary investigator (VJ) will have access to the complete list of Delphi survey panelists. For each round of the Delphi survey, response and attrition rates will be calculated.

Delphi round one

In the first round, participants will be asked to identify the stakeholder group to which they belong, and complete questions about their professional background and experience with clinical research relevant to IBD. They will then be presented with the complete list of efficacy and safety outcomes generated from the literature review and stakeholder interviews. Outcome order will be randomly assigned to mitigate the influence of display order on scoring. Participants will be asked to rank each outcome on a scale from 1 to 9, based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group definitions.[41] Scores of 1-3 indicate an outcome that is not important for inclusion, scores of 4-6 indicate an outcome important but not critical for inclusion, and scores of 7-9 indicate an outcome felt critical for inclusion in the COS. An option to select "Unsure of significance" will also be available. Participants will be asked to focus on ranking the most important outcomes for inclusion highly and excluding outcomes felt to be of lesser importance; regardless of score, all outcomes will be carried to the second round. Finally, through free text entry, participants will have the option to clarify compelling arguments for and against inclusion of outcomes and to identify additional outcomes not included in the first round questionnaire.

Responses from round one will be analyzed and collated into a feedback report. Descriptive statistics will be used to summarize the number of participants scoring each outcome and the distribution of scores. Responses to open-ended questions will be reviewed by the authorship team to evaluate for substantial arguments and additional suggestions will be reviewed for uncaptured outcomes in the first round questionnaire.

Subgroup analysis will be conducted, stratifying scores by stakeholder group to evaluate for differences from other panelist responses. Panelists who do not complete the first round survey will not be invited to participate in round two.

Delphi round two

In round two, each participant will be provided with the number of respondents and distribution of scores for each efficacy and safety outcome from the first round, stratified by stakeholder group. They will then be shown their own score from round one and asked to rescore each outcome, with consideration based on insights from the group. Each outcome will be rescored on a scale from 1-9 as previously described and participants will be specifically asked whether each outcome should be included in the COS. Changes in score from round-to-round will be documented.

Responses from round two will be analyzed with descriptive statistics. Outcomes for which ≥70% of panelists scored it 7 to 9 and fewer than 15% of panelists scored it 1 to 3 will be decided *a priori* to have met consensus for inclusion.[24] Conversely, outcomes for which ≥70% of panelists scored it 1 to 3, and fewer than 15% of panelists scored it 7 to 9 will be defined to have met consensus for exclusion. Outcomes not meeting these definitions will be classified as lack of consensus. While these definitions are subjective, they have been recommended by previous COS authors [24] and avoid *post-hoc* definitions of consensus that may bias the results.

Step 4: Consensus meeting

A face-to-face consensus meeting with key stakeholders will be held after completion of the Delphi process. The meeting will be chaired by an independent facilitator with the objective of finalizing the outcomes for inclusion in the COS. Participants will be purposively sampled from panelists completing both rounds of the Delphi study; approximately 30 participants from diverse stakeholder groups will be invited to participate. The results from each round of the Delphi survey will be reviewed and participants will ratify the efficacy and safety outcomes that meet consensus criteria for inclusion and exclusion. Participants will then discuss the outcomes for which there was lack of agreement; based on the discussion, participants will then anonymously vote for each outcome for inclusion and exclusion in the finalized COS using a format similar to that of the Delphi survey.

ETHICS AND DISSEMINATION

Ethical Considerations

As with previous COS development projects, this project is considered a service evaluation not directly influencing patient care or safety.[27 42] All participants involved will be asked for their consent before participating in either stakeholder interviews or the Delphi survey, and all procedures will be conducted according to the Declaration of Helsinki.

Dissemination

With over 30 novel therapeutic compounds in various stages of clinical development[43], the adoption of an international consensus COS will be critical in ensuring future clinical trials report valid, meaningful, and standardized efficacy outcomes. This need is particularly exigent, commensurate with the transition from traditional symptom-based outcomes such as the Crohn's Disease Activity Index and Mayo Clinic score, to a diverse array of endoscopic, histologic, radiographic, and patient-reported endpoints. Additionally, with the increasing adoption of biologic therapies for IBD management, it is essential for clinical trials to identify unique safety considerations associated with novel therapies. Reporting of treatment-specific safety outcomes such as infectious, malignant, immune, surgical, and drug-related adverse events may promote the development of future preventative strategies for optimizing short- and long-term patient safety. Through this COS, we intend to reduce outcome reporting bias, reduce reporting heterogeneity, improve clinical trial quality in IBD, and facilitate more robust data synthesis of treatment interventions.

A finalized COS reporting guideline and explanatory document will be drafted, including all efficacy and safety outcomes and measurements as determined by the Delphi rounds and consensus meeting. These documents will be disseminated by high impact publication.

DECLARATIONS

Authorship Contributions

CM and VJ were involved in study conception and manuscript drafting and editing. RP, RNF, BGF, WJS and CEP were involved in study conception and manuscript editing. RK and BGL were involved in manuscript editing for important intellectual content. VJ is the guarantor of the article.

Data Sharing Statement

All data from the project will be available upon request from the corresponding author.

Competing interests

Christopher Ma has no conflicts of interest to declare

Remo Panaccione has received scientific advisory board fees from Abbott/AbbVie, Amgen, Janssen, Merck, Pfizer, Prometheus Laboratories, Salix Pharma, Shire, Takeda, Warner Chilcott; consulting fees from Abbott/AbbVie, Amgen, Aptalis, Astra Zeneca, Baxter, BMS, Centocor, Elan/Biogen, Eisai, Ferring, GSK, Janssen, Merck, Millennium, Pfizer, Proctor & Gamble, Prometheus Therapeutics and Diagnostics, Schering-Plough, Shire, Takeda, UCB Pharma, Warner Chilcott; research grants from Abbott/AbbVie, Amgen, Aptalis, Astra Zeneca, Baxter, BMS, Centocor, Eisai, Elan/Biogen, Ferring, GSK, Janssen, Merck, Millennium, Pfizer, Proctor & Gamble, Prometheus, Shire, Schering-Plough, Takeda, UCB Pharma, Warner Chilcott; and speaker's bureau fees from Abbott/AbbVie, Amgen, Aptalis, Astra Zeneca, Baxter, BMS, Centocor, Eisai, Elan/Biogen, Ferring, GSK, Janssen, Merck, Millennium, Pfizer, Proctor & Gamble, Prometheus, Schering-Plough, Shire, Takeda, UCB Pharma, Warner Chilcott

Richard Fedorak has received scientific advisory board fees from Abbott/AbbVie, Celltrion, Ferring, Janssen, Shire, VSL#3; consulting fees from Abbott/AbbVie, Celltrion, Ferring, Janssen, Shire, VSL#3; and research grant support from Abbott/AbbVie, Alba Therapeutics, BMS, Celltrion, Centocor, Genentech, GSK, Janssen, Merck, Millennium, Novartis, Pfizer, Proctor & Gamble, Roche, VSL#3

Claire Parker has no conflicts of interest to declare

Reena Khanna has received consulting fees from AbbVie, Takeda, and Janssen

Barrett Levesque has received consulting fees from AbbVie, Takeda, Nestle Health Sciences, and Prometheus Labs

William Sandborn has served as a consultant to: AbbVie Inc., ActoGeniX NV, AGI Therapeutics, Inc., Alba Therapeutics Corporation, Albireo, Alfa Wasserman, Amgen, AM-Pharma BV, Anaphore, Astellas Pharma, Athersys, Inc., Atlantic Healthcare Limited, Axcan Pharma (now Aptalis), BioBalance Corporation, Boehringer-Ingelheim Inc, Bristol Meyers Squibb, Celgene, Celek Pharmaceuticals, Cellerix SL, Cerimon Pharmaceuticals, ChemoCentryx, CoMentis, Cosmo Technologies, Coronado Biosciences, Cytokine Pharmasciences, Eagle Pharmaceuticals, Eisai Medical Research Inc., Elan Pharmaceuticals, EnGene, Inc., Eli Lilly, Enteromedics, Exagen Diagnostics, Inc., Ferring Pharmaceuticals, Flexion Therapeutics, Inc., Funxional Therapeutics Limited, Genzyme Corporation, Genentech (now Roche), Gilead Sciences, Given Imaging, Glaxo Smith Kline, Human Genome Sciences, Ironwood Pharmaceuticals (previously Microbia Inc.), Janssen (previously Centocor), KaloBios Pharmaceuticals, Inc., Lexicon Pharmaceuticals, Lycera Corporation, Meda Pharmaceuticals (previously Alaven Pharmaceuticals), Merck Research Laboratories, MerckSerono, Millennium Pharmaceuticals (subsequently merged with Takeda), Nisshin Kyorin Pharmaceuticals Co., Ltd., Novo Nordisk A/S, NPS Pharmaceuticals, Optimer Pharmaceuticals, Orexigen Therapeutics, Inc., PDL Biopharma, Pfizer, Procter and Gamble, Prometheus Laboratories, ProtAb Limited, Purgenesis Technologies, Inc., Receptos, Relypsa, Inc., Salient Pharmaceuticals, Salix Pharmaceuticals, Inc., Santarus, Schering Plough Corporation (acquired by Merck), Shire Pharmaceuticals, Sigmoid Pharma Limited, Sirtris Pharmaceuticals, Inc. (a GSK company), S.L.A. Pharma (UK) Limited, Targacept, Teva Pharmaceuticals, Therakos, Tillotts Pharma AG (acquired by Zeria Pharmaceutical Co., Ltd), TxCell SA, UCB Pharma, Viamet Pharmaceuticals, Vascular Biogenics Limited (VBL), Warner Chilcott UK Limited; has received speaker's fees from: AbbVie Inc., Bristol Meyers Squibb, and Janssen (previously Centocor); and financial support for research from: AbbVie Inc., Bristol Meyers Squibb, Genentech, Glaxo Smith Kline, Janssen (previously Centocor), Millennium Pharmaceuticals (now Takeda), Novartis, Pfizer, Procter and Gamble Pharmaceuticals, Shire Pharmaceuticals, and UCB Pharma.

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Abbreviations

CD (Crohn's disease); CDAI (Crohn's Disease Activity Index); CENTRAL (Cochrane Central Register of Controlled Trials); COMET (Core Outcome Measures in Effectiveness Trials); COS (core outcome set); GRADE (Grading of Recommendations Assessment, Development, and Evaluation); IBD (inflammatory bowel disease); ICHOM (International Consortium for Health Outcomes Measurement); OMERACT (Outcome Measures in Rheumatology); PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses); PRO (patient reported outcome); RCT (randomized controlled trial); UC (ulcerative colitis); STRIDE (Selecting Therapeutic Targets in Inflammatory Bowel Disease)

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SUPPLEMENTAL FILE 2

Systematic review search strategies

MEDLINE

1. Inflammatory bowel disease.mp or exp Inflammatory Bowel Diseases/
2. Crohn's disease.mp or exp Crohn Disease/
3. ulcerative colitis.mp or exp Colitis, Ulcerative/
4. 1 or 2 or 3
5. limit #4 to yr="1998-Current"
6. trial.mp. or exp Clinical Trial, Phase I/ or exp Controlled Clinical Trial/ or exp Clinical Trial/ or exp Clinical Trial, Phase II/ or exp Clinical Trial, Phase III/ or exp Randomized Controlled Trial/
7. 5 and 6

PUBMED

1. "Inflammatory Bowel Diseases" [Majr MeSH]
2. "Crohn Disease" [Majr MeSH]
3. "Colitis, Ulcerative" [Majr MeSH]
4. 1 or 2 or 3
5. "Clinical Trial" [Publication Type]
6. 4 and 6
7. Filter Publication date 1998/01/01 to Current

EMBASE

1. exp inflammatory bowel disease/ or exp ulcerative colitis/ or exp Crohn disease
2. limit 1 to yr="1998-Current"
3. exp "phase 2 clinical trial (topic)"/ or exp "phase 4 clinical trial (topic)"/ or exp "clinical trial (topic)"/ or exp "phase 3 clinical trial (topic)"/ or exp "randomized controlled trial (topic)"/ or exp controlled clinical trial/ or exp "phase 1 clinical trial (topic)"/
4. 2 and 3

CENTRAL

1. inflammatory bowel disease:ti,ab,kw (Word variations have been searched)
2. Crohn's disease:ti,ab,kw (Word variations have been searched)
3. Crohn disease:ti,ab,kw (Word variations have been searched)
4. Ulcerative colitis:ti,ab,kw (Word variations have been searched)
5. #1 OR #2 OR #3 OR #4
6. Publication Year from 1998 to 2016

Supplemental File 1 – PRISMA-P Checklist

Section and topic	Item No	Checklist item	Manuscript Page and Section
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1: Title
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 10: Methods and Analysis
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Pages 1-2: Affiliations
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 24: Manuscript Contributions
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 12: No funding
Sponsor	5b	Provide name for the review funder and/or sponsor	Not applicable
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Not applicable
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 8-9, Introduction Page 12, Methods
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 12, Methods (Step 1: Systematic literature review)
METHODS			

Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Pages 12-13, Methods (Types of studies, participants, interventions; Search methods)
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Pages 12-13 – Methods (Search Methods for identification of studies and study eligibility)
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplemental File 2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 15 – Data extraction
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 14 – Data extraction
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 14 – Data extraction
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 12 – Types of studies, participants, and interventions
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 14 – Data extraction
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 13-14 – Assessment of methodologic quality
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Not applicable - qualitative systematic review
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Not applicable – qualitative systematic review
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Not applicable
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 14 – Data presentation

Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Not applicable (systematic review only)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 13-14 – Assessment of Methodologic Quality