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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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3 1 **Development of a core outcome set for clinical trials in inflammatory bowel**  
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5 2 **disease: study protocol for a systematic review of the literature and identification**  
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8 3 **of a core outcome set using a Delphi survey**  
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Ma *et al.* Development of a core outcome set for IBD clinical trials

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Ma *et al.*                      **Development of a core outcome set for IBD clinical trials**42    **ABSTRACT**43    *Introduction:*

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

57    *Methods and Analysis:*

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

Ma *et al.* **Development of a core outcome set for IBD clinical trials**

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

67

68 *Ethics and Dissemination:*

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

73

74 *Keywords:*

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

77

78 **STRENGTHS AND LIMITATIONS**

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

Ma *et al.***Development of a core outcome set for IBD clinical trials**

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4 88     • To develop the COS, we will seek input from multiple stakeholders, including  
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6 89     patients, clinicians, researchers, pharmaceutical industry representatives, health  
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8 90     care payers, and regulators. This will generate diverse viewpoints reflecting  
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10 91     clinical practices from around the world.  
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**93 INTRODUCTION**

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

108  
109 Treatment of CD and UC is focused on controlling inflammation with anti-inflammatory  
110 and immunosuppressive agents, with goals of induction and maintenance of remission.  
111 In particular, the adoption of biologic therapies over the past two decades has  
112 revolutionized IBD management, making sustained remission an achievable therapeutic  
113 target.<sup>6</sup> Approval of these new agents has relied upon data from robust randomized  
114 controlled trials (RCTs)<sup>7-14</sup> that in recent years have increased in size and  
115 sophistication. Advances in this field continue at an increasingly rapid pace with multiple

*Ma et al.*                      **Development of a core outcome set for IBD clinical trials**

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3 116 classes of agents in late phase development.<sup>15 16</sup> In parallel, a paradigm shift in  
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5 117 treatment targets for IBD has occurred, with a move away from symptom-based  
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8 118 scoring<sup>17-19</sup> to normalization of more objective measures of inflammation such as  
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10 119 endoscopic appearance, inflammatory biomarkers, and histologic and radiographic  
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12 120 endpoints. Furthermore, recognizing the need to accurately measure the patient  
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15 121 experience with IBD, the US Food and Drug Administration (FDA) has advocated for  
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17 122 measurement of patient-reported outcomes (PROs) in clinical trials.<sup>20</sup>  
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22 124 In addition to the shift in efficacy outcomes measured in IBD trials, the assessment of  
23  
24 125 safety outcomes has also changed with the introduction of biologic and  
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26 126 immunomodulator therapies, which are often used in combination. As novel treatments  
27  
28 127 are developed to target different components of the immune response, short and long-  
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30 128 term safety evaluations are essential. These include the risks of bacterial infections  
31  
32 129 (including tuberculosis), viral infections (including hepatitis B or herpes zoster virus  
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34 130 reactivation), malignancy, lymphoma, infusion and injection reactions, and development  
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36 131 of anti-drug antibodies.<sup>21</sup>  
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43 133 These shifts in the research environment have led investigators and regulatory  
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45 134 authorities to re-evaluate the key efficacy and safety outcomes measured in IBD clinical  
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47 135 trials. The selection of appropriate outcomes is critical for several reasons. First, their  
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49 136 operating properties determine trial efficiency and ultimately drive both our ability to  
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51 137 accurately identify effective new therapies and the cost of drug development programs.  
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54 138 Second, choice of outcomes can shape clinical practice if the selected endpoints are  
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*Ma et al.*                    **Development of a core outcome set for IBD clinical trials**

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3 139 perceived to be relevant to both patients and health care professionals. Third,  
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5 140 identification of standardized outcomes has potential to facilitate and improve the quality  
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8 141 of systematic reviews and meta-analyses. Finally, outcome measures are critical  
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10 142 components of the analyses used by payers to determine the safety and relative cost-  
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12 143 effectiveness of competing treatments and significantly influence regulatory and  
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15 144 formulary policy.<sup>22</sup>  
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20 146 It is apparent that insufficient attention has been paid to the standardized assessment of  
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22 147 outcome measures for IBD trials. Notably, no formalized consensus exists regarding  
23  
24 148 what to measure, how to measure, and when to measure selected efficacy and safety  
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26  
27 149 outcomes in IBD trials.<sup>23</sup> Given the evolving landscape of IBD treatment endpoints and  
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29 150 the rapid development of new therapies, an international consensus agreement on core  
30  
31 151 outcomes for use in future IBD trials is of critical importance.  
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34 152  
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36 153 A core outcome set (COS) is a consensus derived minimum set of outcomes that  
37  
38 154 should be measured and reported in all clinical trials of a given disease.<sup>22</sup> The  
39  
40 155 expectation is that core outcomes will always be collected and reported, but the COS is  
41  
42 156 not restrictive such that investigators are still encouraged to explore other outcomes in  
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44 157 addition to the COS. COS have been developed and utilized effectively in several  
45  
46 158 specialties, most prominently in rheumatology through the Outcome Measures in  
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48 159 Rheumatology (OMERACT) initiative.<sup>24</sup> Protocols have been proposed for COS  
49  
50 160 development in other areas of health research<sup>25-31</sup> and to facilitate this activity the Core  
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53 161 Outcome Measures in Effectiveness Trials (COMET) initiative has begun.<sup>32</sup>  
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*Ma et al.*                    **Development of a core outcome set for IBD clinical trials**

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3 162 Implementation of a successful COS should reduce heterogeneity in outcome reporting,  
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6 163 enhance the quality of evidence synthesis and systematic reviews, and increase the  
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8 164 relevance of clinical research for multiple stakeholders.<sup>33</sup>  
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13 166 This protocol establishes the context and scope for COS development in IBD, outlines  
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15 167 the methods to be adopted for each step of COS development, and increases  
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17 168 awareness of this effort to encourage IBD researchers and other stakeholders from  
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20 169 around the world to participate.  
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**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](http://www.comet-initiative.org)). This project will use published recommendations<sup>22</sup> 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<sup>34</sup>
- 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 ( $\geq 18$  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

Ma *et al.* **Development of a core outcome set for IBD clinical trials**

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3 192 Health interventions included within the scope of this COS include trials of therapeutic  
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5 193 compounds and treatment algorithms. Effectiveness of surgical interventions will not be  
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8 194 evaluated in this COS.  
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13 196 **Identifying existing knowledge**

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15 197 To our knowledge, two existing initiatives have potential conceptual overlaps with the  
16  
17 198 development of a COS. However, both projects have differing aims and neither of these  
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20 199 identified projects have the same scope as the COS:

21  
22 200 1) The International Consortium for Health Outcomes Measurement (ICHOM) is  
23  
24 201 developing a standardized outcome set for IBD.<sup>35</sup> The ICHOM initiative is  
25  
26 202 centered on devising patient- and value-based health care outcomes, which is  
27  
28  
29 203 most relevant as a quality metric for healthcare payers, with a broader scope on  
30  
31 204 healthcare provision rather than a specific focus on core outcomes for  
32  
33  
34 205 assessment in clinical trials.  
35

36 206 2) The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE)  
37  
38 207 program was initiated by the International Organization for the Study of  
39  
40 208 Inflammatory Bowel Diseases.<sup>6</sup> Their recommendations for clinical, endoscopic,  
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43 209 histologic, imaging, biomarker, and patient-reported targets in CD and UC aim to  
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46 210 guide clinical practice rather than drive endpoint selection for clinical trials and  
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48 211 drug development.  
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53 213 **Step 1: Systematic literature review**  
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Ma *et al.* **Development of a core outcome set for IBD clinical trials**

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3 214 A literature review will be conducted to identify and compare outcomes reported in  
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5 215 existing studies of interventions for adult IBD patients.  
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10 217 *Types of studies, participants, and interventions*

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12 218 RCTs and systematic reviews of RCTs (with or without meta-analysis) will be included.

13 219 Studies not describing IBD treatment outcomes, conference proceedings/abstracts

14  
15 220 without complete trial description, or studies for which full-text is not available in English

16  
17 221 will be excluded. Trial participants will include all adult IBD patients ( $\geq 18$  years),

18  
19 222 including specific subgroups of patients with peri-anal fistulizing CD and UC patients

20  
21 223 developing pouchitis after restorative proctocolectomy. Interventions will include trials of

22  
23 224 therapeutic compounds (including systemic and topical corticosteroids, anti-

24  
25 225 inflammatory and mesalamine compounds, immune modulating agents, pre- and

26  
27 226 probiotic therapies, biologic and biosimilar therapies, fecal microbiota transplantation,

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29 227 and small molecule therapy) and trials of management algorithms applied to IBD

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31 228 patients. Both effectiveness and safety outcomes will be assessed. Surgical

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33 229 interventions will be excluded.

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37 231 *Search methods for identification of studies and study eligibility*

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39 232 Full terms of a comprehensive, electronic search strategy developed in accordance with

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41 233 the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

42  
43 234 guidelines are detailed in Supplemental File 1.<sup>36</sup> The search strategy will be applied to

44  
45 235 MEDLINE, PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials

46  
47 236 (CENTRAL). ClinicalTrials.gov will be searched for relevant projects currently underway

Ma *et al.* **Development of a core outcome set for IBD clinical trials**

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

250

251 *Assessment of methodologic quality*

252 As the primary focus of the systematic review will be to generate a list of potential  
253 outcome measures, the methodologic quality of the reported outcomes in included  
254 studies will be assessed using four questions<sup>37</sup>:

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

Ma *et al.* **Development of a core outcome set for IBD clinical trials**

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3 260 As the primary scope of this project evaluates outcome reporting, the overall  
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6 261 methodological quality of the included studies from systematic reviews will not be  
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8 262 evaluated.

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13 264 *Data extraction, analysis, and presentation*

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15 265 Independent data extraction will be performed by two review authors (CM and CEP) for  
16  
17 266 the following: author details and affiliation, year and journal of publication, study design,  
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20 267 study population (CD, UC, peri-anal fistulizing CD and pouchitis), intervention(s) under  
21  
22 268 review, primary and secondary effectiveness and safety outcome(s) reported, outcome  
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24 269 definition(s), and outcome measurement tool(s). Disagreement will be resolved through  
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26  
27 270 discussion and if resolution is not possible, a third reviewer (VJ) will be consulted.  
28  
29 271 Original study authors will be contacted if there is unclear/unavailable data. The data  
30  
31 272 will be synthesized and presented in a descriptive table, with all reported outcome  
32  
33 273 measures and the quality of outcome reporting. Efficacy outcomes will be stratified by  
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36 274 category: clinical, endoscopic, histologic, radiologic, laboratory, patient-reported, and  
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39 275 composite scales of multiple outcome measures. Safety outcomes will be stratified by  
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41 276 adverse event type (e.g. infections, cardiac adverse events, malignancies, lymphoma,  
42  
43 277 infusion/injection reactions, immunologic adverse events) and by severity  
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46 278 (hospitalization, intervention discontinuation, death). These outcomes will then be  
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48 279 condensed into a preliminary list for consideration in semi-structured interviews and the  
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50 280 Delphi survey.

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55 282 **Step 2: Stakeholder involvement**

Ma *et al.* **Development of a core outcome set for IBD clinical trials**

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3 283 Outcomes measured in clinical trials must be meaningful to patients, health care  
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6 284 providers, and health care systems who receive, deliver, and pay for care, respectively.  
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8 285 Therefore, the input of multiple stakeholders affected by a COS for IBD trials will be  
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10 286 sought. Semi-structured interviews will be conducted with the following aims:

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13 287 1) Preliminary prioritization of the importance of efficacy and safety outcome  
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15 288 measures generated through the systematic review  
16  
17 289 2) Augmentation of this list with additional items considered important to  
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19 290 stakeholders but not captured in the literature  
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24 292 *Stakeholder interview participants and recruitment*

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27 293 We will engage and conduct interviews with the following stakeholder groups: 1)  
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29 294 patients with IBD; 2) specialists caring for patients with IBD, including  
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31 295 gastroenterologists, surgeons, and specialist nurses; 3) representatives from patient  
32  
33 296 advocacy groups; 4) representatives from the pharmaceutical industry and; (5)  
34  
35 297 representatives from regulatory agencies (e.g. FDA, European Medicines Agency,  
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37 298 Health Canada). Participants will be purposively sampled to obtain a comprehensive  
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39 299 representation in demographics, patient clinical characteristics, treatment experiences,  
40  
41 300 and professional expertise. Sample size will be estimated pragmatically to achieve  
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43 301 saturation of views represented in the qualitative data. An initial sample size of 30  
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45 302 interviews is estimated, or at theme saturation.  
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53 304 *Data collection and analysis*  
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*Ma et al.*                    **Development of a core outcome set for IBD clinical trials**

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3 305 Qualitative semi-structured interviews will be conducted, allowing all participants to raise  
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5 306 issues considered of greatest importance. A topic guide will be provided to ensure all  
6  
7 307 interviews address critical topics pertaining to COS development, including: 1) patient  
8  
9 308 experiences of living with IBD and the benefits and harms of IBD-related treatment; 2)  
10  
11 309 outcomes believed to be relevant and important to include in IBD trials and why; 3)  
12  
13 310 measurement tools for use in IBD clinical trials that are effective, reliable, and practical;  
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15 311 and 4) relative importance of outcomes identified from the systematic review. Face-to-  
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17 312 face or telephone interviews lasting 30-60 minutes will be conducted by experts in  
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19 313 qualitative methods and all interviews will be recorded and transcribed verbatim.  
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21 314 Recordings will be imported into qualitative analysis software and narrative data will  
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23 315 then be indexed and mapped to a thematic framework, providing a summary of  
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25 316 participants' key points and priorities.<sup>38</sup>  
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**Step 3: Delphi survey**

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36 319 An international Delphi survey, informed by literature review and semi-structured  
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38 320 stakeholder interviews, will then be performed to achieve consensus on the outcomes  
39  
40 321 for inclusion in the COS. The Delphi method allows panel members to anonymously  
41  
42 322 derive consensus through multiple rounds of sequential questionnaires. After each  
43  
44 323 round, the group responses are provided to panelists who can then reconsider their  
45  
46 324 position in light of other viewpoints. The anonymity of the Delphi method avoids the  
47  
48 325 opinions of prominent personalities from dominating the consensus and also facilitates  
49  
50 326 wide international participation.<sup>34</sup> The Delphi process will consist of two rounds of  
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Ma *et al.*                      **Development of a core outcome set for IBD clinical trials**

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3 327 electronic-based questionnaire, response, and feedback. All electronic questionnaires  
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5 328 will be pilot tested prior to distribution to ensure clarity.  
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10 330 *Selection of panel members*

11  
12 331 For this study, the Delphi panel will include a minimum target sample size of 50  
13  
14 332 respondents. We aim to recruit a diverse participant pool, with involvement from each  
15  
16 333 major stakeholder group, including patients, clinicians, researchers, and representatives  
17  
18 334 from patient advocacy groups, industry, and research funding organizations. Selected  
19  
20 335 participants will reflect a broad range of clinical experiences and geographical expertise,  
21  
22 336 with representation from Canada, the United States, the United Kingdom, continental  
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24 337 Europe, Asia, and Australia.  
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31 339 Researchers with extensive experience in IBD will be sought for the Delphi survey.  
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34 340 During the systematic review, a list of authors with at least 25 publications in the field of  
35  
36 341 IBD over the past 10 years (2006-2016), including at least two clinical trials or one  
37  
38 342 systematic review of clinical trials on IBD will be compiled and invited to participate.  
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40 343 Clinicians experienced in managing IBD will be recruited through convenience  
41  
42 344 sampling. Patients will be eligible for inclusion in the Delphi survey if they have a  
43  
44 345 confirmed history of CD or UC, attendance of healthcare for IBD, and fluent  
45  
46 346 understanding of written English. Patients will be identified through national and  
47  
48 347 international patient advocacy groups and authors connections and collaboration of the  
49  
50 348 authors to ensure multi-national representation.  
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Ma *et al.*                      **Development of a core outcome set for IBD clinical trials**

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3 350 All potential participants will be emailed an invitation letter outlining the aims and details  
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5  
6 351 of the study and the rationale and importance of completing the entire Delphi process.  
7  
8 352 Respondents who agree to take part will be assigned a unique identification number.  
9  
10  
11 353 For each round of the process, participants will have three weeks to complete the  
12  
13 354 survey with generic email reminders sent at the one and two week marks. All data will  
14  
15 355 be stored against the unique identifier only; participants will be blinded to the other  
16  
17 356 respondents in the study. Only the lead author (CM) and primary investigator (VJ) will  
18  
19  
20 357 have access to the complete list of Delphi survey panelists. For each round of the  
21  
22 358 Delphi survey, response and attrition rates will be calculated.  
23

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26  
27 360 *Delphi round one*

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29 361 In the first round, participants will be asked to identify the stakeholder group to which  
30  
31 362 they belong, and complete questions about their professional background and  
32  
33 363 experience with clinical research relevant to IBD. They will then be presented with the  
34  
35 364 complete list of efficacy and safety outcomes generated from the literature review and  
36  
37 365 stakeholder interviews. Outcome order will be randomly assigned to mitigate the  
38  
39 366 influence of display order on scoring. Participants will be asked to rank each outcome  
40  
41 367 on a scale from 1 to 9, based on the Grading of Recommendations Assessment,  
42  
43 368 Development, and Evaluation (GRADE) working group definitions.<sup>39</sup> Scores of 1-3  
44  
45 369 indicate an outcome that is not important for inclusion, scores of 4-6 indicate an  
46  
47 370 outcome important but not critical for inclusion, and scores of 7-9 indicate an outcome  
48  
49 371 felt critical for inclusion in the COS. An option to select “Unsure of significance” will also  
50  
51 372 be available. Participants will be asked to focus on ranking the most important  
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**Ma et al. Development of a core outcome set for IBD clinical trials**

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3 373 outcomes for inclusion highly and excluding outcomes felt to be of lesser importance;  
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5  
6 374 regardless of score, all outcomes will be carried to the second round. Finally, through  
7  
8 375 free text entry, participants will have the option to clarify compelling arguments for and  
9  
10 376 against inclusion of outcomes and to identify additional outcomes not included in the  
11  
12  
13 377 first round questionnaire.

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15 378  
16  
17 379 Responses from round one will be analyzed and collated into a feedback report.  
18  
19  
20 380 Descriptive statistics will be used to summarize the number of participants scoring each  
21  
22 381 outcome and the distribution of scores. Responses to open-ended questions will be  
23  
24 382 reviewed by the authorship team to evaluate for substantial arguments and additional  
25  
26 383 suggestions will be reviewed for uncaptured outcomes in the first round questionnaire.  
27  
28  
29 384 Subgroup analysis will be conducted, stratifying scores by stakeholder group to  
30  
31 385 evaluate for differences from other panelist responses. Panelists who do not complete  
32  
33 386 the first round survey will not be invited to participate in round two.

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36 387  
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39 388 *Delphi round two*  
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41 389 In round two, each participant will be provided with the number of respondents and  
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43 390 distribution of scores for each efficacy and safety outcome from the first round, stratified  
44  
45 391 by stakeholder group. They will then be shown their own score from round one and  
46  
47 392 asked to rescore each outcome, with consideration based on insights from the group.  
48  
49  
50 393 Each outcome will be rescored on a scale from 1-9 as previously described and  
51  
52 394 participants will be specifically asked whether each outcome should be included in the  
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54  
55 395 COS. Changes in score from round-to-round will be documented.

Ma *et al.* **Development of a core outcome set for IBD clinical trials**

396  
397 Responses from round two will be analyzed with descriptive statistics. Outcomes for  
398 which  $\geq 70\%$  of panelists scored it 7 to 9 and fewer than 15% of panelists scored it 1 to 3  
399 were decided *a priori* to have met consensus for inclusion.<sup>22</sup> Conversely, outcomes for  
400 which  $\geq 70\%$  of panelists scored it 1 to 3, and fewer than 15% of panelists scored it 7 to  
401 9 were defined to have met consensus for exclusion. Outcomes not meeting these  
402 definitions were classified as lack of consensus. While these definitions are subjective,  
403 they have been recommended by previous COS authors<sup>22</sup> and avoid *post-hoc*  
404 definitions of consensus that may bias the results.

**Step 4: Consensus meeting**

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

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Ma *et al.* **Development of a core outcome set for IBD clinical trials**

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3 420 **ETHICS AND DISSEMINATION**

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5 421 **Ethical Considerations**

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8 422 As with previous COS development projects, this project is considered a service  
9  
10 423 evaluation not directly influencing patient care or safety.<sup>25 40</sup> All participants involved will  
11  
12 424 be asked for their consent before participating in either stakeholder interviews or the  
13  
14 425 Delphi survey, and all procedures will be conducted according to the Declaration of  
15  
16 426 Helsinki.  
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22 428 **Dissemination**

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24 429 With over 30 novel therapeutic compounds in various stages of clinical development<sup>41</sup>,  
25  
26 430 the adoption of an international consensus COS will be critical in ensuring future clinical  
27  
28 431 trials report valid, meaningful, and standardized outcomes. This need is particularly  
29  
30 432 exigent, commensurate with the transition from traditional symptom-based outcomes  
31  
32 433 such as the Crohn's Disease Activity Index and Mayo Clinic score, to a diverse array of  
33  
34 434 endoscopic, histologic, radiographic, safety, and patient-reported endpoints. Through  
35  
36 435 this COS, we intend to reduce outcome reporting bias, reduce reporting heterogeneity,  
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38 436 improve clinical trial quality in IBD, and facilitate more robust data synthesis of treatment  
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40 437 interventions.  
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48 439 A finalized COS reporting guideline and explanatory document will be drafted, including  
49  
50 440 all efficacy and safety outcomes and measurements as determined by the Delphi  
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52 441 rounds and consensus meeting. These documents will be disseminated by high impact  
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54 442 publication.  
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Ma *et al.* **Development of a core outcome set for IBD clinical trials**

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3 443 **DECLARATIONS**

4  
5 444 **Authorship Contributions**

6  
7  
8 445 CM and VJ were involved in study conception and manuscript drafting and editing. RP,

9  
10 446 RNF, BGF, WJS and CEP were involved in study conception and manuscript editing.

11  
12 447 RK and BGL were involved in manuscript editing for important intellectual content.

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17 449 **Data Sharing Statement**

18  
19 450 All data from the project will be available upon request from the corresponding author.

20  
21 451

22  
23 452 **Competing interests**

24  
25 453 Christopher Ma has no conflicts of interest to declare

26  
27 454  
28 455 Remo Panaccione has received scientific advisory board fees from Abbott/AbbVie,  
29 456 Amgen, Janssen, Merck, Pfizer, Prometheus Laboratories, Salix Pharma, Shire,  
30 457 Takeda, Warner Chilcott; consulting fees from Abbott/AbbVie, Amgen, Aptalis, Astra  
31 458 Zeneca, Baxter, BMS, Centocor, Elan/Biogen, Eisai, Ferring, GSK, Janssen, Merck,  
32 459 Millennium, Pfizer, Proctor & Gamble, Prometheus Therapeutics and Diagnostics,  
33 460 Schering-Plough, Shire, Takeda, UCB Pharma, Warner Chilcott; research grants from  
34 461 Abbott/AbbVie, Amgen, Aptalis, Astra Zeneca, Baxter, BMS, Centocor, Eisai,  
35 462 Elan/Biogen, Ferring, GSK, Janssen, Merck, Millennium, Pfizer, Proctor & Gamble,  
36 463 Prometheus, Shire, Schering-Plough, Takeda, UCB Pharma, Warner Chilcott; and  
37 464 speaker's bureau fees from Abbott/AbbVie, Amgen, Aptalis, Astra Zeneca, Baxter,  
38 465 BMS, Centocor, Eisai, Elan/Biogen, Ferring, GSK, Janssen, Merck, Millennium, Pfizer,  
39 466 Proctor & Gamble, Prometheus, Schering-Plough, Shire, Takeda, UCB Pharma, Warner  
40 467 Chilcott

41  
42 468  
43 469 Richard Fedorak has received scientific advisory board fees from Abbott/AbbVie,  
44 470 Celltrion, Ferring, Janssen, Shire, VSL#3; consulting fees from Abbott/AbbVie, Celltrion,  
45 471 Ferring, Janssen, Shire, VSL#3; and research grant support from Abbott/AbbVie, Alba  
46 472 Therapeutics, BMS, Celltrion, Centocor, Genentech, GSK, Janssen, Merck, Millennium,  
47 473 Novartis, Pfizer, Proctor & Gamble, Roche, VSL#3

48  
49 474  
50 475 Claire Parker has no conflicts of interest to declare

51  
52 476  
53 477 Reena Khanna has received consulting fees from AbbVie, Takeda, and Janssen

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Ma *et al.***Development of a core outcome set for IBD clinical trials**

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2  
3 479 Barrett Levesque has received consulting fees from AbbVie, Takeda, Nestle Health  
4 480 Sciences, and Prometheus Labs  
5 481  
6 482 William Sandborn has served as a consultant to: AbbVie Inc., ActoGeniX NV, AGI  
7 483 Therapeutics, Inc., Alba Therapeutics Corporation, Albireo, Alfa Wasserman, Amgen,  
8 484 AM-Pharma BV, Anaphore, Astellas Pharma, Athersys, Inc., Atlantic Healthcare  
9 485 Limited, Axcan Pharma (now Aptalis), BioBalance Corporation, Boehringer-Ingelheim  
10 486 Inc, Bristol Meyers Squibb, Celgene, Celek Pharmaceuticals, Cellerix SL, Cerimon  
11 487 Pharmaceuticals, ChemoCentryx, CoMentis, Cosmo Technologies, Coronado  
12 488 Biosciences, Cytokine Pharmasciences, Eagle Pharmaceuticals, Eisai Medical  
13 489 Research Inc., Elan Pharmaceuticals, EnGene, Inc., Eli Lilly, Enteromedics, Exagen  
14 490 Diagnostics, Inc., Ferring Pharmaceuticals, Flexion Therapeutics, Inc., Funxional  
15 491 Therapeutics Limited, Genzyme Corporation, Genentech (now Roche), Gilead  
16 492 Sciences, Given Imaging, Glaxo Smith Kline, Human Genome Sciences, Ironwood  
17 493 Pharmaceuticals (previously Microbia Inc.), Janssen (previously Centocor), KaloBios  
18 494 Pharmaceuticals, Inc., Lexicon Pharmaceuticals, Lycera Corporation, Meda  
19 495 Pharmaceuticals (previously Alaven Pharmaceuticals), Merck Research Laboratories,  
20 496 MerckSerono, Millennium Pharmaceuticals (subsequently merged with Takeda), Nisshin  
21 497 Kyorin Pharmaceuticals Co., Ltd., Novo Nordisk A/S, NPS Pharmaceuticals, Optimer  
22 498 Pharmaceuticals, Orexigen Therapeutics, Inc., PDL Biopharma, Pfizer, Procter and  
23 499 Gamble, Prometheus Laboratories, ProtAb Limited, Purgenesis Technologies, Inc.,  
24 500 Receptos, Relypsa, Inc., Salient Pharmaceuticals, Salix Pharmaceuticals, Inc.,  
25 501 Santarus, Schering Plough Corporation (acquired by Merck), Shire Pharmaceuticals,  
26 502 Sigmoid Pharma Limited, Sirtris Pharmaceuticals, Inc. (a GSK company), S.L.A.  
27 503 Pharma (UK) Limited, Targacept, Teva Pharmaceuticals, Therakos, Tillotts Pharma AG  
28 504 (acquired by Zeria Pharmaceutical Co., Ltd), TxCell SA, UCB Pharma, Viamet  
29 505 Pharmaceuticals, Vascular Biogenics Limited (VBL), Warner Chilcott UK Limited; has  
30 506 received speaker's fees from: AbbVie Inc., Bristol Meyers Squibb, and Janssen  
31 507 (previously Centocor); and financial support for research from: AbbVie Inc., Bristol  
32 508 Meyers Squibb, Genentech, Glaxo Smith Kline, Janssen (previously Centocor),  
33 509 Millennium Pharmaceuticals (now Takeda), Novartis, Pfizer, Procter and Gamble  
34 510 Pharmaceuticals, Shire Pharmaceuticals, and UCB Pharma.  
35 511  
36 512 Brian Feagan has received grant/research support from Millennium Pharmaceuticals,  
37 513 Merck, Tillotts Pharma AG, AbbVie, Novartis Pharmaceuticals, Centocor Inc.,  
38 514 Elan/Biogen, UCB Pharma, Bristol-Myers Squibb, Genentech, ActoGenix, and Wyeth  
39 515 Pharmaceuticals Inc.; consulting fees from Millennium Pharmaceuticals, Merck,  
40 516 Centocor Inc., Elan/Biogen, Janssen-Ortho, Teva Pharmaceuticals, Bristol-Myers  
41 517 Squibb, Celgene, UCB Pharma, AbbVie, Astra Zeneca, Serono, Genentech, Tillotts  
42 518 Pharma AG, Unity Pharmaceuticals, Albireo Pharma, Given Imaging Inc., Salix  
43 519 Pharmaceuticals, Novonordisk, GSK, Actogenix, Prometheus Therapeutics and  
44 520 Diagnostics, Athersys, Axcan, Gilead, Pfizer, Shire, Wyeth, Zealand Pharma, Zyngenia,  
45 521 GiCare Pharma Inc., and Sigmoid Pharma; and speakers bureaux fees from UCB,  
46 522 AbbVie, and J&J/Janssen  
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Ma *et al.*

## Development of a core outcome set for IBD clinical trials

524 Vipul Jairath has received scientific advisory board fees from AbbVie, Sandoz, Takeda,  
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Ma *et al.* **Development of a core outcome set for IBD clinical trials**

1  
2  
3 526  
4 527 **Abbreviations**  
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7 528 CD (Crohn's disease); CDAI (Crohn's Disease Activity Index); CENTRAL (Cochrane  
8  
9 529 Central Register of Controlled Trials); COMET (Core Outcome Measures in  
10  
11 530 Effectiveness Trials); COS (core outcome set); GRADE (Grading of Recommendations  
12  
13 531 Assessment, Development, and Evaluation); IBD (inflammatory bowel disease); ICHOM  
14  
15 532 (International Consortium for Health Outcomes Measurement); OMERACT (Outcome  
16  
17 533 Measures in Rheumatology); PRISMA (Preferred Reporting Items for Systematic  
18  
19 534 Reviews and Meta-Analyses); PRO (patient reported outcome); RCT (randomized  
20  
21 535 controlled trial); UC (ulcerative colitis); STRIDE (Selecting Therapeutic Targets in  
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23 536 Inflammatory Bowel Disease)  
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Ma *et al.* **Development of a core outcome set for IBD clinical trials**

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667 **SUPPLEMENTAL FILE 1**

668 Systematic review search strategies

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670 **MEDLINE**

671 1. Inflammatory bowel disease.mp or exp Inflammatory Bowel Diseases/

672 2. Crohn's disease.mp or exp Crohn Disease/

673 3. ulcerative colitis.mp or exp Colitis, Ulcerative/

674 4. 1 or 2 or 3

675 5. limit #4 to yr="1998-Current"

676 6. trial.mp. or exp Clinical Trial, Phase I/ or exp Controlled Clinical Trial/ or exp

677 Clinical Trial/ or exp Clinical Trial, Phase II/ or exp Clinical Trial, Phase III/ or exp

678 Randomized Controlled Trial/

679 7. 5 and 6

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681 **PUBMED**

682 1. "Inflammatory Bowel Diseases" [Majr MeSH]

683 2. "Crohn Disease" [Majr MeSH]

684 3. "Colitis, Ulcerative" [Majr MeSH]

685 4. 1 or 2 or 3

686 5. "Clinical Trial" [Publication Type]

687 6. 4 and 6

688 7. Filter Publication date 1998/01/01 to Current

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Ma *et al.***Development of a core outcome set for IBD clinical trials**690 **EMBASE**

- 691 1. exp inflammatory bowel disease/ or exp ulcerative colitis/ or exp Crohn disease
- 692 2. limit 1 to yr="1998-Current"
- 693 3. exp "phase 2 clinical trial (topic)"/ or exp "phase 4 clinical trial (topic)"/ or exp
- 694 "clinical trial (topic)"/ or exp "phase 3 clinical trial (topic)"/ or exp "randomized
- 695 controlled trial (topic)"/ or exp controlled clinical trial/ or exp "phase 1 clinical trial
- 696 (topic)"/
- 697 4. 2 and 3

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699 **CENTRAL**

- 700 1. inflammatory bowel disease:ti,ab,kw (Word variations have been searched)
- 701 2. Crohn's disease:ti,ab,kw (Word variations have been searched)
- 702 3. Crohn disease:ti,ab,kw (Word variations have been searched)
- 703 4. Ulcerative colitis:ti,ab,kw (Word variations have been searched)
- 704 5. #1 OR #2 OR #3 OR #4
- 705 6. Publication Year from 1998 to 2016

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# BMJ Open

## 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

Journal:	<i>BMJ Open</i>
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<b>Primary Subject Heading</b>:	Gastroenterology and hepatology
Secondary Subject Heading:	Gastroenterology and hepatology, Evidence based practice
Keywords:	Inflammatory bowel disease < GASTROENTEROLOGY, Crohn's disease, ulcerative colitis, core outcome set, systematic review, Delphi

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Manuscripts

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3 1 **Development of a core outcome set for clinical trials in inflammatory bowel**  
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5 2 **disease: study protocol for a systematic review of the literature and identification**  
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7 3 **of a core outcome set using a Delphi survey**  
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Ma *et al.* Development of a core outcome set for IBD clinical trials

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38 41 **Version:** April 24, 2017  
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Ma *et al.*                      **Development of a core outcome set for IBD clinical trials**42    **ABSTRACT**43    *Introduction:*

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

56

57    *Methods and Analysis:*

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

Ma *et al.*                      **Development of a core outcome set for IBD clinical trials**

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2  
3 65 the COS. Finally, a consensus meeting is held to ratify the COS and disseminate  
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5 66 findings for application in future IBD trials.  
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10 68 *Ethics and Dissemination:*

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12 69 Given that over 30 novel therapeutic compounds are in development for IBD treatment,  
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14 70 the design of robust clinical trials measuring relevant and standardized outcomes is  
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16 71 crucial. Standardizing outcomes through a COS will reduce heterogeneity in trial  
17  
18 72 reporting, facilitate valid comparisons of new therapies, and improve clinical trial quality.  
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24 74 *Keywords:*

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26 75 Inflammatory bowel disease, Crohn's disease, ulcerative colitis, core outcome set,  
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28 76 systematic review, consensus methods, Delphi  
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34 78 **STRENGTHS AND LIMITATIONS**

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36 79     • This protocol outlines the first international consensus effort to develop a core  
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38 80       outcome set (COS) for use in IBD clinical trials. With over 30 novel therapeutic  
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40 81       compounds in development for IBD treatment and rapidly evolving treatment  
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42 82       targets, the need to harmonize clinical trial efficacy and safety outcomes in a  
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44 83       COS is exigent.  
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46 84     • The multistep process to develop the COS is rigorous and involves a detailed  
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48 85       systematic literature review, semi-structured interviews with key stakeholder  
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50 86       groups, two-round Delphi survey to prioritize key outcomes, and a consensus  
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52 87       meeting to ratify the COS.  
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Ma *et al.***Development of a core outcome set for IBD clinical trials**

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4 88     • To develop the COS, we will seek input from multiple stakeholders, including  
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6 89           patients, clinicians, researchers, pharmaceutical industry representatives, health  
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8 90           care payers, and regulators. This will generate diverse viewpoints reflecting  
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10 91           clinical practices from around the world.  
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13 92     • Although the scope of this COS will be focused towards use in prospective  
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15 93           clinical trials in IBD, the selected outcomes may not be relevant for open-label or  
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17 94           retrospective studies of IBD treatment  
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*Ma et al.*                      **Development of a core outcome set for IBD clinical trials**96    **INTRODUCTION**

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

111  
112    Treatment of CD and UC is focused on controlling inflammation with anti-inflammatory  
113    and immunosuppressive agents, with goals of induction and maintenance of remission.  
114    In particular, the adoption of biologic therapies over the past two decades has  
115    revolutionized IBD management, making sustained remission an achievable therapeutic  
116    target.<sup>6</sup> Approval of these new agents has relied upon data from robust randomized  
117    controlled trials (RCTs)<sup>7-14</sup> that in recent years have increased in size and  
118    sophistication. Advances in this field continue at an increasingly rapid pace with multiple

Ma *et al.* **Development of a core outcome set for IBD clinical trials**

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3 119 classes of agents in late phase development.<sup>15 16</sup> In parallel, a paradigm shift in  
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5 120 treatment targets for IBD has occurred, with a move away from symptom-based  
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8 121 scoring<sup>17-19</sup> to normalization of more objective measures of inflammation such as  
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10 122 endoscopic appearance, inflammatory biomarkers, and histologic and radiographic  
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13 123 endpoints.

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17 125 Furthermore, recognizing the need to accurately measure the patient experience with  
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19 126 IBD, the US Food and Drug Administration (FDA) has advocated for measurement of  
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21 127 patient-reported outcomes (PROs) in clinical trials.<sup>20</sup> The utilization of PROs as a  
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23 128 treatment endpoint in IBD trials poses unique challenges: importantly, symptom scoring  
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25 129 is likely to remain a central component of IBD PROs, despite poor sensitivity and  
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27 130 specificity for predicting mucosal inflammation.<sup>21</sup> Symptom scoring may also be  
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29 131 confounded by psychological comorbidity and perceived stress,<sup>22</sup> resulting in disparities  
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31 132 between PROs and objectively assessed endoscopic, radiographic, and histologic  
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33 133 disease activity, especially in Crohn's disease. Thus, the adoption of PROs as a primary  
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35 134 therapeutic target in clinical trials would require careful evaluation.  
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43 136 In addition to the shift in efficacy outcomes measured in IBD trials, the assessment of  
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45 137 safety outcomes has also changed with the introduction of biologic and  
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47 138 immunomodulator therapies, which are often used in combination. As novel treatments  
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49 139 are developed to target different components of the immune response, short- and long-  
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51 140 term safety evaluations are essential. These include the risks of bacterial infections  
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53 141 (including tuberculosis), viral infections (including hepatitis B or herpes zoster virus  
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*Ma et al.*                      **Development of a core outcome set for IBD clinical trials**

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3 142 reactivation), malignancy, lymphoma, infusion and injection reactions, and development  
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5 143 of anti-drug antibodies.<sup>23</sup>  
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10 145 These shifts in the research environment have led investigators and regulatory  
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12 146 authorities to re-evaluate the key efficacy and safety outcomes measured in IBD clinical  
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14 147 trials. The selection of appropriate outcomes is critical for several reasons. First, their  
15  
16 148 operating properties determine trial efficiency and ultimately drive both our ability to  
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18 149 accurately identify effective new therapies and the cost of drug development programs.  
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20 150 Second, choice of outcomes can shape clinical practice if the selected endpoints are  
21  
22 151 perceived to be relevant to both patients and health care professionals. Third,  
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24 152 identification of standardized outcomes has potential to facilitate and improve the quality  
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26 153 of systematic reviews and meta-analyses. Finally, outcome measures are critical  
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28 154 components of the analyses used by payers to determine the safety and relative cost-  
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30 155 effectiveness of competing treatments and significantly influence regulatory and  
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32 156 formulary policy.<sup>24</sup>  
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41 158 It is apparent that insufficient attention has been paid to the standardized assessment of  
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43 159 outcome measures for IBD trials. Notably, no formalized consensus exists regarding  
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45 160 what to measure, how to measure, and when to measure selected efficacy and safety  
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47 161 outcomes in IBD trials.<sup>25</sup> Given the evolving landscape of IBD treatment endpoints and  
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49 162 the rapid development of new therapies, an international consensus agreement on core  
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51 163 outcomes for use in future IBD trials is of critical importance.  
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Ma *et al.***Development of a core outcome set for IBD clinical trials**

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3 165 A core outcome set (COS) is a consensus derived minimum set of outcomes that  
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6 166 should be measured and reported in all clinical trials of a given disease.<sup>24</sup> The  
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8 167 expectation is that core outcomes will always be collected and reported, but the COS is  
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10 168 not restrictive such that investigators are still encouraged to explore other outcomes in  
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12 169 addition to the COS. COS have been developed and utilized effectively in several  
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14 170 specialties, most prominently in rheumatology through the Outcome Measures in  
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16 171 Rheumatology (OMERACT) initiative.<sup>26</sup> Protocols have been proposed for COS  
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18 172 development in other areas of health research<sup>27-33</sup> and to facilitate this activity the Core  
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20 173 Outcome Measures in Effectiveness Trials (COMET) initiative has begun.<sup>34</sup>  
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22 174 Implementation of a successful COS should reduce heterogeneity in outcome reporting,  
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24 175 enhance the quality of evidence synthesis and systematic reviews, and increase the  
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26 176 relevance of clinical research for multiple stakeholders.<sup>35</sup>  
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34 178 This protocol establishes the context and scope for COS development in IBD, outlines  
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36 179 the methods to be adopted for each step of COS development, and increases  
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38 180 awareness of this effort to encourage IBD researchers and other stakeholders from  
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41 181 around the world to participate.  
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**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](http://www.comet-initiative.org)). This project will use published recommendations<sup>24</sup> 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<sup>36</sup>
- 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 ( $\geq 18$  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

Ma *et al.* **Development of a core outcome set for IBD clinical trials**

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3 204 Health interventions included within the scope of this COS include trials of therapeutic  
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5 205 compounds and treatment algorithms. Effectiveness of surgical interventions will not be  
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8 206 evaluated in this COS.  
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13 208 **Identifying existing knowledge**

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15 209 To our knowledge, two existing initiatives have potential conceptual overlaps with the  
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17 210 development of a COS. However, both projects have differing aims and neither of these  
18  
19 211 identified projects have the same scope as the COS:

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22 212 1) The International Consortium for Health Outcomes Measurement (ICHOM) is  
23  
24 213 developing a standardized outcome set for IBD.<sup>37</sup> The ICHOM initiative is  
25  
26 214 centered on devising patient- and value-based health care outcomes, which is  
27  
28 215 most relevant as a quality metric for healthcare payers, with a broader scope on  
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30 216 healthcare provision rather than a specific focus on core outcomes for  
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32 217 assessment in clinical trials.  
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36 218 2) The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE)  
37  
38 219 program was initiated by the International Organization for the Study of  
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40 220 Inflammatory Bowel Diseases (IOIBD).<sup>6</sup> Their recommendations for clinical,  
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42 221 endoscopic, histologic, imaging, biomarker, and patient-reported targets in CD  
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44 222 and UC aim to guide clinical practice rather than drive endpoint selection for  
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53 225 **Step 1: Systematic literature review**  
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Ma *et al.* **Development of a core outcome set for IBD clinical trials**

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3 226 A literature review will be conducted to identify and compare outcomes reported in  
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6 227 existing studies of interventions for adult IBD patients. No sources of financial support  
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8 228 will be used for the systematic review.  
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13 230 *Types of studies, participants, and interventions*

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15 231 RCTs and systematic reviews of RCTs (with or without meta-analysis) will be included.  
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17 232 Studies not describing IBD treatment outcomes, conference proceedings/abstracts  
18  
19 233 without complete trial description, or studies for which full-text is not available in English  
20  
21 234 will be excluded. Trial participants will include all adult IBD patients ( $\geq 18$  years),  
22  
23 235 including specific subgroups of patients with peri-anal fistulizing CD and UC patients  
24  
25 236 developing pouchitis after restorative proctocolectomy. Interventions will include trials of  
26  
27 237 therapeutic compounds (including systemic and topical corticosteroids, anti-  
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29 238 inflammatory and mesalamine compounds, immune modulating agents, pre- and  
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31 239 probiotic therapies, biologic and biosimilar therapies, fecal microbiota transplantation,  
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33 240 and small molecule therapy) and trials of management algorithms applied to IBD  
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35 241 patients. Both effectiveness and safety outcomes will be assessed. Surgical  
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37 242 interventions will be excluded.  
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46 244 *Search methods for identification of studies and study eligibility*

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48 245 Full terms of a comprehensive, electronic search strategy developed in accordance with  
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50 246 the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)  
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52 247 guidelines are detailed in Supplemental Files 1 and 2.<sup>38</sup> The search strategy will be  
53  
54 248 applied to MEDLINE, PubMed, EMBASE, and the Cochrane Central Register of  
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Ma *et al.* **Development of a core outcome set for IBD clinical trials**

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3 249 Controlled Trials (CENTRAL). ClinicalTrials.gov will be searched for relevant projects  
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6 250 currently underway and we will also screen abstracts from the American College of  
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8 251 Gastroenterology Annual Scientific Meeting, Digestive Disease Week, United European  
9  
10 252 Gastroenterology Week, and European Crohn's and Colitis Organization conference  
11  
12 253 proceedings published from January 2007 through June 2016. The reference lists of  
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14 254 relevant studies will be searched for additional studies not identified from the electronic  
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16 255 database search. No language restrictions will be applied to the initial search strategy  
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18 256 but studies without English-language full text will be excluded from the selection of  
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20 257 relevant articles. Given the substantial changes in IBD trial design over the past two  
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22 258 decades, we will restrict the search to studies published after 1998 to ensure selection  
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24 259 of more contemporary and relevant outcomes. Two review authors (CM and CEP) will  
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26 260 independently screen the abstracts returned from the search strategy and any studies  
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28 261 not meeting inclusion criteria will be excluded. In cases of dispute, a third review author  
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30 262 (VJ) will be consulted.  
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39 264 *Assessment of methodologic quality*

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41 265 As the primary focus of the systematic review will be to generate a list of potential  
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43 266 outcome measures, the methodologic quality of the reported outcomes in included  
44  
45 267 studies will be assessed using four questions<sup>39</sup>:  
46  
47

- 48 268 1) Is the primary outcome clearly stated?  
49  
50 269 2) Is the primary outcome clearly defined so that another researcher would be able  
51  
52 to reproduce its measurement (e.g. measurement tools, measurement timing)?  
53 270  
54  
55 271 3) Are secondary outcomes clearly stated?  
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Ma *et al.* **Development of a core outcome set for IBD clinical trials**

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3 272 4) Are secondary outcomes clearly defined?  
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5  
6 273 As the primary scope of this project evaluates outcome reporting, the overall  
7  
8 274 methodological quality of the included studies from systematic reviews will not be  
9  
10 275 evaluated.  
11

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13 276

14  
15 277 *Data extraction, analysis, and presentation*  
16

17 278 Independent data extraction will be performed by two review authors (CM and CEP)  
18  
19 279 using a standardized extraction form for the following: author details and affiliation, year  
20  
21 280 and journal of publication, study design, study population (CD, UC, peri-anal fistulizing  
22  
23 281 CD and pouchitis), intervention(s) under review, primary and secondary effectiveness  
24  
25 282 and safety outcome(s) reported, outcome definition(s), and outcome measurement  
26  
27 283 tool(s). Disagreement will be resolved through discussion and if resolution is not  
28  
29 284 possible, a third reviewer (VJ) will be consulted. Original study authors will be contacted  
30  
31 285 if there is unclear/unavailable data. The data will be synthesized and presented in a  
32  
33 286 descriptive table, with all reported outcome measures and the quality of outcome  
34  
35 287 reporting. Efficacy outcomes will be stratified by category: clinical, endoscopic,  
36  
37 288 histologic, radiologic, laboratory, patient-reported, and composite scales of multiple  
38  
39 289 outcome measures. Safety outcomes will be stratified by adverse event type (e.g.  
40  
41 290 infections, cardiac adverse events, malignancies, lymphoma, infusion/injection  
42  
43 291 reactions, immunologic adverse events) and by severity (hospitalization, intervention  
44  
45 292 discontinuation, death). These outcomes will then be condensed into a preliminary list  
46  
47 293 for consideration in semi-structured interviews and the Delphi survey.  
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Ma *et al.* **Development of a core outcome set for IBD clinical trials**

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

297

298 **Step 2: Stakeholder involvement**

299 Outcomes measured in clinical trials must be meaningful to patients, health care  
300 providers, and health care systems who receive, deliver, and pay for care, respectively.

301 Therefore, the input of multiple stakeholders affected by a COS for IBD trials will be  
302 sought. Semi-structured interviews will be conducted with the following aims:

303 1) Preliminary prioritization of the importance of efficacy and safety outcome  
304 measures generated through the systematic review

305 2) Augmentation of this list with additional items considered important to  
306 stakeholders but not captured in the literature

307

308 *Stakeholder interview participants and recruitment*

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

Ma *et al.*                      **Development of a core outcome set for IBD clinical trials**

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3 317 saturation of views represented in the qualitative data. An initial sample size of 30  
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5  
6 318 interviews is estimated, or at theme saturation.

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10 320 *Data collection and analysis*

11  
12 321 Qualitative semi-structured interviews will be conducted, allowing all participants to raise  
13  
14  
15 322 issues considered of greatest importance. A topic guide will be provided to ensure all  
16  
17 323 interviews address critical topics pertaining to COS development, including: 1) patient  
18  
19 324 experiences of living with IBD and the benefits and harms of IBD-related treatment; 2)  
20  
21 325 outcomes believed to be relevant and important to include in IBD trials and why; 3)  
22  
23 326 measurement tools for use in IBD clinical trials that are effective, reliable, and practical;  
24  
25 327 and 4) relative importance of outcomes identified from the systematic review. Face-to-  
26  
27 328 face or telephone interviews lasting 30-60 minutes will be conducted by experts in  
28  
29 329 qualitative methods and all interviews will be recorded and transcribed verbatim.  
30  
31  
32 330 Recordings will be imported into qualitative analysis software and narrative data will  
33  
34 331 then be indexed and mapped to a thematic framework, providing a summary of  
35  
36 332 participants' key points and priorities.<sup>40</sup>

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41 334 **Step 3: Delphi survey**

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43 335 An international Delphi survey, informed by literature review and semi-structured  
44  
45 336 stakeholder interviews, will then be performed to achieve consensus on the outcomes  
46  
47 337 for inclusion in the COS. The Delphi method allows panel members to anonymously  
48  
49 338 derive consensus through multiple rounds of sequential questionnaires. After each  
50  
51 339 round, the group responses are provided to panelists who can then reconsider their  
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Ma *et al.* **Development of a core outcome set for IBD clinical trials**

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3 340 position in light of other viewpoints. The anonymity of the Delphi method avoids the  
4  
5  
6 341 opinions of prominent personalities from dominating the consensus and also facilitates  
7  
8 342 wide international participation.<sup>36</sup> The Delphi process will consist of two rounds of  
9  
10 343 electronic-based questionnaire, response, and feedback. All electronic questionnaires  
11  
12  
13 344 will be pilot tested prior to distribution to ensure clarity.

14 345

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16  
17 346 *Selection of panel members*

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19  
20 347 For this study, the Delphi panel will include a minimum target sample size of 50  
21  
22 348 respondents. We aim to recruit a diverse participant pool, with involvement from each  
23  
24 349 major stakeholder group, including patients, clinicians, researchers, and representatives  
25  
26  
27 350 from patient advocacy groups, industry, and research funding organizations. Selected  
28  
29 351 participants will reflect a broad range of clinical experiences and geographical expertise,  
30  
31 352 with representation from Canada, the United States, the United Kingdom, continental  
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33  
34 353 Europe, and the Asia-Pacific.

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38 355 Researchers with extensive experience in IBD will be sought for the Delphi survey.  
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40 356 During the systematic review, a list of authors with at least 25 publications in the field of  
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43 357 IBD over the past 10 years (2006-2016), including at least two clinical trials or one  
44  
45  
46 358 systematic review of clinical trials on IBD will be compiled and invited to participate. The  
47  
48 359 lead and corresponding authors of clinical trials or systematic reviews will be  
49  
50 360 preferentially invited to participate. Clinicians experienced in managing IBD will be  
51  
52  
53 361 recruited through convenience sampling. Specifically, clinical medical and surgical leads  
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55 362 of dedicated IBD centers from North America, Europe, and the Asia-Pacific will be  
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Ma *et al.* **Development of a core outcome set for IBD clinical trials**

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3 363 identified and recruited; this recruitment strategy has been previously used by other  
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5 364 COS developers.<sup>28 29</sup>  
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8 365  
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10 366 Patients will be eligible for inclusion in the Delphi survey if they have a confirmed history  
11  
12 367 of CD or UC, attendance of healthcare for IBD, and fluent understanding of written  
13  
14 368 English. Patients will be identified through national and international patient advocacy  
15  
16 369 groups and authors' connections. Strong collaborative partnerships between the  
17  
18 370 authorship team and IBD centers in Europe and the Asia-Pacific will aim to incorporate  
19  
20 371 multi-national patient representation. Representatives from the pharmaceutical industry  
21  
22 372 will also be invited to participate; this group will comprise approximately 10% of Delphi  
23  
24 373 survey participants.  
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29 374  
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31 375 All potential participants will be emailed an invitation letter outlining the aims and details  
32  
33 376 of the study and the rationale and importance of completing the entire Delphi process.  
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35 377 Respondents who agree to take part will be assigned a unique identification number.  
36  
37 378 For each round of the process, participants will have three weeks to complete the  
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39 379 survey with generic email reminders sent at the one and two week marks. All data will  
40  
41 380 be stored against the unique identifier only; participants will be blinded to the other  
42  
43 381 respondents in the study. Only the lead author (CM) and primary investigator (VJ) will  
44  
45 382 have access to the complete list of Delphi survey panelists. For each round of the  
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47 383 Delphi survey, response and attrition rates will be calculated.  
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55 385 *Delphi round one*  
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*Ma et al.*                    **Development of a core outcome set for IBD clinical trials**

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3 386 In the first round, participants will be asked to identify the stakeholder group to which  
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5 387 they belong, and complete questions about their professional background and  
6  
7 388 experience with clinical research relevant to IBD. They will then be presented with the  
8  
9 389 complete list of efficacy and safety outcomes generated from the literature review and  
10  
11 390 stakeholder interviews. Outcome order will be randomly assigned to mitigate the  
12  
13 391 influence of display order on scoring. Participants will be asked to rank each outcome  
14  
15 392 on a scale from 1 to 9, based on the Grading of Recommendations Assessment,  
16  
17 393 Development, and Evaluation (GRADE) working group definitions.<sup>41</sup> Scores of 1-3  
18  
19 394 indicate an outcome that is not important for inclusion, scores of 4-6 indicate an  
20  
21 395 outcome important but not critical for inclusion, and scores of 7-9 indicate an outcome  
22  
23 396 felt critical for inclusion in the COS. An option to select “Unsure of significance” will also  
24  
25 397 be available. Participants will be asked to focus on ranking the most important  
26  
27 398 outcomes for inclusion highly and excluding outcomes felt to be of lesser importance;  
28  
29 399 regardless of score, all outcomes will be carried to the second round. Finally, through  
30  
31 400 free text entry, participants will have the option to clarify compelling arguments for and  
32  
33 401 against inclusion of outcomes and to identify additional outcomes not included in the  
34  
35 402 first round questionnaire.  
36  
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46 404 Responses from round one will be analyzed and collated into a feedback report.  
47  
48 405 Descriptive statistics will be used to summarize the number of participants scoring each  
49  
50 406 outcome and the distribution of scores. Responses to open-ended questions will be  
51  
52 407 reviewed by the authorship team to evaluate for substantial arguments and additional  
53  
54 408 suggestions will be reviewed for uncaptured outcomes in the first round questionnaire.  
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Ma *et al.*                      **Development of a core outcome set for IBD clinical trials**

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3 409 Subgroup analysis will be conducted, stratifying scores by stakeholder group to  
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5  
6 410 evaluate for differences from other panelist responses. Panelists who do not complete  
7  
8 411 the first round survey will not be invited to participate in round two.  
9

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12  
13 413 *Delphi round two*

14  
15 414 In round two, each participant will be provided with the number of respondents and  
16  
17 415 distribution of scores for each efficacy and safety outcome from the first round, stratified  
18  
19 416 by stakeholder group. They will then be shown their own score from round one and  
20  
21 417 asked to rescore each outcome, with consideration based on insights from the group.  
22  
23 418 Each outcome will be rescored on a scale from 1-9 as previously described and  
24  
25 419 participants will be specifically asked whether each outcome should be included in the  
26  
27 420 COS. Changes in score from round-to-round will be documented.  
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34 422 Responses from round two will be analyzed with descriptive statistics. Outcomes for  
35  
36 423 which  $\geq 70\%$  of panelists scored it 7 to 9 and fewer than 15% of panelists scored it 1 to 3  
37  
38 424 will be decided *a priori* to have met consensus for inclusion.<sup>24</sup> Conversely, outcomes for  
39  
40 425 which  $\geq 70\%$  of panelists scored it 1 to 3, and fewer than 15% of panelists scored it 7 to  
41  
42 426 9 will be defined to have met consensus for exclusion. Outcomes not meeting these  
43  
44 427 definitions will be classified as lack of consensus. While these definitions are subjective,  
45  
46 428 they have been recommended by previous COS authors<sup>24</sup> and avoid *post-hoc*  
47  
48 429 definitions of consensus that may bias the results.  
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55 431 **Step 4: Consensus meeting**  
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Ma *et al.***Development of a core outcome set for IBD clinical trials**

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3 432 A face-to-face consensus meeting with key stakeholders will be held after completion of  
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5  
6 433 the Delphi process. The meeting will be chaired by an independent facilitator with the  
7  
8 434 objective of finalizing the outcomes for inclusion in the COS. Participants will be  
9  
10 435 purposively sampled from panelists completing both rounds of the Delphi study;  
11  
12 436 approximately 30 participants from diverse stakeholder groups will be invited to  
13  
14  
15 437 participate. The results from each round of the Delphi survey will be reviewed and  
16  
17 438 participants will ratify the efficacy and safety outcomes that meet consensus criteria for  
18  
19 439 inclusion and exclusion. Participants will then discuss the outcomes for which there was  
20  
21 440 lack of agreement; based on the discussion, participants will then anonymously vote for  
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23 441 each outcome for inclusion and exclusion in the finalized COS using a format similar to  
24  
25 442 that of the Delphi survey.  
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**445 ETHICS AND DISSEMINATION****446 Ethical Considerations**

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

452

**453 Dissemination**

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

Ma *et al.***Development of a core outcome set for IBD clinical trials**

468

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

For peer review only

**473 DECLARATIONS****474 Authorship Contributions**

475 CM and VJ were involved in study conception and manuscript drafting and editing. RP,

476 RNF, BGF, WJS and CEP were involved in study conception and manuscript editing.

477 RK and BGL were involved in manuscript editing for important intellectual content. VJ is

478 the guarantor of the article.

479

**480 Data Sharing Statement**

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

482

**483 Competing interests**

484 Christopher Ma has no conflicts of interest to declare

485

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

499

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

505

506 Claire Parker has no conflicts of interest to declare

507

*Ma et al.*                      **Development of a core outcome set for IBD clinical trials**

1  
2  
3 508 Reena Khanna has received consulting fees from AbbVie, Takeda, and Janssen

4 509  
5 510 Barrett Levesque has received consulting fees from AbbVie, Takeda, Nestle Health  
6 511 Sciences, and Prometheus Labs  
7 512

8 513 William Sandborn has served as a consultant to: AbbVie Inc., ActoGeniX NV, AGI  
9 514 Therapeutics, Inc., Alba Therapeutics Corporation, Albireo, Alfa Wasserman, Amgen,  
10 515 AM-Pharma BV, Anaphore, Astellas Pharma, Athersys, Inc., Atlantic Healthcare  
11 516 Limited, Axcan Pharma (now Aptalis), BioBalance Corporation, Boehringer-Ingelheim  
12 517 Inc, Bristol Meyers Squibb, Celgene, Celek Pharmaceuticals, Cellerix SL, Cerimon  
13 518 Pharmaceuticals, ChemoCentryx, CoMentis, Cosmo Technologies, Coronado  
14 519 Biosciences, Cytokine Pharmasciences, Eagle Pharmaceuticals, Eisai Medical  
15 520 Research Inc., Elan Pharmaceuticals, EnGene, Inc., Eli Lilly, Enteromedics, Exagen  
16 521 Diagnostics, Inc., Ferring Pharmaceuticals, Flexion Therapeutics, Inc., Funxional  
17 522 Therapeutics Limited, Genzyme Corporation, Genentech (now Roche), Gilead  
18 523 Sciences, Given Imaging, Glaxo Smith Kline, Human Genome Sciences, Ironwood  
19 524 Pharmaceuticals (previously Microbia Inc.), Janssen (previously Centocor), KaloBios  
20 525 Pharmaceuticals, Inc., Lexicon Pharmaceuticals, Lycera Corporation, Meda  
21 526 Pharmaceuticals (previously Alaven Pharmaceuticals), Merck Research Laboratories,  
22 527 MerckSerono, Millennium Pharmaceuticals (subsequently merged with Takeda), Nisshin  
23 528 Kyorin Pharmaceuticals Co., Ltd., Novo Nordisk A/S, NPS Pharmaceuticals, Optimer  
24 529 Pharmaceuticals, Orexigen Therapeutics, Inc., PDL Biopharma, Pfizer, Procter and  
25 530 Gamble, Prometheus Laboratories, ProtAb Limited, Purgensis Technologies, Inc.,  
26 531 Receptos, Relypsa, Inc., Salient Pharmaceuticals, Salix Pharmaceuticals, Inc.,  
27 532 Santarus, Schering Plough Corporation (acquired by Merck), Shire Pharmaceuticals,  
28 533 Sigmoid Pharma Limited, Sirtris Pharmaceuticals, Inc. (a GSK company), S.L.A.  
29 534 Pharma (UK) Limited, Targacept, Teva Pharmaceuticals, Therakos, Tillotts Pharma AG  
30 535 (acquired by Zeria Pharmaceutical Co., Ltd), TxCell SA, UCB Pharma, Viamet  
31 536 Pharmaceuticals, Vascular Biogenics Limited (VBL), Warner Chilcott UK Limited; has  
32 537 received speaker's fees from: AbbVie Inc., Bristol Meyers Squibb, and Janssen  
33 538 (previously Centocor); and financial support for research from: AbbVie Inc., Bristol  
34 539 Meyers Squibb, Genentech, Glaxo Smith Kline, Janssen (previously Centocor),  
35 540 Millennium Pharmaceuticals (now Takeda), Novartis, Pfizer, Procter and Gamble  
36 541 Pharmaceuticals, Shire Pharmaceuticals, and UCB Pharma.  
37 542

38 543 Brian Feagan has received grant/research support from Millennium Pharmaceuticals,  
39 544 Merck, Tillotts Pharma AG, AbbVie, Novartis Pharmaceuticals, Centocor Inc.,  
40 545 Elan/Biogen, UCB Pharma, Bristol-Myers Squibb, Genentech, ActoGenix, and Wyeth  
41 546 Pharmaceuticals Inc.; consulting fees from Millennium Pharmaceuticals, Merck,  
42 547 Centocor Inc., Elan/Biogen, Janssen-Ortho, Teva Pharmaceuticals, Bristol-Myers  
43 548 Squibb, Celgene, UCB Pharma, AbbVie, Astra Zeneca, Serono, Genentech, Tillotts  
44 549 Pharma AG, Unity Pharmaceuticals, Albireo Pharma, Given Imaging Inc., Salix  
45 550 Pharmaceuticals, Novonordisk, GSK, Actogenix, Prometheus Therapeutics and  
46 551 Diagnostics, Athersys, Axcan, Gilead, Pfizer, Shire, Wyeth, Zealand Pharma, Zyngenia,  
47 552 GiCare Pharma Inc., and Sigmoid Pharma; and speakers bureaux fees from UCB,  
48 553 AbbVie, and J&J/Janssen  
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Ma *et al.*

## Development of a core outcome set for IBD clinical trials

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4 555 Vipul Jairath has received scientific advisory board fees from AbbVie, Sandoz, Takeda,  
5 556 Janssen; speakers fees from Takeda, Janssen, Shire, Ferring  
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*Ma et al.*                      **Development of a core outcome set for IBD clinical trials**

1  
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3 557  
4 558 **Abbreviations**  
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7 559 CD (Crohn's disease); CDAI (Crohn's Disease Activity Index); CENTRAL (Cochrane  
8  
9 560 Central Register of Controlled Trials); COMET (Core Outcome Measures in  
10  
11 561 Effectiveness Trials); COS (core outcome set); GRADE (Grading of Recommendations  
12  
13 562 Assessment, Development, and Evaluation); IBD (inflammatory bowel disease); ICHOM  
14  
15 563 (International Consortium for Health Outcomes Measurement); OMERACT (Outcome  
16  
17 564 Measures in Rheumatology); PRISMA (Preferred Reporting Items for Systematic  
18  
19 565 Reviews and Meta-Analyses); PRO (patient reported outcome); RCT (randomized  
20  
21 566 controlled trial); UC (ulcerative colitis); STRIDE (Selecting Therapeutic Targets in  
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26 567 Inflammatory Bowel Disease)  
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Ma *et al.*                      **Development of a core outcome set for IBD clinical trials**

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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
<b>ADMINISTRATIVE INFORMATION</b>			
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
<b>INTRODUCTION</b>			
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)
<b>METHODS</b>			



1 2 3 4 5 6 7 8	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)
9 10 11 12	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)
13 14	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
15	Study records:			
16 17	Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 15 – Data extraction
18 19	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
20 21 22	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
23 24 25 26	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
27 28	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
29 30 31	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
32 33 34 35 36 37 38 39 40 41 42	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 $\tau$ )	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

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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

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