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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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6 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**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

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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.

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3 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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11 91 clinical practices from around the world.
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For peer review only

Ma et al. **Development of a core outcome set for IBD clinical trials**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 Asia¹ 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.² 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.³ 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.^{4,5}

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.⁶ Approval of these new agents has relied upon data from robust randomized
114 controlled trials (RCTs)⁷⁻¹⁴ that in recent years have increased in size and
115 sophistication. Advances in this field continue at an increasingly rapid pace with multiple

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3 116 classes of agents in late phase development.^{15 16} In parallel, a paradigm shift in
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6 117 treatment targets for IBD has occurred, with a move away from symptom-based
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8 118 scoring¹⁷⁻¹⁹ 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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14 121 experience with IBD, the US Food and Drug Administration (FDA) has advocated for
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16 122 measurement of patient-reported outcomes (PROs) in clinical trials.²⁰
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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
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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.²¹
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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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53 138 Second, choice of outcomes can shape clinical practice if the selected endpoints are
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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-
11
12 143 effectiveness of competing treatments and significantly influence regulatory and
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15 144 formulary policy.²²
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20 146 It is apparent that insufficient attention has been paid to the standardized assessment of
21
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
25
26 149 outcomes in IBD trials.²³ Given the evolving landscape of IBD treatment endpoints and
27
28
29 150 the rapid development of new therapies, an international consensus agreement on core
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31 151 outcomes for use in future IBD trials is of critical importance.
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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.²² 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
43
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
47
48 159 Rheumatology (OMERACT) initiative.²⁴ Protocols have been proposed for COS
49
50 160 development in other areas of health research²⁵⁻³¹ and to facilitate this activity the Core
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53 161 Outcome Measures in Effectiveness Trials (COMET) initiative has begun.³²
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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.³³
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12 166 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). This project will use published recommendations²² 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 survey³⁴
- 4) Ratification of the COS in a consensus meeting of global experts

Scope of the core outcome set

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

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

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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.³⁵ The ICHOM initiative is
25
26 202 centered on devising patient- and value-based health care outcomes, which is
27
28 203 most relevant as a quality metric for healthcare payers, with a broader scope on
29
30 204 healthcare provision rather than a specific focus on core outcomes for
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32 205 assessment in clinical trials.
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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
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40 208 Inflammatory Bowel Diseases.⁶ Their recommendations for clinical, endoscopic,
41
42 209 histologic, imaging, biomarker, and patient-reported targets in CD and UC aim to
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44 210 guide clinical practice rather than drive endpoint selection for clinical trials and
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46 211 drug development.
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53 213 **Step 1: Systematic literature review**
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3 214 A literature review will be conducted to identify and compare outcomes reported in
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6 215 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

14
15 219 Studies not describing IBD treatment outcomes, conference proceedings/abstracts
16

17
18 220 without complete trial description, or studies for which full-text is not available in English
19

20 221 will be excluded. Trial participants will include all adult IBD patients (≥ 18 years),
21

22 222 including specific subgroups of patients with peri-anal fistulizing CD and UC patients
23

24 223 developing pouchitis after restorative proctocolectomy. Interventions will include trials of
25

26 224 therapeutic compounds (including systemic and topical corticosteroids, anti-
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28 225 inflammatory and mesalamine compounds, immune modulating agents, pre- and
29

30 226 probiotic therapies, biologic and biosimilar therapies, fecal microbiota transplantation,
31

32 227 and small molecule therapy) and trials of management algorithms applied to IBD
33

34 228 patients. Both effectiveness and safety outcomes will be assessed. Surgical
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36 229 interventions will be excluded.
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43 231 *Search methods for identification of studies and study eligibility*

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45 232 Full terms of a comprehensive, electronic search strategy developed in accordance with
46

47 233 the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)
48

49 234 guidelines are detailed in Supplemental File 1.³⁶ The search strategy will be applied to
50

51 235 MEDLINE, PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials
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53 236 (CENTRAL). ClinicalTrials.gov will be searched for relevant projects currently underway
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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 questions³⁷:

- 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?

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

263

264 *Data extraction, analysis, and presentation*

265 Independent data extraction will be performed by two review authors (CM and CEP) for
266 the following: author details and affiliation, year and journal of publication, study design,
267 study population (CD, UC, peri-anal fistulizing CD and pouchitis), intervention(s) under
268 review, primary and secondary effectiveness and safety outcome(s) reported, outcome
269 definition(s), and outcome measurement tool(s). Disagreement will be resolved through
270 discussion and if resolution is not possible, a third reviewer (VJ) will be consulted.

271 Original study authors will be contacted if there is unclear/unavailable data. The data
272 will be synthesized and presented in a descriptive table, with all reported outcome
273 measures and the quality of outcome reporting. Efficacy outcomes will be stratified by
274 category: clinical, endoscopic, histologic, radiologic, laboratory, patient-reported, and
275 composite scales of multiple outcome measures. Safety outcomes will be stratified by
276 adverse event type (e.g. infections, cardiac adverse events, malignancies, lymphoma,
277 infusion/injection reactions, immunologic adverse events) and by severity
278 (hospitalization, intervention discontinuation, death). These outcomes will then be
279 condensed into a preliminary list for consideration in semi-structured interviews and the
280 Delphi survey.

281

282 **Step 2: Stakeholder involvement**

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

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

291

292 Stakeholder interview participants and recruitment

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

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304 Data collection and analysis

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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
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8 307 interviews address critical topics pertaining to COS development, including: 1) patient
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10 308 experiences of living with IBD and the benefits and harms of IBD-related treatment; 2)
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12 309 outcomes believed to be relevant and important to include in IBD trials and why; 3)
13
14 310 measurement tools for use in IBD clinical trials that are effective, reliable, and practical;
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16 311 and 4) relative importance of outcomes identified from the systematic review. Face-to-
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18 312 face or telephone interviews lasting 30-60 minutes will be conducted by experts in
19
20 313 qualitative methods and all interviews will be recorded and transcribed verbatim.
21
22 314 Recordings will be imported into qualitative analysis software and narrative data will
23
24 315 then be indexed and mapped to a thematic framework, providing a summary of
25
26 316 participants' key points and priorities.³⁸
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34 318 **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
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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
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50 326 wide international participation.³⁴ The Delphi process will consist of two rounds of
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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*

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12 331 For this study, the Delphi panel will include a minimum target sample size of 50
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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
23
24 337 Europe, Asia, and Australia.
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29 339 Researchers with extensive experience in IBD will be sought for the Delphi survey.
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32 340 During the systematic review, a list of authors with at least 25 publications in the field of
33
34 341 IBD over the past 10 years (2006-2016), including at least two clinical trials or one
35
36 342 systematic review of clinical trials on IBD will be compiled and invited to participate.
37
38

39 343 Clinicians experienced in managing IBD will be recruited through convenience
40
41 344 sampling. Patients will be eligible for inclusion in the Delphi survey if they have a
42
43 345 confirmed history of CD or UC, attendance of healthcare for IBD, and fluent
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45 346 understanding of written English. Patients will be identified through national and
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47 347 international patient advocacy groups and authors connections and collaboration of the
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49 348 authors to ensure multi-national representation.
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3 350 All potential participants will be emailed an invitation letter outlining the aims and details
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6 351 of the study and the rationale and importance of completing the entire Delphi process.
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8 352 Respondents who agree to take part will be assigned a unique identification number.
9
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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
19 357 have access to the complete list of Delphi survey panelists. For each round of the
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21 358 Delphi survey, response and attrition rates will be calculated.
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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.³⁹ 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
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49 371 felt critical for inclusion in the COS. An option to select “Unsure of significance” will also
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51 372 be available. Participants will be asked to focus on ranking the most important
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3 373 outcomes for inclusion highly and excluding outcomes felt to be of lesser importance;
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6 374 regardless of score, all outcomes will be carried to the second round. Finally, through
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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
12 377 first round questionnaire.

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17 379 Responses from round one will be analyzed and collated into a feedback report.
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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
28 384 Subgroup analysis will be conducted, stratifying scores by stakeholder group to
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30 385 evaluate for differences from other panelist responses. Panelists who do not complete
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32 386 the first round survey will not be invited to participate in round two.

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38 388 *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
49 393 Each outcome will be rescored on a scale from 1-9 as previously described and
50
51 394 participants will be specifically asked whether each outcome should be included in the
52
53 395 COS. Changes in score from round-to-round will be documented.
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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.²² 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 authors²² and avoid *post-hoc*
404 definitions of consensus that may bias the results.

405

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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3 420 **ETHICS AND DISSEMINATION**

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5 421 **Ethical Considerations**

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7
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.^{25 40} 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
17 426 Helsinki.

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22 428 **Dissemination**

23
24 429 With over 30 novel therapeutic compounds in various stages of clinical development⁴¹,
25
26
27 430 the adoption of an international consensus COS will be critical in ensuring future clinical
28
29 431 trials report valid, meaningful, and standardized outcomes. This need is particularly
30
31 432 exigent, commensurate with the transition from traditional symptom-based outcomes
32
33 433 such as the Crohn's Disease Activity Index and Mayo Clinic score, to a diverse array of
34
35 434 endoscopic, histologic, radiographic, safety, and patient-reported endpoints. Through
36
37 435 this COS, we intend to reduce outcome reporting bias, reduce reporting heterogeneity,
38
39 436 improve clinical trial quality in IBD, and facilitate more robust data synthesis of treatment
40
41 437 interventions.

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46
47 439 A finalized COS reporting guideline and explanatory document will be drafted, including
48
49 440 all efficacy and safety outcomes and measurements as determined by the Delphi
50
51 441 rounds and consensus meeting. These documents will be disseminated by high impact
52
53 442 publication.

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**

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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.

13
14 448

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16
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**

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

481
482 William Sandborn has served as a consultant to: AbbVie Inc., ActoGenix NV, AGI
483 Therapeutics, Inc., Alba Therapeutics Corporation, Albireo, Alfa Wasserman, Amgen,
484 AM-Pharma BV, Anaphore, Astellas Pharma, Athersys, Inc., Atlantic Healthcare
485 Limited, Axcan Pharma (now Aptalis), BioBalance Corporation, Boehringer-Ingelheim
486 Inc, Bristol Meyers Squibb, Celgene, Celek Pharmaceuticals, Cellerix SL, Cerimon
487 Pharmaceuticals, ChemoCentryx, CoMentis, Cosmo Technologies, Coronado
488 Biosciences, Cytokine Pharmasciences, Eagle Pharmaceuticals, Eisai Medical
489 Research Inc., Elan Pharmaceuticals, EnGene, Inc., Eli Lilly, Enteromedics, Exagen
490 Diagnostics, Inc., Ferring Pharmaceuticals, Flexion Therapeutics, Inc., Funxional
491 Therapeutics Limited, Genzyme Corporation, Genentech (now Roche), Gilead
492 Sciences, Given Imaging, Glaxo Smith Kline, Human Genome Sciences, Ironwood
493 Pharmaceuticals (previously Microbia Inc.), Janssen (previously Centocor), KaloBios
494 Pharmaceuticals, Inc., Lexicon Pharmaceuticals, Lycera Corporation, Meda
495 Pharmaceuticals (previously Alaven Pharmaceuticals), Merck Research Laboratories,
496 MerckSerono, Millennium Pharmaceuticals (subsequently merged with Takeda), Nisshin
497 Kyorin Pharmaceuticals Co., Ltd., Novo Nordisk A/S, NPS Pharmaceuticals, Optimer
498 Pharmaceuticals, Orexigen Therapeutics, Inc., PDL Biopharma, Pfizer, Procter and
499 Gamble, Prometheus Laboratories, ProtAb Limited, Purgenesis Technologies, Inc.,
500 Receptos, Relypsa, Inc., Salient Pharmaceuticals, Salix Pharmaceuticals, Inc.,
501 Santarus, Schering Plough Corporation (acquired by Merck), Shire Pharmaceuticals,
502 Sigmoid Pharma Limited, Sirtris Pharmaceuticals, Inc. (a GSK company), S.L.A.
503 Pharma (UK) Limited, Targacept, Teva Pharmaceuticals, Therakos, Tillotts Pharma AG
504 (acquired by Zeria Pharmaceutical Co., Ltd), TxCell SA, UCB Pharma, Viamet
505 Pharmaceuticals, Vascular Biogenics Limited (VBL), Warner Chilcott UK Limited; has
506 received speaker's fees from: AbbVie Inc., Bristol Meyers Squibb, and Janssen
507 (previously Centocor); and financial support for research from: AbbVie Inc., Bristol
508 Meyers Squibb, Genentech, Glaxo Smith Kline, Janssen (previously Centocor),
509 Millennium Pharmaceuticals (now Takeda), Novartis, Pfizer, Procter and Gamble
510 Pharmaceuticals, Shire Pharmaceuticals, and UCB Pharma.

511
512 Brian Feagan has received grant/research support from Millennium Pharmaceuticals,
513 Merck, Tillotts Pharma AG, AbbVie, Novartis Pharmaceuticals, Centocor Inc.,
514 Elan/Biogen, UCB Pharma, Bristol-Myers Squibb, Genentech, ActoGenix, and Wyeth
515 Pharmaceuticals Inc.; consulting fees from Millennium Pharmaceuticals, Merck,
516 Centocor Inc., Elan/Biogen, Janssen-Ortho, Teva Pharmaceuticals, Bristol-Myers
517 Squibb, Celgene, UCB Pharma, AbbVie, Astra Zeneca, Serono, Genentech, Tillotts
518 Pharma AG, Unity Pharmaceuticals, Albireo Pharma, Given Imaging Inc., Salix
519 Pharmaceuticals, Novonordisk, GSK, Actogenix, Prometheus Therapeutics and
520 Diagnostics, Athersys, Axcan, Gilead, Pfizer, Shire, Wyeth, Zealand Pharma, Zyngenia,
521 GiCare Pharma Inc., and Sigmoid Pharma; and speakers bureaux fees from UCB,
522 AbbVie, and J&J/Janssen

523

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524 Vipul Jairath has received scientific advisory board fees from AbbVie, Sandoz, Takeda,
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For peer review only

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1
2
3 526
4 527 **Abbreviations**
5
6
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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26 536 Inflammatory Bowel Disease)
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538 REFERENCES

- 539 1. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the
540 inflammatory bowel diseases with time, based on systematic review.
541 *Gastroenterology* 2012;142(1):46-54. doi: 10.1053/j.gastro.2011.10.001
- 542 2. Peyrin-Biroulet L, Loftus EV, Jr., Colombel JF, et al. The natural history of adult
543 Crohn's disease in population-based cohorts. *Am J Gastroenterol*
544 2010;105(2):289-97. doi: 10.1038/ajg.2009.579
- 545 3. de Souza HS, Fiocchi C. Immunopathogenesis of IBD: current state of the art. *Nat*
546 *Rev Gastroenterol Hepatol* 2016;13(1):13-27. doi: 10.1038/nrgastro.2015.186
- 547 4. Gibson TB, Ng E, Ozminkowski RJ, et al. The direct and indirect cost burden of
548 Crohn's disease and ulcerative colitis. *J Occup Environ Med* 2008;50(11):1261-
549 72. doi: 10.1097/JOM.0b013e318181b8ca
- 550 5. Kappelman MD, Rifas-Shiman SL, Porter CQ, et al. Direct health care costs of
551 Crohn's disease and ulcerative colitis in US children and adults.
552 *Gastroenterology* 2008;135(6):1907-13. doi: 10.1053/j.gastro.2008.09.012
- 553 6. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting Therapeutic Targets in
554 Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for
555 Treat-to-Target. *Am J Gastroenterol* 2015;110(9):1324-38. doi:
556 10.1038/ajg.2015.233
- 557 7. Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical
558 remission in moderately to severely active ulcerative colitis: results of a
559 randomised controlled trial. *Gut* 2011;60(6):780-7. doi: 10.1136/gut.2010.221127

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

- 1
2
3 560 8. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains
4
5 561 clinical remission in patients with moderate-to-severe ulcerative colitis.
6
7 562
8 *Gastroenterology* 2012;142(2):257-65 e1-3. doi: 10.1053/j.gastro.2011.10.032
9
10 563 9. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and
11
12 564 maintenance therapy for ulcerative colitis. *N Engl J Med* 2005;353(23):2462-76.
13
14 565 doi: 10.1056/NEJMoa050516
15
16 566 10. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and
17
18 567 maintenance therapy for ulcerative colitis. *N Engl J Med* 2013;369(8):699-710.
19
20 568 doi: 10.1056/NEJMoa1215734
21
22 569 11. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's
23
24 570 disease: the ACCENT I randomised trial. *Lancet* 2002;359(9317):1541-9. doi:
25
26 571 10.1016/S0140-6736(02)08512-4
27
28 572 12. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor
29
30 573 monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial.
31
32 574 *Gastroenterology* 2006;130(2):323-33; quiz 591. doi:
33
34 575 10.1053/j.gastro.2005.11.030
35
36 576 13. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of
37
38 577 clinical response and remission in patients with Crohn's disease: the CHARM
39
40 578 trial. *Gastroenterology* 2007;132(1):52-65. doi: 10.1053/j.gastro.2006.11.041
41
42 579 14. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and
43
44 580 maintenance therapy for Crohn's disease. *N Engl J Med* 2013;369(8):711-21. doi:
45
46 581 10.1056/NEJMoa1215739
47
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49
50
51
52
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55
56
57
58
59
60

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

- 1
2
3 582 15. Khanna R, Jairath V, Vande Casteele N, et al. Efficient Early Drug Development for
4
5 583 Ulcerative Colitis. *Gastroenterology* 2016;150(5):1056-60. doi:
6
7 584 10.1053/j.gastro.2016.03.013
8
9
10 585 16. Jairath V, Levesque BG, Vande Casteele N, et al. Evolving Concepts in Phases I
11
12 586 and II Drug Development for Crohn's Disease. *J Crohns Colitis* 2016 doi:
13
14 587 10.1093/ecco-jcc/jjw137
15
16
17 588 17. Hindryckx P, Baert F, Hart A, et al. Clinical trials in luminal Crohn's disease: a
18
19 589 historical perspective. *J Crohns Colitis* 2014;8(11):1339-50. doi:
20
21 590 10.1016/j.crohns.2014.04.007
22
23
24 591 18. Best WR, Bectel JM, Singleton JW, et al. Development of a Crohn's disease
25
26 592 activity index. National Cooperative Crohn's Disease Study. *Gastroenterology*
27
28 593 1976;70(3):439-44.
29
30
31 594 19. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy
32
33 595 for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J*
34
35 596 *Med* 1987;317(26):1625-9. doi: 10.1056/NEJM198712243172603
36
37
38 597 20. Williet N, Sandborn WJ, Peyrin-Biroulet L. Patient-reported outcomes as primary
39
40 598 end points in clinical trials of inflammatory bowel disease. *Clin Gastroenterol*
41
42 599 *Hepatol* 2014;12(8):1246-56 e6. doi: 10.1016/j.cgh.2014.02.016
43
44
45 600 21. Bonovas S, Fiorino G, Allocca M, et al. Biologic Therapies and Risk of Infection and
46
47 601 Malignancy in Patients With Inflammatory Bowel Disease: A Systematic Review
48
49 602 and Network Meta-analysis. *Clin Gastroenterol Hepatol* 2016;14(10):1385-97
50
51 603 e10. doi: 10.1016/j.cgh.2016.04.039
52
53
54
55
56
57
58
59
60

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

- 1
2
3 604 22. Williamson PR, Altman DG, Blazeby JM, et al. Developing core outcome sets for
4
5 605 clinical trials: issues to consider. *Trials* 2012;13:132. doi: 10.1186/1745-6215-13-
6
7
8 606 132
9
10 607 23. D'Haens G, Feagan B, Colombel JF, et al. Challenges to the design, execution, and
11
12 608 analysis of randomized controlled trials for inflammatory bowel disease.
13
14 609 *Gastroenterology* 2012;143(6):1461-9. doi: 10.1053/j.gastro.2012.09.031
15
16 610 24. Boers M, Kirwan JR, Wells G, et al. Developing core outcome measurement sets for
17
18 611 clinical trials: OMERACT filter 2.0. *J Clin Epidemiol* 2014;67(7):745-53. doi:
19
20 612 10.1016/j.jclinepi.2013.11.013
21
22 613 25. Chiarotto A, Terwee CB, Deyo RA, et al. A core outcome set for clinical trials on
23
24 614 non-specific low back pain: study protocol for the development of a core domain
25
26 615 set. *Trials* 2014;15:511. doi: 10.1186/1745-6215-15-511
27
28 616 26. Egan AM, Smith V, Devane D, et al. Effectiveness of prepregnancy care for women
29
30 617 with pregestational diabetes mellitus: protocol for a systematic review of the
31
32 618 literature and identification of a core outcomes set using a Delphi survey. *Trials*
33
34 619 2015;16:356. doi: 10.1186/s13063-015-0894-8
35
36 620 27. Harman NL, Bruce IA, Callery P, et al. MOMENT--Management of Otitis Media with
37
38 621 Effusion in Cleft Palate: protocol for a systematic review of the literature and
39
40 622 identification of a core outcome set using a Delphi survey. *Trials* 2013;14:70. doi:
41
42 623 10.1186/1745-6215-14-70
43
44 624 28. Iyengar S, Williamson PR, Schmitt J, et al. Development of a core outcome set for
45
46 625 clinical trials in rosacea: study protocol for a systematic review of the literature
47
48
49
50
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56
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60

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

- 1
2
3 626 and identification of a core outcome set using a Delphi survey. *Trials*
4
5 627 2016;17(1):429. doi: 10.1186/s13063-016-1554-3
6
7
8 628 29. Kelly LE, Jansson LM, Mouldsdale W, et al. A core outcome set for neonatal
9
10 629 abstinence syndrome: study protocol for a systematic review, parent interviews
11
12 630 and a Delphi survey. *Trials* 2016;17(1):536. doi: 10.1186/s13063-016-1666-9
13
14
15 631 30. MacLennan S, Bekema HJ, Williamson PR, et al. A core outcome set for localised
16
17 632 prostate cancer effectiveness trials: protocol for a systematic review of the
18
19 633 literature and stakeholder involvement through interviews and a Delphi survey.
20
21 634 *Trials* 2015;16:76. doi: 10.1186/s13063-015-0598-0
22
23
24 635 31. Tong A, Manns B, Hemmelgarn B, et al. Standardised outcomes in nephrology -
25
26 636 Haemodialysis (SONG-HD): study protocol for establishing a core outcome set in
27
28 637 haemodialysis. *Trials* 2015;16:364. doi: 10.1186/s13063-015-0895-7
29
30
31 638 32. Gargon E. The COMET (Core Outcome Measures in Effectiveness Trials) Initiative.
32
33 639 *Maturitas* 2016;91:91-2. doi: 10.1016/j.maturitas.2016.06.007
34
35
36 640 33. Kirkham JJ, Gorst S, Altman DG, et al. COS-STAR: a reporting guideline for studies
37
38 641 developing core outcome sets (protocol). *Trials* 2015;16:373. doi:
39
40 642 10.1186/s13063-015-0913-9
41
42
43 643 34. Sinha IP, Smyth RL, Williamson PR. Using the Delphi technique to determine which
44
45 644 outcomes to measure in clinical trials: recommendations for the future based on
46
47 645 a systematic review of existing studies. *PLoS Med* 2011;8(1):e1000393. doi:
48
49 646 10.1371/journal.pmed.1000393
50
51
52 647 35. The ICHOM Standard Set for Inflammatory Bowel Disease [Available from:
53
54 648 <http://www.ichom.org/medical-conditions/inflammatory-bowel-disease/2016>.
55
56
57
58
59
60

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

- 1
2
3 649 36. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic
4
5 650 reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*
6
7 651 2009;62(10):1006-12. doi: 10.1016/j.jclinepi.2009.06.005
8
9
10 652 37. Mokkink LB, Terwee CB, Knol DL, et al. The COSMIN checklist for evaluating the
11
12 653 methodological quality of studies on measurement properties: a clarification of its
13
14 654 content. *BMC Med Res Methodol* 2010;10:22. doi: 10.1186/1471-2288-10-22
15
16
17 655 38. Kuper A, Reeves S, Levinson W. An introduction to reading and appraising
18
19 656 qualitative research. *BMJ* 2008;337:a288. doi: 10.1136/bmj.a288
20
21
22 657 39. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question
23
24 658 and deciding on important outcomes. *J Clin Epidemiol* 2011;64(4):395-400. doi:
25
26 659 10.1016/j.jclinepi.2010.09.012
27
28
29 660 40. Hirsch M, Duffy JM, Barker C, et al. Protocol for developing, disseminating and
30
31 661 implementing a core outcome set for endometriosis. *BMJ Open*
32
33 662 2016;6(12):e013998. doi: 10.1136/bmjopen-2016-013998
34
35
36 663 41. Amiot A, Peyrin-Biroulet L. Current, new and future biological agents on the horizon
37
38 664 for the treatment of inflammatory bowel diseases. *Therap Adv Gastroenterol*
39
40 665 2015;8(2):66-82. doi: 10.1177/1756283X14558193
41
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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

680

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

689

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

698

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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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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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**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

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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.

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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
9
10 91 clinical practices from around the world.
11
12
13 92 • Although the scope of this COS will be focused towards use in prospective
14
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 Asia¹ 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.² 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.³ 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.^{4 5}

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.⁶ Approval of these new agents has relied upon data from robust randomized
117 controlled trials (RCTs)⁷⁻¹⁴ that in recent years have increased in size and
118 sophistication. Advances in this field continue at an increasingly rapid pace with multiple

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3 119 classes of agents in late phase development.^{15 16} In parallel, a paradigm shift in
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6 120 treatment targets for IBD has occurred, with a move away from symptom-based
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8 121 scoring¹⁷⁻¹⁹ to normalization of more objective measures of inflammation such as
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11 122 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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20 126 IBD, the US Food and Drug Administration (FDA) has advocated for measurement of
21
22 127 patient-reported outcomes (PROs) in clinical trials.²⁰ The utilization of PROs as a
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24
25 128 treatment endpoint in IBD trials poses unique challenges: importantly, symptom scoring
26
27 129 is likely to remain a central component of IBD PROs, despite poor sensitivity and
28
29 130 specificity for predicting mucosal inflammation.²¹ Symptom scoring may also be
30
31 131 confounded by psychological comorbidity and perceived stress,²² resulting in disparities
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34 132 between PROs and objectively assessed endoscopic, radiographic, and histologic
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36 133 disease activity, especially in Crohn's disease. Thus, the adoption of PROs as a primary
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39 134 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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46 137 safety outcomes has also changed with the introduction of biologic and
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48 138 immunomodulator therapies, which are often used in combination. As novel treatments
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50 139 are developed to target different components of the immune response, short- and long-
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53 140 term safety evaluations are essential. These include the risks of bacterial infections
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55 141 (including tuberculosis), viral infections (including hepatitis B or herpes zoster virus
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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.²³
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10 145 These shifts in the research environment have led investigators and regulatory
11
12 146 authorities to re-evaluate the key efficacy and safety outcomes measured in IBD clinical
13
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
17
18 149 accurately identify effective new therapies and the cost of drug development programs.
19
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,
23
24 152 identification of standardized outcomes has potential to facilitate and improve the quality
25
26 153 of systematic reviews and meta-analyses. Finally, outcome measures are critical
27
28 154 components of the analyses used by payers to determine the safety and relative cost-
29
30 155 effectiveness of competing treatments and significantly influence regulatory and
31
32 156 formulary policy.²⁴
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41 158 It is apparent that insufficient attention has been paid to the standardized assessment of
42
43 159 outcome measures for IBD trials. Notably, no formalized consensus exists regarding
44
45 160 what to measure, how to measure, and when to measure selected efficacy and safety
46
47 161 outcomes in IBD trials.²⁵ Given the evolving landscape of IBD treatment endpoints and
48
49 162 the rapid development of new therapies, an international consensus agreement on core
50
51 163 outcomes for use in future IBD trials is of critical importance.
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3 165 A core outcome set (COS) is a consensus derived minimum set of outcomes that
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5
6 166 should be measured and reported in all clinical trials of a given disease.²⁴ The
7
8 167 expectation is that core outcomes will always be collected and reported, but the COS is
9
10 168 not restrictive such that investigators are still encouraged to explore other outcomes in
11
12 169 addition to the COS. COS have been developed and utilized effectively in several
13
14 170 specialties, most prominently in rheumatology through the Outcome Measures in
15
16 171 Rheumatology (OMERACT) initiative.²⁶ Protocols have been proposed for COS
17
18 172 development in other areas of health research²⁷⁻³³ and to facilitate this activity the Core
19
20 173 Outcome Measures in Effectiveness Trials (COMET) initiative has begun.³⁴
21
22 174 Implementation of a successful COS should reduce heterogeneity in outcome reporting,
23
24 175 enhance the quality of evidence synthesis and systematic reviews, and increase the
25
26 176 relevance of clinical research for multiple stakeholders.³⁵
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34 178 This protocol establishes the context and scope for COS development in IBD, outlines
35
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
39
40 181 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). This project will use published recommendations²⁴ 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 survey³⁶
- 4) Ratification of the COS in a consensus meeting of global experts

Scope of the core outcome set

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

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

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

207

208 **Identifying existing knowledge**

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

212 1) The International Consortium for Health Outcomes Measurement (ICHOM) is
213 developing a standardized outcome set for IBD.³⁷ The ICHOM initiative is
214 centered on devising patient- and value-based health care outcomes, which is
215 most relevant as a quality metric for healthcare payers, with a broader scope on
216 healthcare provision rather than a specific focus on core outcomes for
217 assessment in clinical trials.

218 2) The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE)
219 program was initiated by the International Organization for the Study of
220 Inflammatory Bowel Diseases (IOIBD).⁶ Their recommendations for clinical,
221 endoscopic, histologic, imaging, biomarker, and patient-reported targets in CD
222 and UC aim to guide clinical practice rather than drive endpoint selection for
223 clinical trials and drug development.

224

225 **Step 1: Systematic literature review**

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

229

230 *Types of studies, participants, and interventions*

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

243

244 *Search methods for identification of studies and study eligibility*

245 Full terms of a comprehensive, electronic search strategy developed in accordance with
246 the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)
247 guidelines are detailed in Supplemental Files 1 and 2.³⁸ The search strategy will be
248 applied to MEDLINE, PubMed, EMBASE, and the Cochrane Central Register of

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

263

264 *Assessment of methodologic quality*

265 As the primary focus of the systematic review will be to generate a list of potential
266 outcome measures, the methodologic quality of the reported outcomes in included
267 studies will be assessed using four questions³⁹:

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

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3 272 4) Are secondary outcomes clearly defined?
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6 273 As the primary scope of this project evaluates outcome reporting, the overall
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8 274 methodological quality of the included studies from systematic reviews will not be
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10 275 evaluated.
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15 277 *Data extraction, analysis, and presentation*

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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
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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
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47 293 for consideration in semi-structured interviews and the Delphi survey.
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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

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3 317 saturation of views represented in the qualitative data. An initial sample size of 30
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5 318 interviews is estimated, or at theme saturation.
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10 320 *Data collection and analysis*
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12 321 Qualitative semi-structured interviews will be conducted, allowing all participants to raise
13 322 issues considered of greatest importance. A topic guide will be provided to ensure all
14 323 interviews address critical topics pertaining to COS development, including: 1) patient
15 324 experiences of living with IBD and the benefits and harms of IBD-related treatment; 2)
16 325 outcomes believed to be relevant and important to include in IBD trials and why; 3)
17 326 measurement tools for use in IBD clinical trials that are effective, reliable, and practical;
18 327 and 4) relative importance of outcomes identified from the systematic review. Face-to-
19 328 face or telephone interviews lasting 30-60 minutes will be conducted by experts in
20 329 qualitative methods and all interviews will be recorded and transcribed verbatim.
21 330 Recordings will be imported into qualitative analysis software and narrative data will
22 331 then be indexed and mapped to a thematic framework, providing a summary of
23 332 participants' key points and priorities.⁴⁰
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43 334 **Step 3: Delphi survey**
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45 335 An international Delphi survey, informed by literature review and semi-structured
46 336 stakeholder interviews, will then be performed to achieve consensus on the outcomes
47 337 for inclusion in the COS. The Delphi method allows panel members to anonymously
48 338 derive consensus through multiple rounds of sequential questionnaires. After each
49 339 round, the group responses are provided to panelists who can then reconsider their
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3 340 position in light of other viewpoints. The anonymity of the Delphi method avoids the
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6 341 opinions of prominent personalities from dominating the consensus and also facilitates
7
8 342 wide international participation.³⁶ The Delphi process will consist of two rounds of
9
10 343 electronic-based questionnaire, response, and feedback. All electronic questionnaires
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12
13 344 will be pilot tested prior to distribution to ensure clarity.
14

15 345

346 Selection of panel members

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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,
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32 352 with representation from Canada, the United States, the United Kingdom, continental
33
34 353 Europe, and the Asia-Pacific.
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39 355 Researchers with extensive experience in IBD will be sought for the Delphi survey.
40
41 356 During the systematic review, a list of authors with at least 25 publications in the field of
42
43 357 IBD over the past 10 years (2006-2016), including at least two clinical trials or one
44
45 358 systematic review of clinical trials on IBD will be compiled and invited to participate. The
46
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
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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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3 363 identified and recruited; this recruitment strategy has been previously used by other
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5 364 COS developers.^{28 29}
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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
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24 373 survey participants.
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31 375 All potential participants will be emailed an invitation letter outlining the aims and details
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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.
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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
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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
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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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3 386 In the first round, participants will be asked to identify the stakeholder group to which
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6 387 they belong, and complete questions about their professional background and
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8 388 experience with clinical research relevant to IBD. They will then be presented with the
9
10 389 complete list of efficacy and safety outcomes generated from the literature review and
11
12 390 stakeholder interviews. Outcome order will be randomly assigned to mitigate the
13
14 391 influence of display order on scoring. Participants will be asked to rank each outcome
15
16 392 on a scale from 1 to 9, based on the Grading of Recommendations Assessment,
17
18 393 Development, and Evaluation (GRADE) working group definitions.⁴¹ Scores of 1-3
19
20 394 indicate an outcome that is not important for inclusion, scores of 4-6 indicate an
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22 395 outcome important but not critical for inclusion, and scores of 7-9 indicate an outcome
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24 396 felt critical for inclusion in the COS. An option to select “Unsure of significance” will also
25
26 397 be available. Participants will be asked to focus on ranking the most important
27
28 398 outcomes for inclusion highly and excluding outcomes felt to be of lesser importance;
29
30 399 regardless of score, all outcomes will be carried to the second round. Finally, through
31
32 400 free text entry, participants will have the option to clarify compelling arguments for and
33
34 401 against inclusion of outcomes and to identify additional outcomes not included in the
35
36 402 first round questionnaire.

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46 404 Responses from round one will be analyzed and collated into a feedback report.
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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
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54 408 suggestions will be reviewed for uncaptured outcomes in the first round questionnaire.
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409 Subgroup analysis will be conducted, stratifying scores by stakeholder group to
410 evaluate for differences from other panelist responses. Panelists who do not complete
411 the first round survey will not be invited to participate in round two.

412

413 *Delphi round two*

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

421

422 Responses from round two will be analyzed with descriptive statistics. Outcomes for
423 which $\geq 70\%$ of panelists scored it 7 to 9 and fewer than 15% of panelists scored it 1 to 3
424 will be decided *a priori* to have met consensus for inclusion.²⁴ Conversely, outcomes for
425 which $\geq 70\%$ of panelists scored it 1 to 3, and fewer than 15% of panelists scored it 7 to
426 9 will be defined to have met consensus for exclusion. Outcomes not meeting these
427 definitions will be classified as lack of consensus. While these definitions are subjective,
428 they have been recommended by previous COS authors²⁴ and avoid *post-hoc*
429 definitions of consensus that may bias the results.

430

431 **Step 4: Consensus meeting**

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3 432 A face-to-face consensus meeting with key stakeholders will be held after completion of
4
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
14 437 participate. The results from each round of the Delphi survey will be reviewed and
15
16 438 participants will ratify the efficacy and safety outcomes that meet consensus criteria for
17
18 439 inclusion and exclusion. Participants will then discuss the outcomes for which there was
19
20 440 lack of agreement; based on the discussion, participants will then anonymously vote for
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22 441 each outcome for inclusion and exclusion in the finalized COS using a format similar to
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24 442 that of the Delphi survey.
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3 445 **ETHICS AND DISSEMINATION**

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5 446 **Ethical Considerations**

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8 447 As with previous COS development projects, this project is considered a service
9
10 448 evaluation not directly influencing patient care or safety.^{27 42} All participants involved will
11
12 449 be asked for their consent before participating in either stakeholder interviews or the
13
14 450 Delphi survey, and all procedures will be conducted according to the Declaration of
15
16
17 451 Helsinki.

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22 453 **Dissemination**

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24 454 With over 30 novel therapeutic compounds in various stages of clinical development⁴³,
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26
27 455 the adoption of an international consensus COS will be critical in ensuring future clinical
28
29 456 trials report valid, meaningful, and standardized efficacy outcomes. This need is
30
31 457 particularly exigent, commensurate with the transition from traditional symptom-based
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33 458 outcomes such as the Crohn's Disease Activity Index and Mayo Clinic score, to a
34
35 459 diverse array of endoscopic, histologic, radiographic, and patient-reported endpoints.
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38 460 Additionally, with the increasing adoption of biologic therapies for IBD management, it is
39
40 461 essential for clinical trials to identify unique safety considerations associated with novel
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42 462 therapies. Reporting of treatment-specific safety outcomes such as infectious,
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44 463 malignant, immune, surgical, and drug-related adverse events may promote the
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46 464 development of future preventative strategies for optimizing short- and long-term patient
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48 465 safety. Through this COS, we intend to reduce outcome reporting bias, reduce reporting
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50 466 heterogeneity, improve clinical trial quality in IBD, and facilitate more robust data
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53 467 synthesis of treatment interventions.
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6 469 A finalized COS reporting guideline and explanatory document will be drafted, including
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8 470 all efficacy and safety outcomes and measurements as determined by the Delphi
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10 471 rounds and consensus meeting. These documents will be disseminated by high impact
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13 472 publication.
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2
3 473 **DECLARATIONS**

4
5 474 **Authorship Contributions**

6
7
8 475 CM and VJ were involved in study conception and manuscript drafting and editing. RP,

9
10 476 RNF, BGF, WJS and CEP were involved in study conception and manuscript editing.

11
12 477 RK and BGL were involved in manuscript editing for important intellectual content. VJ is

13
14 478 the guarantor of the article.

15
16
17 479

18
19
20 480 **Data Sharing Statement**

21
22 481 All data from the project will be available upon request from the corresponding author.

23
24 482

25
26
27 483 **Competing interests**

28
29 484 Christopher Ma has no conflicts of interest to declare

30 485
31 486 Remo Panaccione has received scientific advisory board fees from Abbott/AbbVie,
32 487 Amgen, Janssen, Merck, Pfizer, Prometheus Laboratories, Salix Pharma, Shire,
33 488 Takeda, Warner Chilcott; consulting fees from Abbott/AbbVie, Amgen, Aptalis, Astra
34 489 Zeneca, Baxter, BMS, Centocor, Elan/Biogen, Eisai, Ferring, GSK, Janssen, Merck,
35 490 Millennium, Pfizer, Proctor & Gamble, Prometheus Therapeutics and Diagnostics,
36 491 Schering-Plough, Shire, Takeda, UCB Pharma, Warner Chilcott; research grants from
37 492 Abbott/AbbVie, Amgen, Aptalis, Astra Zeneca, Baxter, BMS, Centocor, Eisai,
38 493 Elan/Biogen, Ferring, GSK, Janssen, Merck, Millennium, Pfizer, Proctor & Gamble,
39 494 Prometheus, Shire, Schering-Plough, Takeda, UCB Pharma, Warner Chilcott; and
40 495 speaker's bureau fees from Abbott/AbbVie, Amgen, Aptalis, Astra Zeneca, Baxter,
41 496 BMS, Centocor, Eisai, Elan/Biogen, Ferring, GSK, Janssen, Merck, Millennium, Pfizer,
42 497 Proctor & Gamble, Prometheus, Schering-Plough, Shire, Takeda, UCB Pharma, Warner
43 498 Chilcott

44
45
46
47 499
48 500 Richard Fedorak has received scientific advisory board fees from Abbott/AbbVie,
49 501 Celltrion, Ferring, Janssen, Shire, VSL#3; consulting fees from Abbott/AbbVie, Celltrion,
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51 503 Therapeutics, BMS, Celltrion, Centocor, Genentech, GSK, Janssen, Merck, Millennium,
52 504 Novartis, Pfizer, Proctor & Gamble, Roche, VSL#3

53 505
54 506 Claire Parker has no conflicts of interest to declare

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

509

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512

513 William Sandborn has served as a consultant to: AbbVie Inc., ActoGeniX NV, AGI
514 Therapeutics, Inc., Alba Therapeutics Corporation, Albireo, Alfa Wasserman, Amgen,
515 AM-Pharma BV, Anaphore, Astellas Pharma, Athersys, Inc., Atlantic Healthcare
516 Limited, Axcan Pharma (now Aptalis), BioBalance Corporation, Boehringer-Ingelheim
517 Inc, Bristol Meyers Squibb, Celgene, Celek Pharmaceuticals, Cellerix SL, Cerimon
518 Pharmaceuticals, ChemoCentryx, CoMentis, Cosmo Technologies, Coronado
519 Biosciences, Cytokine Pharmasciences, Eagle Pharmaceuticals, Eisai Medical
520 Research Inc., Elan Pharmaceuticals, EnGene, Inc., Eli Lilly, Enteromedics, Exagen
521 Diagnostics, Inc., Ferring Pharmaceuticals, Flexion Therapeutics, Inc., Funxional
522 Therapeutics Limited, Genzyme Corporation, Genentech (now Roche), Gilead
523 Sciences, Given Imaging, Glaxo Smith Kline, Human Genome Sciences, Ironwood
524 Pharmaceuticals (previously Microbia Inc.), Janssen (previously Centocor), KaloBios
525 Pharmaceuticals, Inc., Lexicon Pharmaceuticals, Lycera Corporation, Meda
526 Pharmaceuticals (previously Alaven Pharmaceuticals), Merck Research Laboratories,
527 MerckSerono, Millennium Pharmaceuticals (subsequently merged with Takeda), Nisshin
528 Kyorin Pharmaceuticals Co., Ltd., Novo Nordisk A/S, NPS Pharmaceuticals, Optimer
529 Pharmaceuticals, Orexigen Therapeutics, Inc., PDL Biopharma, Pfizer, Procter and
530 Gamble, Prometheus Laboratories, ProtAb Limited, Purgensis Technologies, Inc.,
531 Receptos, Relypsa, Inc., Salient Pharmaceuticals, Salix Pharmaceuticals, Inc.,
532 Santarus, Schering Plough Corporation (acquired by Merck), Shire Pharmaceuticals,
533 Sigmoid Pharma Limited, Sirtris Pharmaceuticals, Inc. (a GSK company), S.L.A.
534 Pharma (UK) Limited, Targacept, Teva Pharmaceuticals, Therakos, Tillotts Pharma AG
535 (acquired by Zeria Pharmaceutical Co., Ltd), TxCell SA, UCB Pharma, Viamet
536 Pharmaceuticals, Vascular Biogenics Limited (VBL), Warner Chilcott UK Limited; has
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542

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549 Pharma AG, Unity Pharmaceuticals, Albireo Pharma, Given Imaging Inc., Salix
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553 AbbVie, and J&J/Janssen

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554
555 Vipul Jairath has received scientific advisory board fees from AbbVie, Sandoz, Takeda,
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1
2
3 557
4 558 **Abbreviations**
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6
7 559 CD (Crohn's disease); CDAI (Crohn's Disease Activity Index); CENTRAL (Cochrane
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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
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13 562 Assessment, Development, and Evaluation); IBD (inflammatory bowel disease); ICHOM
14
15 563 (International Consortium for Health Outcomes Measurement); OMERACT (Outcome
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17 564 Measures in Rheumatology); PRISMA (Preferred Reporting Items for Systematic
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19 565 Reviews and Meta-Analyses); PRO (patient reported outcome); RCT (randomized
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21 566 controlled trial); UC (ulcerative colitis); STRIDE (Selecting Therapeutic Targets in
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569 REFERENCES

- 570 1. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the
571 inflammatory bowel diseases with time, based on systematic review.
572 *Gastroenterology* 2012;142(1):46-54. doi: 10.1053/j.gastro.2011.10.001
- 573 2. Peyrin-Biroulet L, Loftus EV, Jr., Colombel JF, et al. The natural history of adult
574 Crohn's disease in population-based cohorts. *Am J Gastroenterol*
575 2010;105(2):289-97. doi: 10.1038/ajg.2009.579
- 576 3. de Souza HS, Fiocchi C. Immunopathogenesis of IBD: current state of the art. *Nat*
577 *Rev Gastroenterol Hepatol* 2016;13(1):13-27. doi: 10.1038/nrgastro.2015.186
- 578 4. Gibson TB, Ng E, Ozminkowski RJ, et al. The direct and indirect cost burden of
579 Crohn's disease and ulcerative colitis. *J Occup Environ Med* 2008;50(11):1261-
580 72. doi: 10.1097/JOM.0b013e318181b8ca
- 581 5. Kappelman MD, Rifas-Shiman SL, Porter CQ, et al. Direct health care costs of
582 Crohn's disease and ulcerative colitis in US children and adults.
583 *Gastroenterology* 2008;135(6):1907-13. doi: 10.1053/j.gastro.2008.09.012
- 584 6. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting Therapeutic Targets in
585 Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for
586 Treat-to-Target. *Am J Gastroenterol* 2015;110(9):1324-38. doi:
587 10.1038/ajg.2015.233
- 588 7. Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical
589 remission in moderately to severely active ulcerative colitis: results of a
590 randomised controlled trial. *Gut* 2011;60(6):780-7. doi: 10.1136/gut.2010.221127

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

- 1
2
3 591 8. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains
4
5 592 clinical remission in patients with moderate-to-severe ulcerative colitis.
6
7 593 *Gastroenterology* 2012;142(2):257-65 e1-3. doi: 10.1053/j.gastro.2011.10.032
8
9
10 594 9. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and
11
12 595 maintenance therapy for ulcerative colitis. *N Engl J Med* 2005;353(23):2462-76.
13
14 596 doi: 10.1056/NEJMoa050516
15
16
17 597 10. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and
18
19 598 maintenance therapy for ulcerative colitis. *N Engl J Med* 2013;369(8):699-710.
20
21 599 doi: 10.1056/NEJMoa1215734
22
23
24 600 11. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's
25
26 601 disease: the ACCENT I randomised trial. *Lancet* 2002;359(9317):1541-9. doi:
27
28 602 10.1016/S0140-6736(02)08512-4
29
30
31 603 12. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor
32
33 604 monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial.
34
35 605 *Gastroenterology* 2006;130(2):323-33; quiz 591. doi:
36
37 606 10.1053/j.gastro.2005.11.030
38
39
40
41 607 13. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of
42
43 608 clinical response and remission in patients with Crohn's disease: the CHARM
44
45 609 trial. *Gastroenterology* 2007;132(1):52-65. doi: 10.1053/j.gastro.2006.11.041
46
47
48 610 14. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and
49
50 611 maintenance therapy for Crohn's disease. *N Engl J Med* 2013;369(8):711-21. doi:
51
52 612 10.1056/NEJMoa1215739
53
54
55
56
57
58
59
60

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

- 1
2
3 613 15. Khanna R, Jairath V, Vande Casteele N, et al. Efficient Early Drug Development for
4
5 614 Ulcerative Colitis. *Gastroenterology* 2016;150(5):1056-60. doi:
6
7 615 10.1053/j.gastro.2016.03.013
8
9
10 616 16. Jairath V, Levesque BG, Vande Casteele N, et al. Evolving Concepts in Phases I
11
12 617 and II Drug Development for Crohn's Disease. *J Crohns Colitis* 2016 doi:
13
14 618 10.1093/ecco-jcc/jjw137
15
16
17 619 17. Hindryckx P, Baert F, Hart A, et al. Clinical trials in luminal Crohn's disease: a
18
19 620 historical perspective. *J Crohns Colitis* 2014;8(11):1339-50. doi:
20
21 621 10.1016/j.crohns.2014.04.007
22
23
24 622 18. Best WR, Bectel JM, Singleton JW, et al. Development of a Crohn's disease
25
26 623 activity index. National Cooperative Crohn's Disease Study. *Gastroenterology*
27
28 624 1976;70(3):439-44.
29
30
31 625 19. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy
32
33 626 for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J*
34
35 627 *Med* 1987;317(26):1625-9. doi: 10.1056/NEJM198712243172603
36
37
38 628 20. Williet N, Sandborn WJ, Peyrin-Biroulet L. Patient-reported outcomes as primary
39
40 629 end points in clinical trials of inflammatory bowel disease. *Clin Gastroenterol*
41
42 630 *Hepatol* 2014;12(8):1246-56 e6. doi: 10.1016/j.cgh.2014.02.016
43
44
45 631 21. Targownik LE, Sexton KA, Bernstein MT, et al. The Relationship Among Perceived
46
47 632 Stress, Symptoms, and Inflammation in Persons With Inflammatory Bowel
48
49 633 Disease. *Am J Gastroenterol* 2015;110(7):1001-12; quiz 13. doi:
50
51 634 10.1038/ajg.2015.147
52
53
54
55
56
57
58
59
60

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

- 1
2
3 635 22. Gracie DJ, Williams CJ, Sood R, et al. Poor Correlation Between Clinical Disease
4
5 636 Activity and Mucosal Inflammation, and the Role of Psychological Comorbidity, in
6
7 637 Inflammatory Bowel Disease. *Am J Gastroenterol* 2016;111(4):541-51. doi:
8
9 638 10.1038/ajg.2016.59
10
11
12 639 23. Bonovas S, Fiorino G, Allocca M, et al. Biologic Therapies and Risk of Infection and
13
14 640 Malignancy in Patients With Inflammatory Bowel Disease: A Systematic Review
15
16 641 and Network Meta-analysis. *Clin Gastroenterol Hepatol* 2016;14(10):1385-97
17
18 642 e10. doi: 10.1016/j.cgh.2016.04.039
19
20 643 24. Williamson PR, Altman DG, Blazeby JM, et al. Developing core outcome sets for
21
22 644 clinical trials: issues to consider. *Trials* 2012;13:132. doi: 10.1186/1745-6215-13-
23
24 645 132
25
26
27 646 25. D'Haens G, Feagan B, Colombel JF, et al. Challenges to the design, execution, and
28
29 647 analysis of randomized controlled trials for inflammatory bowel disease.
30
31 648 *Gastroenterology* 2012;143(6):1461-9. doi: 10.1053/j.gastro.2012.09.031
32
33
34 649 26. Boers M, Kirwan JR, Wells G, et al. Developing core outcome measurement sets for
35
36 650 clinical trials: OMERACT filter 2.0. *J Clin Epidemiol* 2014;67(7):745-53. doi:
37
38 651 10.1016/j.jclinepi.2013.11.013
39
40
41 652 27. Chiarotto A, Terwee CB, Deyo RA, et al. A core outcome set for clinical trials on
42
43 653 non-specific low back pain: study protocol for the development of a core domain
44
45 654 set. *Trials* 2014;15:511. doi: 10.1186/1745-6215-15-511
46
47
48 655 28. Egan AM, Smith V, Devane D, et al. Effectiveness of prepregnancy care for women
49
50 656 with pregestational diabetes mellitus: protocol for a systematic review of the
51
52
53
54
55
56
57
58
59
60

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

- 1
2
3 657 literature and identification of a core outcomes set using a Delphi survey. *Trials*
4
5 658 2015;16:356. doi: 10.1186/s13063-015-0894-8
6
7
8 659 29. Harman NL, Bruce IA, Callery P, et al. MOMENT--Management of Otitis Media with
9
10 660 Effusion in Cleft Palate: protocol for a systematic review of the literature and
11
12 661 identification of a core outcome set using a Delphi survey. *Trials* 2013;14:70. doi:
13
14 662 10.1186/1745-6215-14-70
15
16
17 663 30. Iyengar S, Williamson PR, Schmitt J, et al. Development of a core outcome set for
18
19 664 clinical trials in rosacea: study protocol for a systematic review of the literature
20
21 665 and identification of a core outcome set using a Delphi survey. *Trials*
22
23 666 2016;17(1):429. doi: 10.1186/s13063-016-1554-3
24
25
26
27 667 31. Kelly LE, Jansson LM, Mouldsdale W, et al. A core outcome set for neonatal
28
29 668 abstinence syndrome: study protocol for a systematic review, parent interviews
30
31 669 and a Delphi survey. *Trials* 2016;17(1):536. doi: 10.1186/s13063-016-1666-9
32
33
34 670 32. MacLennan S, Bekema HJ, Williamson PR, et al. A core outcome set for localised
35
36 671 prostate cancer effectiveness trials: protocol for a systematic review of the
37
38 672 literature and stakeholder involvement through interviews and a Delphi survey.
39
40 673 *Trials* 2015;16:76. doi: 10.1186/s13063-015-0598-0
41
42
43 674 33. Tong A, Manns B, Hemmelgarn B, et al. Standardised outcomes in nephrology -
44
45 675 Haemodialysis (SONG-HD): study protocol for establishing a core outcome set in
46
47 676 haemodialysis. *Trials* 2015;16:364. doi: 10.1186/s13063-015-0895-7
48
49
50 677 34. Gargon E. The COMET (Core Outcome Measures in Effectiveness Trials) Initiative.
51
52 678 *Maturitas* 2016;91:91-2. doi: 10.1016/j.maturitas.2016.06.007
53
54
55
56
57
58
59
60

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

- 1
2
3 679 35. Kirkham JJ, Gorst S, Altman DG, et al. COS-STAR: a reporting guideline for studies
4
5 680 developing core outcome sets (protocol). *Trials* 2015;16:373. doi:
6
7 681 10.1186/s13063-015-0913-9
8
9
10 682 36. Sinha IP, Smyth RL, Williamson PR. Using the Delphi technique to determine which
11
12 683 outcomes to measure in clinical trials: recommendations for the future based on
13
14 684 a systematic review of existing studies. *PLoS Med* 2011;8(1):e1000393. doi:
15
16 685 10.1371/journal.pmed.1000393
17
18
19 686 37. The ICHOM Standard Set for Inflammatory Bowel Disease [Available from:
20
21 687 <http://www.ichom.org/medical-conditions/inflammatory-bowel-disease/2016>.
22
23
24 688 38. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic
25
26 689 reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*
27
28 690 2009;62(10):1006-12. doi: 10.1016/j.jclinepi.2009.06.005
29
30
31 691 39. Mokkink LB, Terwee CB, Knol DL, et al. The COSMIN checklist for evaluating the
32
33 692 methodological quality of studies on measurement properties: a clarification of its
34
35 693 content. *BMC Med Res Methodol* 2010;10:22. doi: 10.1186/1471-2288-10-22
36
37
38 694 40. Kuper A, Reeves S, Levinson W. An introduction to reading and appraising
39
40 695 qualitative research. *BMJ* 2008;337:a288. doi: 10.1136/bmj.a288
41
42
43 696 41. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question
44
45 697 and deciding on important outcomes. *J Clin Epidemiol* 2011;64(4):395-400. doi:
46
47 698 10.1016/j.jclinepi.2010.09.012
48
49
50 699 42. Hirsch M, Duffy JM, Barker C, et al. Protocol for developing, disseminating and
51
52 700 implementing a core outcome set for endometriosis. *BMJ Open*
53
54 701 2016;6(12):e013998. doi: 10.1136/bmjopen-2016-013998
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Ma *et al.* **Development of a core outcome set for IBD clinical trials**

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3 702 43. Amiot A, Peyrin-Biroulet L. Current, new and future biological agents on the horizon
4
5 703 for the treatment of inflammatory bowel diseases. *Therap Adv Gastroenterol*
6
7 704 2015;8(2):66-82. doi: 10.1177/1756283X14558193
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SUPPLEMENTAL FILE 2

Systematic review search strategies

MEDLINE

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

PUBMED

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

EMBASE

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

CENTRAL

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

Supplemental File 1 – PRISMA-P Checklist

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

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

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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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