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CORE-IBD: A Multidisciplinary International Consensus Initiative to Develop a Core Outcome Set for Randomized Controlled Trials in Inflammatory Bowel Disease

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KEYWORDS: End Point; Crohn's Disease; Ulcerative Colitis; Outcomes.

BACKGROUND & AIMS: End points to determine the efficacy and safety of medical therapies for Crohn's disease (CD) and ulcerative colitis (UC) are evolving. Given the heterogeneity in current outcome measures, harmonizing end points in a core outcome set for randomized controlled trials is a priority for drug development in inflammatory bowel disease. **METHODS**: Candidate outcome domains and outcome measures were generated from systematic literature reviews and patient engagement surveys and interviews. An iterative Delphi process was conducted to establish consensus: panelists anonymously voted on items using a 9-point Likert scale, and feedback was incorporated between rounds to refine statements. Consensus meetings were held to ratify the outcome domains and core outcome measures. Stakeholders were recruited internationally, and included gastroenterologists, colorectal surgeons, methodologists, and clinical trialists. **RESULTS**: A total of 235 patients and 53 experts participated. Patient-reported outcomes, quality of life, endoscopy, biomarkers, and safety were considered core domains; histopathology was an additional domain for UC. In CD, there was consensus to use the 2-item patient-reported outcome

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(ie, abdominal pain and stool frequency), Crohn's Disease Activity Index, Simple Endoscopic Score for Crohn's Disease, C-reactive protein, fecal calprotectin, and co-primary end points of symptomatic remission and endoscopic response. In UC, there was consensus to use the 9-point Mayo Clinic Score, fecal urgency, Robarts Histopathology Index or Geboes Score, fecal calprotectin, and a composite primary end point including both symptomatic and endoscopic remission. Safety outcomes should be reported using the Medical Dictionary for Regulatory Activities. **CONCLUSIONS:** This multidisciplinary collaboration involving patients and clinical experts has produced the first core outcome set that can be applied to randomized controlled trials of CD and UC.

Abbreviations used in this paper: CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; COMET, Core Outcome Measures in Effectiveness Trials; COS, core outcome set; CRP, C-reactive protein; AE, adverse event; IBD, inflammatory bowel disease; MCS, Mayo Clinic score; mMES, modified Mayo Endoscopic Subscore; PRO, patient-reported outcome; PRO2, 2-item patient-reported outcome; RCT, randomized controlled trial; SES-CD, Simple Endoscopic Score for Crohn's Disease; UC, ulcerative colitis.

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The current paradigm for medical therapy for Crohn's disease (CD) and ulcerative colitis (UC) focuses on controlling inflammatory activity. Although the armamentarium of treatment options for inflammatory bowel disease (IBD) has expanded substantially over the past several decades, with the adoption of biologic and novel small molecule therapies, these developments have not resulted in transformational efficacy. Clinical remission rates remain low, and most patients do not achieve endoscopic, radiographic, histologic, or biomarker-based definitions of remission with currently available agents, underscoring the importance of continued efforts to improve drug development in CD and UC.[1]

The approval of new therapies relies on data from robust randomized controlled trials (RCTs), which have become larger and more complex over time.[2] Advances in our understanding of CD and UC have also resulted in the evolution of study designs for these indications. For example, there is increasing recognition that symptom-based measurements alone are insensitive and poorly specific for assessing disease activity, resulting in a paradigm shift towards normalizing objective measures of inflammation.[3,4] Trials now routinely incorporate endoscopic evaluation for qualifying patients at enrollment and for assessing efficacy. Beyond endoscopic mucosal appearance, the added value of targeting aspirational goals, such as histologic remission in UC or transmural healing in CD, is under evaluation.[5] Simultaneously, there has been an emphasis at the regulatory level to more accurately capture the patient experience using validated patient-reported outcomes (PROs).[6] Given the evolving landscape of treatment end points and the rapid development of novel therapies, standardizing what, how, and when to measure key efficacy and safety outcomes in IBD trials is a research priority.[7]

The standardized assessment of outcome measures in IBD trials has received insufficient attention.[8,9] For example, multiple versions of the Mayo Clinic Score (MCS) are currently used in phase 2 and 3 trials, with no universally accepted convention having been defined. The development of a core outcome set (COS) for use in IBD RCTs will increase the relevance of clinical research for multiple stakeholder groups, reduce heterogeneity in outcome reporting, and enhance the quality of evidence synthesis.[10] A COS is a consensus-derived minimum set of outcomes that should be measured and reported in all trials of a given disease.[11] The CORE-IBD consensus was a multiple phase program, that included patients, gastroenterologists, colorectal surgeons, methodologists, and clinical trialists, that aimed to develop the first international consensus-based COS for use in CD and UC RCTs.

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WHAT YOU NEED TO KNOW
BACKGROUND AND CONTEXT
Standardizing what, how, and when to measure key efficacy and safety outcomes in a core outcome set for Crohn's disease and ulcerative colitis is a research priority.
NEW FINDINGS
An international, multidisciplinary expert panel has established consensus on core patient-reported, clinical, endoscopic, biomarker, histologic, and safety end points for Crohn's disease and ulcerative colitis trials.
LIMITATIONS
This core outcome set may not apply to nonrandomized controlled trials and nondrug studies.
IMPACT
Adoption of this core outcome set will improve the quality of evidence synthesis and reduce heterogeneity in outcome reporting; validation of existing and novel instruments can be incorporated into future iterations.

Methods

REGISTRATION AND SCOPE

The CORE-IBD initiative is registered with Core Outcome Measures in Effectiveness Trials (COMET)[12] and was conducted in accordance with recommendations outlined in the COMET handbook and the Core Outcome Set-Standards for Develop- ment.[11,13,14] All patient-related activities were approved by the Conjoint Health Research Ethics Board at the University of Calgary (REB20-1827).

The scope of this COS is for use in RCTs of pharmacologic therapies for adult patients (18 years and older) with CD or UC. Interventions involving surgical treatment were outside the scope of this COS. We primarily considered luminal CD and excluded trials of patients with specific phenotypes, such as pouchitis or perianal fistulizing CD. This COS may not apply to pediatric patients when outcomes unique to this population, such as growth failure, are measured. However, older adolescents are increasingly included in adult RCTs. We focused on outcomes relevant for RCTs and acknowledge that the measures recommended may be infeasible in certain contexts (eg, in real-world registries and nonrandomized, prospective cohorts) due to cost or operational considerations.

OVERVIEW OF CORE OUTCOME SET DEVELOPMENT

A multiple phase approach was used to develop the CORE- IBD consensus (Figure 1). In phase 1, candidate outcomes that have been measured in IBD RCTs previously were identified in a series of comprehensive systematic literature reviews and organized into outcome domains. In phase 2, patient engagement surveys and qualitative interviews were conducted to prioritize outcome

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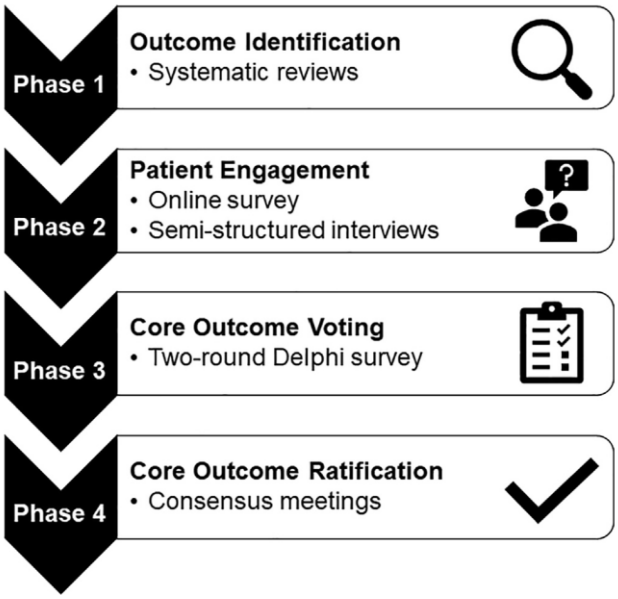
domains of importance for patients and to identify any additional end points that may not have been captured in existing studies. In phase 3, a comprehensive list of outcome measures developed in phases 1 and 2 was evaluated by an international panel of multidisciplinary experts in a 2- round Delphi survey. Finally, in phase 4, virtual ratification meetings were held to vote on the final outcomes included in the COS

PHASE 1: Outcome identification through systematic review. End points relevant to the scope of the COS were identified in previously published systematic literature reviews of placebo controlled IBD trials,[8,9] and searches were updated to 2021. These end points were categorized into outcome domains, including patient-reported, endoscopic, histologic, radiographic, biomarker, and composite outcomes of efficacy.

PHASE 2: Patient engagement surveys and interviews. Patients were engaged in the COS development through online surveys and semi-structured interviews. An anonymous survey consisting of semi-structured and singleselection, multiple-choice responses was used to assess patient perceptions and preferences of different outcome domains relevant to IBD care. The online survey was distributed using an IBD e-mail listserv of patients in Southern Alberta, who had previously agreed to be contacted for research. All patients presenting to clinical care, who had previously been started on a biologic treatment or who had participated in prior studies, were included in the listserv. This captured a broad range of responses from a diverse population of adult patients with IBD, including patients of different ages, disease durations, disease activity statuses, and treatment experiences. The online survey was developed with input from patient advocates, clinicians, and IBD nurse specialists, and the language and format of the survey were piloted before being distributed (Supplementary Appendix 1). Open-ended free-text responses aimed at identifying other measures of treatment efficacy, beyond those identified in the systematic review, were also included.

Figure 1. *Development of a core outcome set for IBD RCTs.*



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Semi-structured interviews were then conducted with patients who had previously participated in an IBD RCT. For feasibility, patients were purposely sampled from the IBD Trials Unit at the University of Calgary, Canada, and patients were enrolled until thematic saturation was achieved. All interviews were conducted in English, using a topic guide to identify the patient's lived experiences with IBD, benefits and harms of IBD- related treatment, specific experience in the RCT, and outcomes that patients believed to be relevant and important to include in IBD trials. Narrative data were indexed and mapped to a thematic framework to summarize key points and outcomes of priority.

PHASE 3: Delphi panel. A comprehensive list of outcomes identified in phases 1 and 2 was incorporated in a 2- round Delphi survey in phase 3. The Delphi method allows panelists to anonymously derive consensus through multiple rounds of sequential questionnaires.[11] After each of the 2 electronic voting rounds, the group responses and each panelist's individual responses were provided in a feedback sum- mary.[15] For each survey, a minimum sample size of 30 respondents was targeted. A diverse pool of gastroenterologists, colorectal surgeons, methodologists, and clinical trialists, who brought a broad range of clinical knowledge, RCT-related experience, and geographical diversity were identified and invited to participate by the lead (C.M.) and senior investigator (V.J.). Minimum requirements for participation included expertise in IBD trial conduct or outcome assessment, as reflected by metrics such as authorship of at least 25 publications related to IBD or involvement in at least 2 IBD clinical trials (either as an investigator or through input into the trial design); or clinical expertise as demonstrated by being the medical or surgical leads of a dedicated IBD center.

Participants were asked to rate each outcome on a scale from 1 to 9, based on the Grading of Recommendations Assessment, Development, and Evaluation Working Group definitions.[16] Panelists were instructed to rate the most important outcomes highly (7-9 range), and to downgrade outcomes of lesser importance (scores of 1-3 indicate an outcome that is not important for inclusion). Scores of 4-6 indicated an outcome of some importance that was not critical for inclusion. All outcomes had free-text entry options for participants to provide clarifying statements or identify additional outcomes of interest. Responses were collated and descriptive statistics were used to summarize the scoring and distribution of the entire panel.

Based on panelist feedback regarding the length of the survey, only outcomes for which >50% of panelists voted in the 7-9 range were carried forward from the first round to the second round of voting. The panelists were asked to consider insight from the group when rescoring these outcomes on a Likert scale from 1-9. Outcomes for which >70% of panelists scored in the 7-9 range and <15% of panelists scored in the 13 range during the second round of voting were decided *a priori* to have met consensus for inclusion.

PHASE 4: Ratification meetings. Consensus ratification meetings were held by videoconference on November 3, 2021, and November 6, 2021. The criteria for COS inclusion were reviewed for each meeting. All items from round 2 were reviewed, with a focus on potentially contentious items rated in the 7-9 range by 60%-80% of panelists. Items for inclusion were discussed and arguments for and against inclusion were synthesized in a summary document. After discussion, panelists re-voted on these candidate items in an anonymous third round, where voting was simplified to "include in the

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COS," "do not include in the COS," or "unsure." Outcomes receiving >70% of votes in the "include" category and <15% of votes in the "do not include" category were ratified for final inclusion in the COS, similar to phase 3.

RATIONALE FOR PARTICIPANT SELECTION

We included a broad range of patient and multidisciplinary expert participants in this COS to maximize its application to end users. We specifically used a staged approach to ensure appropriateness of voting at each phase. Patients were engaged early in the process to provide feedback on the most relevant outcome domains of interest, modeled on the framework used by the Outcome Measures in Rheumatology (OMERACT) Group.[17] During the Delphi process, the panel was asked to critically examine highly technical considerations around measurement instruments and thresholds. Informed and valid voting on these statements requires a detailed understanding of the operating properties of different outcome measures and their performance within a clinical trial context. Therefore, we set stringent criteria for Delphi panelist eligibility. We did consider inclusion of industry representatives but, given that this is an academic exercise and to avoid any real or perceived conflicts of interest, industry sponsors were not invited. Finally, this COS was meant to be complementary to, and not replace, regulatory guidance.

Results

PARTICIPANTS

Demographics of the patient participants and expert panelists are summarized in Supplementary Table 1. A total of 235 patients (52% were female) with IBD completed the online engagement survey (response rate 47.0%). A total of 22 patients (50% were female) who had previously participated in an IBD RCT underwent qualitative interviews. Of the 76 experts invited, 53 (69.7%) from 17 countries participated in the Delphi panel. Most panelists practiced in academic hospitals (51 of 53 [96.2%]), typically in mixed roles as clinician-researchers (46 of 53 [86.8%]), and had more than 20 years of experience in IBD care (38 of 53 [71.7%]).

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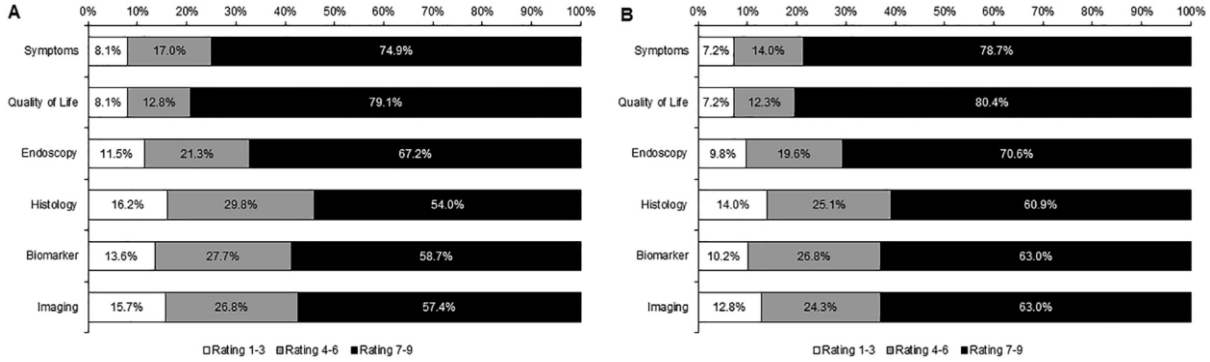
Figure 2. *Patient rating of outcome domains of importance for assessing treatment efficacy in the short (A) and long (B) term.*



PATIENT ENGAGEMENT SURVEYS AND SEMISTRUCTURED INTERVIEWS

Patients rated the relative importance of 6 different outcome domains (ie, symptoms, quality of life, endoscopy, histology, biomarkers, and imaging) on a 9-point Likert scale. Consistently, patients rated improvement in IBD- related symptoms and quality of life as the most important measures of efficacy (Figure 2). Improvements in abdominal pain and stool frequency were commonly reported as the most important aspects of symptomatic improvement, as were associated symptoms, such as control over bowel movements, urgency, continence, and stool form. A summary of additional patient-identified end points is presented in Supplementary Table 2. Achievement of endoscopic improvement in the long term was voted as very important by 70.6% of patients (166 of 235), although approximately 10% of patients rated achievement of endoscopic, histologic, biomarker, or imaging outcomes as not important (ratings of 1-3 on a 9-point Likert scale). In semistructured interviews, almost all participants were satisfied with their clinical trial experience, although the burden of frequent visits and long, complex surveys was highlighted.

DELPHI SURVEY RESULTS AND OUTCOME DOMAINS

A total of 475 statements were included in the first- round survey, and 228 of these statements were voted as important for inclusion in a COS by >50% of the panel and included in round 2. In the ratification meeting, panelists discussed and re-voted on 111 candidate statements rated in the 7-9 range by 60%-80% of panelists during round 2. A summary of voting results from the final round of the Delphi survey and from the ratification meetings are presented in Supplementary Tables 3 and 4. In CD and UC, there was consensus that core domains of treatment efficacy should include PROs, quality of life, endoscopy, and biomarkers. In UC, there was also consensus that histopathology should be a core outcome domain.

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CORE OUTCOMES FOR CROHN'S DISEASE TRIALS

Patient-reported outcomes and composite indices. Core outcomes for CD RCTs are summarized in Table 1. There was consensus that symptomatic outcomes in CD RCTs should be defined using a PRO measure that incorporates stool frequency and abdominal pain, with symptoms assessed using daily diary cards for at least 7 days before a study visit (excluding the day before, day of, and day after a colonoscopy) to capture potential symptom variability. It was recognized that completing a 7-day recall is burdensome for patients and this was highlighted in the patient interviews, although the burden may be mitigated in trials using electronic handheld devices that improve feasibility of daily data collection. Shorter recall periods and the simpler Harvey-Bradshaw Index were considered but did not reach consensus because the panel felt that capturing potential symptom variability over multiple days, particularly given the imperfect correlation between symptoms and objective evidence of inflammation in CD, was important.

Additional symptoms, such as liquid stool frequency, nocturnal bowel movements, urgency, cramping, nausea, vomiting, extraintestinal manifestations, reduced general wellbeing, depression, anxiety, fatigue, poor sleep quality, sexual dysfunction, and need for dietary modifications, were considered. However, the panel discussed that the correlation between these symptoms and objective disease activity may be poor, and some of these symptoms may be challenging to define or quantify. It was acknowledged that symptoms such as fatigue and mental wellness are important to patients and will be assessed in some RCTs, yet they do not constitute core outcomes that must be measured in every trial. Although many different PRO or symptom-based indices were considered, the panel also recognized that a fully validated PRO is not yet available, although several are in development.[18-20] In the interim, only the 2-item patient reported outcome (PRO2), which incorporates abdominal pain and stool frequency, was voted as a core outcome. A definition of remission based on the PRO2 with a mean abdominal pain score <1 and stool frequency subscore <2.8 was discussed at length. This definition identified a similar proportion of clinical remitters when compared with the Crohn's Disease Activity Index (CDAI) in phase 3 trials of risankizumab.[21] However, a consensus threshold was not reached for this definition, as it was felt that the operating properties of PRO2 are still being evaluated in ongoing RCTs.

The CDAI was included as a core composite outcome measure with response defined as a reduction of >100 points compared with baseline. The panel discussed limitations of the CDAI, including its complexity of calculation, applicability to routine clinical care, weighting towards stool frequency, and poor correlation with endoscopy. However, given that the CDAI has been used in all registrational CD trials for modern therapies, it was determined that this instrument should continue to be measured as a core outcome until additional validated PROs are developed. In addition, the panel

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discussed that the CDAI has been used to define relatively homogeneous disease populations for trial enrollment. A consensus definition of CDAI-based remission was not agreed upon. Although a CDAI score of <150 has historically been used to define clinical remission, some panelists felt that this definition was poorly specific and could be improved with the addition of a >70- to 100-point reduction from baseline. However, other panelists contended that such a caveat would reduce the sensitivity of the remission threshold, and that a reduction would already be captured based on the inclusion requirements of most moderate-to-severe CD trials, which use a CDAI score of 220-450 as an enrollment criterion.

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Table 1. *Summary of Core Outcomes in Crohn's Disease and Ulcerative Colitis Randomized Controlled Trials*

Domain	CD	UC
Configuration of outcomes	The co-primary end point of symptomatic remission and endoscopic response should be used in CD trials Induction outcomes: co-primary symptomatic remission and endoscopic response, symptomatic response, corticosteroid-free remission, endoscopic response, and biomarker remission/response Maintenance outcomes: co-primary symptomatic remission and endoscopic response, symptomatic and endoscopic remission, corticosteroid free remission, sustained remission, endoscopic remission/response, biomarker remission Loss of response should be defined by worsening symptoms and either worsening	The composite end point of symptomatic and endoscopic remission should be used in UC trials Response should be defined by the composite of symptomatic and endoscopic response in UC trials Induction outcomes: composite symptomatic and endoscopic remission, composite symptomatic and endoscopic response, endoscopic response, endoscopic remission, histologic remission, combined clinical and biomarker remission Maintenance outcomes: clinical response and remission (composite outcomes), corticosteroid-free remission, sustained remission, loss of remission/response, endoscopic remission/response, histologic remission, mucosal healing (combined endoscopic and histologic remission), biomarker remission Loss of response should be defined by worsening symptoms and either endoscopy or biomarkers
PROs, symptom-based measures, and composite indices	A PRO for CD should include stool frequency and abdominal pain CDAI should be used as a composite outcome measure Clinical response should be defined by CDAI reduction >100 points compared with baseline	A PRO for UC should include rectal bleeding, stool frequency, and fecal urgency The adapted 9-point MCS (including rectal bleeding, stool frequency, and mMES) should be used in UC trials Symptomatic remission should be defined by rectal bleeding subscore =
Endoscopic outcomes	Endoscopic outcomes should be assessed using the SES-CD Endoscopic response should be defined by >50% reduction in SES-CD vs baseline Endoscopic remission should be defined by absence of ulcerations in all segments Endoscopic remission in isolated ileal CD should be defined by SES-CD <2 Missing segments should be reported at baseline and after	Endoscopic outcomes should be assessed by flexible sigmoidoscopy in UC trials Scoring should be based on the most affected segment Endoscopic remission should be defined as mMES = 0 Endoscopic response should be defined by reduction in mMES >1 from baseline Endoscopic response and remission should be measured in UC induction trials at 9-12 wk Endoscopic response and remission should be measured in UC maintenance trials at 52 wk
Histopathology	Not voted as a core domain for CD	Histopathology should be scored using the Robarts Histopathology Index (RHI) Histologic remission should be defined by RHI <3 with absence of neutrophils (or Geboes Score <3.0 with no neutrophilic inflammation in the
Biomarker outcomes	CRP and fecal calprotectin should be measured in CD induction and maintenance trials Biomarker remission should be defined in CD trials by CRP <5 mg/L Biomarker response should be defined by >50% reduction in CRP and fecal calprotectin among those with elevated levels at baseline	Fecal calprotectin should be measured in UC induction and maintenance trials Biomarker remission should be defined by UC trials by CRP <5 mg/L or fecal calprotectin <150 mg/g Biomarker response should be defined by >50% reduction in fecal calprotectin among those with elevated levels at baseline

ENDOSCOPIC OUTCOMES. The Simple Endoscopic Score for Crohn's Disease (SES-CD) was endorsed over the Crohn's Disease Endoscopic Index of Severity, given the simplicity of the SES-CD calculation. There was considerable discussion regarding the optimal definition of endoscopic remission. Conceptually, there was consensus that endoscopic remission should be defined by the absence of any ulcerations in all segments, given that ulcerations are the hallmark lesion in CD. Accordingly, a stringent threshold of SES-CD ≤2 (which would capture absence of ulcerations) was considered an appropriate threshold for defining endoscopic remission. The panel recognized that

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achieving a SES-CD ≤2 with existing therapies is challenging, although this is most in keeping with the concept of "ulcer-free" endoscopic remission, and that placebo rates with this outcome would be similarly low. There was consensus to use SES-CD ≤2 as the threshold in isolated ileal CD. Although no trials to date have recruited patients with ileal disease only, multiple programs have set separate thresholds for ileal vs colonic/ ileocolonic involvement, given that the SES-CD score in patients with isolated ileal disease is limited by only having 1 segment involved.

The panel voted that endoscopic response should be defined as a >50% reduction in SES-CD compared with baseline. Both endoscopic response and endoscopic remission should be measured in all induction and maintenance trials. There was also consensus that endoscopic outcomes should be reported at 52 weeks for maintenance trials, although no consensus on the timing of endoscopy during induction was reached. Performing endoscopic assessment too early in induction trials could risk missing delayed improvement; however, panelists highlighted that this risk must be balanced against a prolonged induction period leading to higher rates of patient dropout and potential prolonged exposure to fixed corticosteroid dosing regimens.

Biomarker outcomes. There was consensus that C- reactive protein (CRP) and fecal calprotectin should be measured and reported in CD induction and maintenance trials. Although other biomarkers, such as the Endoscopic Healing Index were considered, limitations with respect to availability, cost, and accuracy precluded inclusion of these biomarkers as core outcomes for measurement in all tri- als.[22] Biomarker-based remission in CD trials should include a CRP <5 mg/L. There was no consensus on the threshold definition for fecal calprotectin-based remission, although multiple cutoffs ranging from 50 to 250 μg/g were considered. However, a >50% reduction in fecal calpro- tectin among patients with an elevated level at baseline was considered a core outcome for defining biomarker response. The merits and drawbacks of using a relative reduction vs thresholds for biomarkers were considered in detail during panel discussions. For example, a patient with a baseline fecal calprotectin of 2000 μg/g who achieves a 50% reduction to 1000 μg/g would be considered a biomarker responder, yet still has substantial inflammation. Conversely, many panelists felt that this reduction is still meaningful, and potential variations in fecal calprotectin concentrations according to disease location and extent were contributing factors to the lack of consensus on a threshold for remission. Although biomarkers were considered an informative surrogate measure of pharmacodynamic effects, the panel discussed that biomarker assessment should be balanced against the potential patient burden of collection, which may be increasingly relevant for virtual trial visits. There was support for measuring biomarkers at all visits during induction and every 3 months during maintenance, although the threshold for consensus was not reached.

CONFIGURATION OF OUTCOMES IN CROHN'S DISEASE TRIALS. There was consensus that remission in CD trials should be defined using co-primary end points of symptomatic

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remission and endoscopic response, which captures the patient experience and objective assessment of disease activity. There was considerable discussion, and consensus that corticosteroid-free remission should also be reported in induction trials was ultimately reached. Although corticosteroid dosing is typically fixed during the induction period of a trial, there was discussion about potential trial designs that allow for early corticosteroid tapering, which would increase the sensitivity for detecting treatment efficacy and would favor highly efficacious agents. Endoscopic remission was considered but was thought to be too stringent an end point to be used as the primary outcome in induction trials.

In maintenance trials, consensus was reached to measure co-primary symptomatic and endoscopic response, coprimary symptomatic and endoscopic remission, corticosteroid-free remission, endoscopic response, endoscopic remission, biomarker-defined remission, and sustained remission (defined as remission at enrolment in the maintenance trial and at every study visit thereafter). There was also consensus that worsening symptoms, as assessed by PROs, in combination with either worsening endoscopy or biomarkers are required for defining loss of response. Definitions of loss of response that include need for rescue corticosteroids or surgery were not considered adequate because of the substantial heterogeneity in how clinical decision making influences these end points.

The panel discussed that the timing of measuring outcomes in induction and maintenance CD trials will vary, depending on the mechanism of action. Generally, 9-12 weeks was thought to be an appropriate duration for induction studies and there was consensus that 52 weeks was an appropriate time point to measure maintenance outcomes for re-randomization and treat-through study designs.

CORE OUTCOMES IN ULCERATIVE COLITIS TRIALS

Patient-reported outcomes and composite indices. Core outcomes for UC RCTs are summarized in Table 1. There was consensus that symptomatic remission and response in UC trials should be defined using a PRO encompassing rectal bleeding and stool frequency as the hallmark symptoms. In addition, there was agreement that fecal urgency should be captured as a core outcome, given patient input on the debilitating nature of this symptom. Recently, an 11-point numeric rating scale for bowel urgency has been developed by Dubinsky et al,[23] although this scale was not available at the time of the consensus voting. Other symptoms considered, including abdominal pain, cramping, nausea, vomiting, loss of appetite, stool consistency, and tenesmus or sensation of incomplete evacuation, were not voted as critical for inclusion. Nocturnal bowel movements were discussed as a potential marker of pathology, yet the threshold for inclusion was not met.

Experts agreed that the adapted 9-point MCS, comprising rectal bleeding, stool frequency, and endoscopic appearance, should be the core composite measure of

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efficacy, as opposed to the full 12-point MCS, which includes Physician Global Assessment. This recommendation was driven by concerns regarding the reliability and reproducibility of the Physician Global Assessment, which is not congruent with the notion of a PRO. However, it was discussed that the full MCS has been the benchmark for drug development in UC for the past 30 years, and that the 9- point MCS could be calculated post hoc from the full MCS parameters. A consensus definition of response or remission based on the 9-point MCS was not reached, although experts agreed that symptomatic remission should be defined as a rectal bleeding subscore of 0 and stool frequency subscore of ≤ 1. The panel recognized that patients might not achieve normalization of stool frequency even when in endoscopic remission, for several reasons, such as decreased rectal compliance or overlapping functional bowel disorders associated with diarrhea. A definition of remission based on a 9-point MCS <2 with stool frequency subscore of 0 or 1 (and no greater than baseline), rectal bleeding subscore of 0, and modified Mayo Endoscopic Subscore (mMES) of 0 or 1 was the closest definition to reaching consensus.

ENDOSCOPIC OUTCOMES. There was consensus that sigmoidoscopy should be used to assess endoscopic outcomes in UC RCTs, with scoring based on the worst affected segment. The panel discussed that, in some instances, colonoscopy may be required at enrollment to exclude dysplasia in patients with long-standing disease. However, the following arguments supported the use of sigmoidoscopy for outcome measurement: 1) current endoscopic scores were developed based on sigmoidoscopic examination; 2) there are substantive practical advantages with respect to need for bowel preparation, time, and cost of sigmoidoscopy, especially in trials that require multiple endoscopies; and 3) most patients have the most severe disease activity in the distal rectosigmoid, which is representative of the more proximal colon.[24]

Both the mMES and UC Endoscopic Index of Severity were considered. The mMES excludes "mild friability" and scores any friability as mMES = 2.[25] This modification is used almost exclusively in contemporary UC RCTs, although the panel recognized that the dynamic range of the score (03) is narrow and differences between mMES = 0 and 1 are subtle. The score may be overly restrictive for outcome assessment if ulcerations have improved but not completely healed and all other components, including healing extent, have improved (still scored as mMES = 3 in this scenario). The UC Endoscopic Index of Severity has advantages of scoring individual component items (eg, vascularity, bleeding, and erosions and ulcerations), with a broader range of scores for assessment of responsiveness after therapy. However, some features, such as friability, are not captured, and practitioners may be less familiar with this score in day-to-day practice.

For UC RCTs, there was consensus that endoscopic remission and response should be measured and reported at 9-12 weeks in induction trials and at 52 weeks in maintenance trials. The panel voted that endoscopic remission should be defined as

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an mMES = 0 and that response should be defined as an mMES reduction ≥1 compared with baseline. The previous definition of endoscopic remission (mMES = 0 or 1) is now termed *endoscopic improvement* in trials of moderately to severely active UC that require a baseline mMES ≥2 for enrollment.[26] The panel voted to use the term *endoscopic response* based on a reduction of ≥1 point in the mMES, which could also be used in trials of mildly to moderately active UC where endoscopic enrollment requirements vary.

HISTOPATHOLOGY OUTCOMES. Histopathology was considered a core outcome domain in UC induction and maintenance RCTs. There was consensus to use the Robarts Histopathology Index or the Geboes Score in the trial setting. The ordinal Nancy Index was considered a highly practical and validated index for use in routine clinical practice; however, the wider and continuous range of the Robarts Histopathology Index was discussed as an advantage for demonstrating responsiveness in studies with relatively small sample sizes, such as dose-finding studies. The absence of neutrophilic inflammation in the epithelium was an important determinant of histologic remission: Robarts Histopathology Index <3 without neutrophils and a Geboes Score <3.0 without neutrophilic inflammation in the epithelium achieved consensus for defining histologic remission. There was no consensus on measuring histologic response, as the panel thought that a meaningful change in histology score from baseline had not yet been defined, and baseline histologic activity is not used as an entry criterion for most RCTs.[27,28]

BIOMARKER OUTCOMES. Fecal calprotectin was recognized as the most important biomarker for assessing inflammatory activity. There was discussion that the operating properties of fecal calprotectin depend on the threshold chosen, and consensus was reached that biomarker-defined remission should be based on a fecal calprotectin <150 μg/g. Biomarker response was defined similarly in UC and CD by a reduction of >50% compared with baseline among those with an elevated fecal calpro- tectin at baseline. There was consensus that fecal calprotectin should be measured relatively early, at 4-8 weeks, to assess dynamics of initial treatment response, and then again at 9-12 weeks in induction trials, and at 24 and 52 weeks during maintenance therapy.

CONFIGURATION OF OUTCOMES. Symptomatic and endoscopic remission were voted to be the core components of a composite primary end point in UC induction trials. Additional outcomes that were voted as core induction end points included the composite outcome of clinical and endoscopic response, clinical remission/response, endoscopic remission/response, and histologic remission. Corticosteroid-free remission was not voted as a core outcome in UC induction trials, but was considered important during maintenance, as was sustained remission (defined similarly in CD). Panel members expressed the importance of clear instructions for corticosteroid dosing during induction and maintenance, given that UC symptoms are highly sensitive to corticosteroids. There were lengthy conversations about the most appropriate

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definition of "corticosteroid-free remission"; no individual definition met the threshold for consensus, although the definition preferred by most panelists was the withdrawal of systemic corticosteroids for at least 12 consecutive weeks before the final study visit during maintenance. Mucosal healing, defined by endoscopic and histologic remission, was considered a core outcome in maintenance studies. There was also support for reporting loss of response in UC maintenance trials, defined as worsening symptoms and worsening of either endoscopy or biomarkers. Although the need for colectomy is a relatively infrequent occurrence, it was voted as a core end point in UC trials.

The panel discussed the importance of achieving early symptomatic response with UC therapies, although measurements at 4-8 weeks may be too early to observe a response, depending on the mechanism of action. Consensus was reached to measure induction end points at 9-12 weeks. For maintenance trials, week 52 was considered appropriate for measuring outcomes in re-randomization and treat-through designs.

SAFETY OUTCOMES

There was consensus that safety outcomes including all serious adverse events (AEs) and AEs occurring in >5% of the trial population, should be reported in all IBD trials. The panel voted that the terminology used to describe AEs should be common across all IBD RCTs, and consensus was reached to use the Medical Dictionary for Regulatory Activities, which is a clinically validated international terminology supported by regulatory agencies.[29]

Discussion

This international, multidisciplinary collaborative effort has led to the development of the first consensus-based COS for standardizing outcome reporting in RCTs of pharmacologic therapies for the treatment of IBD. Selecting appropriate end points is critical because their operating properties are key determinants of precisely measuring trial efficacy and safety, ultimately driving the ability to

efficiently identify new agents in an increasingly challenging time for RCT recruitment. The choice of outcomes used in pivotal trials also shapes clinical practice because these outcomes are considered by payers when determining relative cost-effectiveness of a treatment, which consequently influences health policy decisions.[30] This first iteration of the CORE-IBD COS will improve the quality of research in IBD, minimize reporting bias, standardize endpoint definitions, and serve as the impetus for additional research to address unanswered questions for the field.

In assessing outcomes used in CD and UC RCTs, it was evident that several factors have driven a tremendous evolution in end points over time. First, there has been

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increasing recognition that symptoms alone are neither sufficiently sensitive nor specific for assessing mucosal inflammation, resulting in a greater focus on achieving objective measures of remission. In clinical care, objective measurement of remission has been practically applied using treat-to-target approaches that emphasize endoscopic and biomarker targets, in addition to symptomatic response. Our work in developing this COS is complementary to recent guidelines from the Selecting Therapeutic Targets in IBD (STRIDE)-II Group, with many of the symptomatic, biomarker, and endoscopy core outcome domains overlapping with short-term, intermediate-term, and long-term (endoscopy) targets in clinical care, respectively.[31] Second, it should be recognized that drug development has been highly influenced by regulatory guidance, which has also evolved over time. Some examples include the increasing emphasis placed by regulators on capturing how patients feel, function, and survive using PROs; the exclusion of the Physician Global Assessment in UC assessment, resulting in adoption of the 9-point MCS; and changes in what constitutes mucosal healing, which now incorporates endoscopic and histologic remission in UC.[32] These concepts have been captured in our COS, although it was emphasized to panelists that outcome measures thought to be important for assessment were not required to map precisely onto current regulatory recommendations.

Given the changes in outcome measures over time, it is not surprising that consensus definitions could not be reached on several end points, highlighting the uncertainty that exists even among experts. Notably, consensus was not reached for thresholds defining clinical remission using the PRO2 in CD and clinical remission or response using the 9- point MCS in UC, with panel discussions focusing on the need for data from continuing clinical trials to fully characterize the operating properties of these measures. Disease-specific PROs, such as the CD-PRO Signs and Symptoms diary, UC-PRO Signs and Symptoms diary, Symptoms and Impacts Questionnaire for CD, and Symptoms and Impacts Questionnaire for UC, were considered for inclusion, however, further validation work is required before these tools can be included in a COS.[18-20] In contrast, the PRO2 and the 9-point MCS have been used successfully in recent phase 3 programs, with demonstrated effect sizes similar to those of the CDAI and full 12-point MCS.[33]

An important limitation of the PRO2 and 9-point MCS is the inability to capture potentially important disease-related symptoms beyond stool frequency, abdominal pain, or rectal bleeding. Commonly endorsed symptoms, such as anxiety, depression, dietary changes, fatigue, sleep disturbance, and incontinence, were identified by patients during phases 1 and 2 as important to their care. These symptoms were included for voting in the Delphi panel, in addition to other potentially novel PRO components not captured within current RCT instruments, such as stool consistency, tenesmus, incomplete evacuation, abdominal cramping, nausea, vomiting, poor appetite, mood changes, and sexual dysfunction. There was substantial discussion regarding potential advantages and disadvantages of including these as "core"

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outcomes. Some symptoms, such as sleep disturbance or mood changes, are nonspecific and potentially prone to a high "noise-to-signal" ratio as it pertains to differentiating treatment efficacy. Conversely, it was also recognized that other symptoms, such as fatigue, have likely been overlooked in previous trials and may discriminate patients treated with active drug compared with placebo. For example, it has been reported recently that approximately 15%-20% more patients with UC receiving upada- citinib had normalization of fatigue compared with patients treated with placebo in the phase 3 U-ACHIEVE trial, yet the magnitude of this difference was smaller than that observed for clinical remission (approximately 30%-40%).[34] Additional research is required to ensure that these symptombased outcomes can be measured in a reliable, meaningful, and interpretable way. In the interim, we would strongly encourage sponsors to measure relevant PROs as potential secondary end points, which will also help generate the data required to validate novel outcome measures.

Several potentially novel innovations in study design for IBD RCTs were identified in the development of this COS. First, the panel discussed the appropriate handling of corticosteroids, particularly during induction. Historically, corticosteroid dosing was fixed during induction to minimize confounding the interpretation of therapeutic effects. However, the emergence of endoscopy as a co-primary or composite primary outcome, the potential risk of overlooking mucosal improvement on early endoscopy, and the desire to mitigate potential corticosteroid-related AEs have contributed to a growing appetite for earlier corticosteroid tapering, even during induction. The panel stressed that clear tapering rules should be applied and assessing corticosteroid-free remission in induction would be more sensitive for identifying highly effective agents. For instance, the recently completed phase 3 upadacitinib U-EXCEL (ClinicalTrials.gov number NCT03345849) and U-EXCEED (ClinicalTrials.gov number NCT03653026) trials in CD permitted early corticosteroid withdrawal during induction. Second, although rectal bleeding and stool frequency have been the hallmark symptoms associated with UC, fecal urgency was added as a core outcome for RCTs. Urgency was consistently identified in patient surveys as a debilitating symptom, which is associated with incontinence, social impairment, anxiety, depression, and reduced quality of life. In addition, a recent study in the IBD Partners research network identified that urgency was associated with an increased risk of hospitalization, corticosteroid use, and colectomy.[35] Measuring urgency in addition to rectal bleeding and stool frequency may better capture the patient's disease experience in UC RCTs.

Development of this COS underscored some important areas of research priority. First, radiographic end points were notably not included as a core outcome domain in CD, despite the importance of computed tomography, magnetic resonance imaging, and ultrasound in clinical practice for evaluating disease activity.[36] This may result in an inadequate assessment of small bowel CD, which is generally not perfectly evaluated by endoscopy, biomarkers, or PROs. Delineating the role of transmural healing, which

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could be associated with better long-term outcomes in CD, may change the prioritization of radiographic end points for future COS iterations.[37-39] Second, it was evident that better instruments for measuring disease activity should be developed, particularly for endoscopic assessment. Limitations of the SES-CD were acknowledged, such as its weighting toward extent of disease, inability to capture ulcer depth, and uncertainty regarding the most appropriate method to analyze missing segments when using this tool.

This is the first iteration of a COS for IBD RCTs; establishing this baseline likely influenced our results and highlighted critical considerations for COS uptake and implementation. For instance, many "traditional" outcome measures, such as the CDAI, were still considered important for inclusion in this consensus. Although we acknowledge that this may perpetuate limitations of existing scores, it must also be balanced against the fact that instruments such as the CDAI have been used in every major CD drug development program over the past 30 years. Through this lens, the COS offers an opportunity for researchers to optimize instruments for disease assessment, and trial sponsors and researchers are encouraged to measure not only outcomes defined in this COS, but also explore novel end points and compare these with existing benchmarks. Broad uptake of this COS represents the next major hurdle for implementation. A recent systematic review by Hughes et al[40] showed that COS uptake in other fields varied substantially, from 0% to 82%. Poor uptake of a COS limits its impact on the field and, paradoxically, increases research waste if the COS needs to be continually updated without implementation.

Several barriers to COS uptake have been identified, including lack of awareness, absence of validated outcome measures or consensus on outcome measures, and lack of patient or stakeholder involvement. Mitigation strategies have been proposed to maximize COS implementation. From an awareness perspective, we aim to disseminate the findings through our respective national IBD societies. Given that 17 different countries are represented, we hope this will draw significant attention internationally to our results. Many of the CORE-IBD collaborators are leading members of the International Organization for the Study of Inflammatory Bowel Diseases, Crohn's & Colitis Foundation, and European Crohn's and Colitis Organisation, and the steering committees for almost all major ongoing or planned drug development programs in IBD feature members of our group. In terms of outcome measures, the expert panel discussed at length which outcomes have been formally validated and the operating properties of the selected instruments. In addition, we have highlighted throughout this article where gaps still exist for index development in IBD and have identified multiple research priorities for outcome validation. With respect to stakeholder involvement, this first iteration of the COS has been developed with engagement of both patients and IBD trial experts. Future iterations of the COS will need to focus on broader applicability to community practitioners and patient partners. Industry participation was not invited for this first version, although feedback from

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sponsors and regulators is encouraged. Given the changing landscape of outcome measures in the field, the CORE-IBD collaborators will continue to meet on an annual basis to review updates and discuss ongoing research initiatives as they pertain to outcome validation in CD and UC. Although we fully anticipate future iterations of this COS, we are cognizant of the time required for uptake of a COS into new trial programs, the time needed to develop and validate novel outcomes, and the efforts and resources required to fully update the COS. Therefore, we would anticipate that, conservatively, the next full update of the COS would be in approximately 5 years.

Our study has several strengths. We used a rigorous, mixed-methods approach consistent with COMET recommendations to develop this COS.[11] This approach allowed us to include different stakeholders, capture patient perspectives, and garner insights from a large panel of internationally recognized experts in IBD with a wealth of research and clinical experience. The Delphi method has been endorsed for generating a consensus in COS exercises, and iterative rounds of feedback allowed panelists to consider a broad range of viewpoints.[13] However, we also acknowledge some important limitations. First, as discussed previously, there were several outcomes that did not reach the threshold of consensus for inclusion, which likely reflects evolution in end-point definitions over time. In addition, given that the process for COS development is informed by systematic reviews of the literature, it is inherently more challenging for "novel" instruments that may not be frequently reported in existing trials to meet the threshold for inclusion. We attempted to mitigate this by ensuring that panelists voted on a comprehensive list of outcomes that captured both the existing literature and patient perspectives. Panelists were also encouraged to identify other potential outcomes that may have been missed, and we collated feedback from more than 150 patient responses to identify outcomes not captured within historical instruments used in RCTs. This resulted in a survey with nearly 500 voting items in the first round, which included a comprehensive breadth of both existing and potentially novel outcomes for IBD RCTs. We cannot exclude the possibility of voter fatigue, given the length of the surveys. To mitigate voter fatigue, we provided projected times for survey completion, allowed panelists to complete their responses over multiple sittings, carried forward only items that were reasonably likely to be included in a COS (according to defined rules used in other COS development programs[41]), and we organized the statements into outcome domains. Although we had originally planned to present the panelists with the statements in random order, voting in random order was extremely difficult during pilot testing due to the length and complexity of the survey. Third, patients were asked to prioritize the outcome domains of importance and identify other relevant outcomes, but patients did not provide specific input on measurement tools because decisions to include these tools in the COS were based primarily on technical factors. For example, whether histologic remission should be defined as an absence of neutrophilic inflammation was deemed to be less relevant to patients compared with the overall importance of histologic assessment. We also

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recognize that patients were more likely to rate symptom control and quality of life as most important to their own care, and that framing these domains in relation to more "technical" outcomes, such as endoscopic or histologic remission, in both the short and long term, may have been challenging in the survey format. For feasibility, only English-speaking patients recruited exclusively from Canada were included. Therefore, cultural differences in outcome domain prioritization may not have been captured. This work would be strengthened by inclusion of a more diverse range of patients, including those from international backgrounds, although we did engage a large number of patients with different disease experiences, and are confident that we have broadly captured important outcomes of interest for patient stakeholders. Greater involvement from nonacademic community gastroenterologists would also have been a strength. Fourth, the scope of this COS does not apply to nondrug trials, which may limit some aspects of its generalizability. For example, these outcomes may not be appropriate for therapeutic withdrawal studies or surgical interventions. Finally, we recognize that individual Delphi panelists may have been involved in development or validation of existing outcome measures. A detailed list of potential other conflicts of interest beyond established financial conflicts is provided in Supplementary Appendix 2. We performed a sensitivity analysis excluding the votes of these participants for any instruments they had been involved in development/validation for, and this did not change the results of the COS for any included items.

In conclusion, we have developed the first internationally guided minimum set of core outcomes for use in RCTs of adult patients with IBD treated with pharmacologic therapies. This COS captures the evolution of end points over the past several decades, and its adoption will improve the quality of evidence synthesis and reduce heterogeneity in outcome reporting. We anticipate further iterations of this COS for IBD trials, as several key areas of research priority were highlighted in our panel discussions. Additional work to validate existing and novel instruments for measuring disease activity will shape the next iteration of this IBD COS.

SUPPLEMENTARY MATERIAL

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2022.06.068.

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DATA AVAILABILITY

Data, analytic methods, and study materials will be made available to other researchers upon request.

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