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Development of a Core Outcome Set for Real-world Data in Inflammatory Bowel Disease: A European Crohn's and Colitis Organization (ECCO) Position Paper

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Abstract

Background and aims: The utility of real-world data is dependent on the quality and homogeneity of reporting. We aimed to develop a core outcome set for real-world studies in adult patients with inflammatory bowel disease (IBD).

Methods: Candidate outcomes and outcome measures were identified and categorised in a systematic review. An international panel including patients, dietitians, epidemiologists, gastroenterologists, nurses, pathologists, radiologists, and surgeons participated in a modified Delphi consensus process. A consensus meeting was held to ratify the final core outcome set.

Results: A total of 26 panellists from 13 countries participated in the consensus process. A total of 271 items (130 outcomes, 141 outcomes measures) in nine study domains were included in the first-round survey. Panellists agreed that real-world studies on disease activity should report clinical, endoscopic, and biomarker disease activity. A disease-specific clinical index (Harvey-Bradshaw Index, Partial Mayo score, Simple Clinical Colitis Activity Index), rather than physician global assessment should be used. In ulcerative colitis (UC), either the UC Endoscopic Index of Severity or the Mayo endoscopic score can be used, but there was no consensus on an endoscopic index for Crohn's disease, nor was there consensus on the use of the presence of ulcers. There was consensus to use faecal calprotectin and C-reactive protein. There was no consensus on the use of histology in real-world studies.

Conclusions: A core outcome set for real-world studies in IBD has been developed based on international multidisciplinary consensus. Its adoption will facilitate synthesis in the generation of real-world evidence.

Keywords: Crohn’s disease; ulcerative colitis; real-world study

1. Introduction

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a chronic progressive condition with considerable morbidity and a substantial impact on the quality of life of patients.[1,2] Recently, considerable advances have been made with several new drugs approaching or recently receiving regulatory approval.[3-5]

Although randomised controlled trials are the gold standard for regulatory approval,[6] they incompletely reflect the patient population in everyday clinical practice due to stringent inclusion and exclusion criteria resulting in underrepresentation of certain subgroups.[7-9] Real-world observational studies can complement findings from randomised controlled trials by providing long term follow-up data for safety and effectiveness in routine practice. Furthermore, observational studies extend far beyond narrowly defined questions in regulatory trials to include patient perspectives and natural history of the disease. Real-world data is information gathered through observations of routine clinical practice from multiple sources, real-world evidence is generated through subsequent analysis of these data.[10] The value of such evidence is being increasingly recognised both by the European Medicines Agency and by the Food and Drug Administration.[11,12]

The utility of real-world data is heavily dependent on the homogeneity of collection and reporting to facilitate pooling from multiple sources and studies. Evolving treatment targets, the expanding therapeutic armamentarium and country-specific reimbursement policies all create significant heterogeneity in which outcomes are reported. A core outcome set for real-world studies in IBD supported by multiple stakeholder groups could help reduce heterogeneity in reporting and increase the quality of data synthesis. A core outcome set is a consensus-derived minimum set of outcomes to be reported in all clinical studies in specific areas of health and healthcare.[13] Bearing in mind the broader scope of real-world studies, a core

outcome set should be interpreted within the context and research questions of an individual study.

Although core outcome sets exist for perianal fistulizing CD,[14] patient-centred outcomes,[15] paediatric IBD,[16] and a core outcome set for randomised controlled trials is in development,[17] none are available for real-world studies. Our aim was to develop an international consensus-based core outcome set for real-world observational studies in IBD supported by patients, dietitians, epidemiologists, gastroenterologists, nurses, pathologists, radiologists, and surgeons.

2. Methods

2.1. Scope and registration

European Crohn's and Colitis Organisation [ECCO] Position Statements are the result of expert opinion consensus and are endorsed by ECCO. The scope of this core outcome set is for use in real-world observational studies for adult patients with IBD. We excluded studies specifically focusing solely on perianal fistulizing CD, acute severe UC, and pouchitis. The study was prospectively registered in the Core Outcome Measures in Effectiveness Trials (COMET) database (http://www.comet-initiative.org/studies/details/1883) and conducted in accordance with recommendations outlined in the COMET handbook, the Core Outcome Set STAndards for Development (COS-STAD), and the Core Outcome Set STAndards for Reporting (COS-STAR).[13,18,19]

2.2. Participant recruitment and item generation

A panel of 15 experts in the field of IBD (epidemiologists, gastroenterologists, nurses, pathologists, surgeons) was selected after an open call to all ECCO members and committees. Two representatives of the European Federation of Crohn's and Colitis Associations (EFCCA), a patient advocacy organisation, were invited and included. The full list of panellists is shown in Supplementary table 1, available as Supplementary data at ECCO-JCC online. A four-member steering group (NA, PB, KBG, VP) coordinated the project.

A systematic review facilitated the development of a list of outcomes and outcome measures used in real-world observational studies of IBD.[20] Outcomes were categorized into domains according to recommendations from the Outcome Measures in Rheumatology (OMERACT) consensus initiative,[21] supported by the international Consensus-based

Standards for the selection of health Measurement Instruments (COSMIN)/COMET guidelines.[13]

The panellists were divided in four working groups by domains to evaluate the full list of outcomes and accompanying outcome measures identified in the systematic review. Each working group prepared a list of outcomes and outcome measures to be included in a Delphi consensus process. This list of outcomes and outcome measures were reviewed by the steering group for duplicates and was offered for additional input from the patient representatives. The final list was included in the Delphi consensus process.

2.3. Delphi process

The list of outcomes and outcome measures identified by the four working groups was incorporated in a two-round Delphi survey. The Delphi method allows panellists to anonymously achieve consensus through multiple rounds of sequential questionnaires.[13]

Further experts were recruited for participation in the voting process to include radiologists, dietitians, and additional members of professional groups already represented. In an online voting process, participants were provided with a list of outcomes and outcome measures organized by domains to rate them for their suitability for inclusion in the core outcome set. Scores from 7 to 9 indicated items “essential for inclusion”, scores from 4 to 6 “important, but not essential”, and scores from 1 to 3 “limited importance”. All sections of the survey had a free-text entry option for participants to add clarifying statements and propose additional outcomes or outcome measures for inclusion in the survey.

The two surveys were administered online (December 2021, January 2022). Responses were collated and summarised using descriptive statistics. Panellists were blinded to each other’s votes and an anonymized summary feedback report with the group scores and comments was provided after each round.

Items which were scored in the 7-9 range by ≥70% of participants in the first or second round of voting were determined *a priori* to have met consensus for inclusion. Items which were scored in the 1-3 range by ≥70% of participants in the first or second round of voting were excluded from further voting. All other items were carried forward for additional voting.

2.4. Final consensus meeting

A virtual consensus meeting was convened on 5th May 2022 to discuss and vote on the proposed final core outcome set as defined by the two Delphi surveys. Items which had reached consensus for inclusion through prior voting were eligible for re-wording or re-grouping, but could no longer be removed from the core outcome set. Items which had not yet reached consensus for either inclusion or removal were discussed further and voted on for a third time. These items were included in the final core outcome set if ≥80% of the participants scored them in the 7-9 range. Additionally, planned votes included the merging and re-wording of items as proposed by the steering group. *Ad hoc* votes could include the re-wording, re-grouping or re-naming of items as proposed in the discussion during the final consensus meeting.

3. Results

3.1. Panellists

Demographics of expert panellists are summarised in Supplementary table 2. Briefly, 26 panellists from 13 countries representing Europe, North and South America, and Asia-Pacific participated in the voting process. Most panellists were gastroenterologists (11/26; 42%) from Europe (21/26; 80%) practicing in academic hospitals (17/26; 65%). Two patient representatives were included in the panel.

3.2. Delphi survey results, core outcomes, and core outcome measures

A total of 271 items (130 outcomes, 141 outcomes measures) were included in the first-round survey, 95 of which (57 outcomes, 38 outcome measures) reached consensus and no items were discarded. Nine items (2 outcomes, 7 outcome measures) were added to the second-round of the survey based on panellist feedback. Seven additional outcomes reached consensus in the second round. A flowchart of the consensus process is presented in Supplementary Figure 1, a summary of voting results from both surveys and the final consensus meeting are shown in Supplementary table 3 and the Supplementary Appendix 1. The set of core outcomes and outcome measures for real-world observational studies in IBD by research domain is presented in Table 1. It should be noted that the selection of outcomes and outcome measures for an individual study is dependent on its research question.

3.2.1. Disease complications

There was consensus that the Montréal classification[22] was a core outcome measure for studies of disease complications, while individual components defining the phenotype of CD within the classification should be included as core outcomes (Table 1). Although death attributable

to IBD is an infrequent occurrence, it was judged to be a necessary element of a core outcome set due to its overriding relevance. The panellists acknowledged that the inclusion of disease progression as a core outcome was aspirational in the absence of holistic and widely adopted definition of this outcome. The Lémann index[23] may fulfil this role in the future pending further validation and wider adoption in practice.[24] The panellists recognized the importance of multidisciplinary specialist expertise to record extraintestinal manifestations. A number of outcomes (e.g., anaemia, osteoporosis, nutritional status) were judged to be important, but not essential for inclusion in the core outcome set.

3.2.2. Disease activity

The panellists agreed that real-world studies on disease activity should report clinical, endoscopic, and biomarker disease activity (Table 1). There was less certainty about radiologic disease activity and no consensus on histologic disease activity. The panel did not mandate the reporting of all aspects of disease activity in all studies, the choice of activity domain (clinical, endoscopic, biomarker) is at the discretion of the investigators in a given study.

The panel stressed that clinical disease activity should be captured using a disease-specific index, such as the Harvey-Bradshaw Index, the partial Mayo score or Simple Clinical Colitis Activity Index[25-27] and that physician global assessment was not appropriate for inclusion as a core outcome measure. By extension, the modification of the Mayo clinic score with the exclusion of physician global assessment should be used. Both the Mayo endoscopic score[27] and the UC Endoscopic Index of Severity[28] achieved consensus as outcome measures for the assessment of endoscopic activity in UC. Despite agreement that an endoscopic index should be used for the assessment of CD, neither the Simple endoscopic score for CD[29] (69% of votes in 7–9 range) nor the CD endoscopic index of severity[30] (37% of votes in 7–9 range) reached consensus for inclusion as a core outcome measure. Panellists cited the questionable

feasibility of using these indices in real-world studies as barriers to their inclusion in a core outcome set. The presence of ulcers did not reach consensus either as a potential simplification of endoscopic evaluation of CD. Faecal calprotectin and C-reactive protein were recognized as the most important biomarkers for assessing disease activity.

None of the radiologic activity outcomes reached consensus during the first two survey rounds. Following discussion at the consensus meeting, radiologic evidence of active disease, disease complications, and their location reached consensus. Cross-sectional imaging was judged to be particularly valuable in the assessment of complications and parts of the intestine, inaccessible to endoscopy. There was no consensus about radiologic outcome measures. Finally, none of the histologic outcomes reached consensus, even after re-wording that histologic remission should only be assessed in UC. Panellists felt that there was yet insufficient evidence to mandate the inclusion of histologic outcomes into a core outcome set.

3.2.3. Patient-reported outcomes

There was consensus that health-related quality of life, disability, sexual function, and fatigue should be reported in real-world studies of patient-reported outcomes (Table 1). The only outcome measure reaching consensus for inclusion was the Short Inflammatory Bowel Disease Questionnaire (SIBDQ).[31] Both the IBD Disk[32] and IBD Control Questionnaire[33] the were rated as important, but did not meet the consensus threshold. The panellists judged the latter questionnaire to be feasible for use in daily practice with good operating characteristics. Overall, the panellists agreed that validated instruments tailored to the research question in individual studies should be used.

3.2.4. Specific symptoms

A number of symptoms, which are all included in clinical disease activity indices or patient-reported outcome measures already included in the core outcome set, reached consensus for inclusion in real-world studies of specific symptoms (Table 1). Although other symptoms, such as abdominal bloating, decreased well-being and anorexia, were considered, they may be difficult to define and measure and therefore did not classify as core outcomes to be measured in all real-world studies.

3.2.5. Medical therapy and medical therapy-related safety

General measures of medical therapy use, mainly agnostic of drug class, were included in the core outcome set for real-world studies on medical therapy (Table 1). The only two items specific to drug class referred to systemic corticosteroids. The panellists emphasized the potential for significant harm with excess steroid exposure and the utility of this outcome as a marker of quality.[34]

The panellists recognized the distinction between clinical trials and real-world studies, where all non-serious adverse events are unlikely to be captured, and focused on outcomes which are almost invariably recorded due to their impact on the patient and subsequent management decisions. The occurrence of serious adverse events, infections, malignancy, and infusion or injection reactions reached the consensus threshold for inclusion in real-world studies of medical therapy-related safety.

3.2.6. Surgical intervention and surgical intervention-related safety

The panellists recognized the impact of surgery on patients and the natural history of disease (Table 1). Besides merely recording the occurrence of a surgical procedure, the panellists agreed to report intestinal resections separately, as they have different prognostic significance,

compared to procedures where no bowel is lost (e.g., perianal surgery, ileostomy reversal). In postoperative CD, clinical, endoscopic, and surgical recurrence should be reported.

Safety outcomes should ideally be recorded during 90 days after surgery, although the panellists agreed that 30 days was the minimal time frame. The need for a temporary stoma was identified as an important outcome for patients and hence was included in the core outcome set. Consensus was reached that postoperative complications should be graded using a validated classification to allow for a meaningful appraisal, but there was no consensus about the specific instrument to be used – either the Clavien-Dindo classification[35] or the Comprehensive Complication Index could be equally used.[36]

3.2.7. Healthcare utilisation

An IBD-related hospitalisation was the only outcome selected for the core outcome set for real-world studies on healthcare utilisation (Table 1). The number of visits to the emergency department narrowly missed the threshold for consensus in both survey rounds. Panellists judged that emergency care practices differ across jurisdictions and that hospitalisations may better reflect disease severity.

4. Discussion

In an international multidisciplinary collaborative effort, we developed the first consensus core outcome set for real-world studies of adult patients with IBD. The process has followed reporting guidelines for core outcome sets.[19] The core outcomes and outcome measures are organised by research domains as the scope of real-world studies is broad and the measured variables differ by study aim. The proposed core outcome set could serve to reduce variation in reporting of real-world studies and thereby promote more widespread utilisation of real-world evidence.

The development process was based on a systematic review of outcomes and outcome measures used in real-world studies,[20] which revealed a number of temporal trends, which have paralleled the evolution of treatment goals in IBD[37] and regulatory guidance for the approval of new medical therapies. These trends include the increasing reporting of endoscopy- and biomarker-based outcomes in real-world studies.

In contrast to regulatory trials aimed at assessing treatment efficacy and safety, the uptake of histologic and radiologic outcomes in real-world studies has been slower. This is reflected in the core outcome, which includes endoscopic and biomarker outcomes, but only a limited number of radiologic outcomes and no histologic outcomes. Panellists highlighted the yet uncertain incremental benefit of transmural healing assessed radiologically in the absence of studies with long-term follow-up[38] and questioned the feasibility of including radiology in a core outcome set for real-world studies. The heterogeneity of outcome definitions, particularly for response, as opposed to remission, was cited as a further barrier. Radiologic outcomes in the core outcome set were included as an adjunct to assess for disease complications and complement disease activity assessment in segments inaccessible to endoscopy. However, with the uptake of point-of-care intestinal ultrasound, this might change in the future.

Notably, the panellists emphasized the need to use validated indices in real-world studies assessing clinical and endoscopic disease activity. Physician global assessment, which is often used in real-world studies,[20] did not reach consensus for inclusion. Patient-reported outcomes are an area of research priority both in real-world and regulatory studies. The panellists universally acknowledged their importance, but there was considerable uncertainty regarding the best outcome measure to provide a comprehensive overview of all relevant outcomes. Ultimately, the SIBDQ[31] was selected, recognizing that new instruments, which have not been extensively used in real-world studies, are undergoing validation.[39,40]

The core outcome set for real-world studies expands on the scope of a previously published standard set for patient-centred outcomes[15] to accommodate a broader range of studies. A number of outcomes reached consensus in both processes, such as mortality, development of colorectal cancer, corticosteroid use, and IBD-related hospitalisation. Recommendations on the preferred evaluative indices for tracking clinical disease activity and quality of life differ as the core outcome set for patient-centred outcomes recommends the Manitoba IBD Index[41] and the IBD Control Questionnaire,[33] respectively. The Manitoba IBD Index is a single-item disease activity measure where a patient rates their perception of disease activity. The index has good correlation with other instruments for assessment of disease activity, although it does not explicitly capture specific symptoms (e.g., abdominal pain, stool frequency) and disease complications (e.g., extraintestinal manifestations), which were all identified as core outcomes in the current consensus process. The IBD Control questionnaire narrowly missed the consensus threshold for inclusion as a core outcome measure for real-world studies.

Our study used a methodologically rigorous approach to produce a core outcome set supported by combined insights of patients with IBD and large international multidisciplinary panel of experts treating IBD. Outcomes and outcome measures were systematically

categorised to incorporate the wide range of research questions addressed by real-world studies. Limitations to our study should also be acknowledged. For reasons of feasibility, we were unable to recruit a larger number of patients or clinicians from outside Europe. Furthermore, the length of surveys may have contributed to panellist fatigue, although an attempt to minimise it was made by enabling its completion in multiple sittings. Finally, neither the proposed timing of assessment nor thresholds for individual evaluative indices or biomarkers were voted upon, as this was judged to extend beyond the scope of the current consensus process.

In summary, we have developed the first core outcome set for real-world studies of patients with IBD through a Delphi consensus process of patients and an international multidisciplinary group of healthcare professionals. Adoption of this core outcome set will reduce heterogeneity of reporting in real-world studies and facilitate synthesis in the generation of real-world evidence.

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Conflict of interest

ECCO has diligently maintained a disclosure policy of potential conflicts of interests. The conflict of interest declaration is based on a form used by the International Committee of Medical Journal Editors. The conflict of interest disclosures are not only stored at the ECCO Office and the editorial office of Journal of Crohn's and Colitis. Conflict of interest disclosures are also open to public scrutiny on the ECCO Website [https://www.ecco-ibd.eu/about-ecco/ecco-disclosures.html] providing a comprehensive overview of potential conflicts of interest of authors.

Disclaimer
The ECCO Position Statements are targeted at health care professionals only and are based on an international consensus process. Any treatment decisions are a matter for the individual clinicians and should not be based exclusively on the content of the ECCO Position Statement. The ECCO and/or any of its staff members and/or any contributor may not be held liable for any information published in good faith in an ECCO Position Statement.

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Author contributions

This paper is a joint expert consensus activity. Hence, all authors participated sufficiently, intellectually and practically in this work and take public responsibility for the content of the article, including the conception, design, data interpretation and writing of the manuscript. All authors and the ECCO Governing Board approved the final version for submission.

Table 1. Summary of core outcomes and outcome measures for real-world studies in inflammatory bowel disease. The selection of core outcomes and outcome measures is dependent on the domain of the study. Abbreviations: CD – Crohn's disease; IBD – inflammatory bowel disease; UC – ulcerative colitis.

Domain	Outcome	Outcome measure*
Disease complications *Real-world studies on disease complications should report the following outcomes and outcome measures*	Presence of stricture (incident or prevalent) Presence of abscess or fistula (incident or prevalent) Colorectal cancer Cancer (regardless of site) Colorectal dysplasia Mortality by cause (Mortality due to complications of IBD or due to colorectal cancer reported separately) Disease phenotype Disease progression Extraintestinal manifestations	Montréal classification
Disease activity *Real-world studies on disease activity should report the following outcomes and outcome measures*	*Clinical disease activity* Clinical remission Corticosteroid-free clinical remission Primary non-response Secondary loss of response	*Clinical disease activity* Harvey-Bradshaw Index Partial Mayo clinic score Simple Clinical Colitis Activity Index When more than one disease-specific activity index is listed, the panel suggests the use of at least one of these indices in an individual study at the discretion of the investigator
	Endoscopic disease activity Endoscopic remission Endoscopic response	*Endoscopic disease activity* Mayo endoscopic score Ulcerative colitis endoscopic index of severity Endoscopic extent

		An endoscopic index should be used to assess endoscopic activity of CD in real-world studies
	Biomarker disease activity Biomarker remission Biomarker response *Radiologic disease activity* Location of bowel damage Radiologic inflammation Radiologic evidence of disease complications	*Biomarker disease activity* C-reactive protein concentration Faecal calprotectin concentration
Patient-reported outcomes *Real-world studies on patient-reported outcomes should report the following outcomes and outcome measures*	Health-related quality of life Disability Sexual function Fatigue	Short Inflammatory Bowel Disease Questionnaire A specific instrument, tailored to the individual study question should be used
Specific symptoms *Real-world studies on specific symptoms should report the following outcomes and outcome measures*	Abdominal pain Rectal bleeding Diarrhoea Bowel frequency Urgency Faecal incontinence Extraintestinal manifestations Perianal fistula	
Medical therapy *Real-world studies on medical therapy should report the following outcomes and outcome measures*	Drug discontinuation/drug survival Dose escalation Corticosteroid refractoriness Systemic corticosteroid use	

Medical therapy-related safety *Real-world studies on medical therapy-related safety should report the following outcomes and outcome measures*	Serious adverse event Infusion/injection reaction Anaphylactic reaction Infection Serious infection Opportunistic infection Malignancy (specified by location)	Treatment discontinuation Hospital admission Medical therapy-related mortality
Surgical intervention *Real-world studies on surgical intervention should report the following outcomes and outcome measures*	Surgical intervention Colectomy (in UC) Clinical post-operative recurrence (in CD) Endoscopic post-operative recurrence (in CD) Surgical post-operative recurrence (in CD) Intestinal resection Pouch creation (in UC)	
Surgical intervention-related safety *Real-world studies on surgical intervention-related safety should report the following outcomes and outcome measures*	30–90-day postoperative morbidity 30–90-day postoperative mortality Peri-operative complications Septic surgical complications Need for temporary stoma	A validated classification of morbidity should be used to assess surgical complications within 30–90 days of surgery
Healthcare utilisation *Real-world studies on healthcare utilisation should report the following outcomes and outcome measures*	IBD-related hospitalisation	

* Items referring to e.g., “Number of patients/events”, “Mean/median”, “Incidence/prevalence”, “Time to event” are included in the core outcome set and their use is dependent on study design and the distribution of data in individual studies

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Supplementary data

Supplementary table 1. List of panellists involved in the consensus process for a core outcome set for real-world studies in inflammatory bowel disease.

Name	Role	Country
Michel Adamina	Surgeon	Switzerland
Behrooz Alizadeh	Epidemiologist	The Netherlands
Naila Arebi	Gastroenterologist	United Kingdom
Filip Baert	Gastroenterologist	Belgium
Peter Bossuyt	Gastroenterologist	Belgium
Johan Burisch	Gastroenterologist	Denmark
Wladyslawa Czuber-Dohan	Nurse	United Kingdom
Krisztina Gecse	Gastroenterologist	The Netherlands
Lihi Godny	Dietitian	Israel
Hannah Gordon	Gastroenterologist	United Kingdom
Jurij Hanzel	Gastroenterologist	Slovenia
Ana Ibarra	Nurse	United Kingdom
Susanna Jäghult	Nurse	Sweden
Uri Kopylov	Gastroenterologist	Israel
Paulo Gustavo Kotze	Surgeon	Brazil
Salvatore Leone	Patient	Italy
Joep van Oostrom	PhD Fellow	The Netherlands
Konstantinos Papamichael	Gastroenterologist	United States
Valerie Pittet	Epidemiologist	Switzerlands
Jordi Rimola	Radiologist	Spain
Roberto Saldaña	Patient	Spain
Mark Samaan	Gastroenterologist	United Kingdom
Monika Tripathi	Pathologist	United Kingdom
Catherine Wall	Dietitian	New Zealand
Charlotte Wong	PhD Fellow	United Kingdom
Henit Yanai	Gastroenterologist	Israel

Supplementary table 2. Demographics of panellists involved in the consensus process for a core outcome set for real-world studies in inflammatory bowel disease.

Variable	
Female, n (%)	12/26 (46)
Age group, n (%)	
20–29 years	1/26 (4)
30–39 years	7/26 (27)
40–49 years	10/26 (38)
50–59 years	8/26 (31)
Role, n (%)	
Dietitian	2/26 (8)
Epidemiologist	2/26 (8)
Gastroenterologist	11/26 (42)
Nurse	3/26 (12)
Pathologist	1/26 (4)
Patient	2/26 (8)
PhD Fellow	2/26 (8)
Radiologist	1/26 (4)
Surgeon	2/26 (8)
Continent, n (%)	
Europe	21/26 (80)
Asia-Pacific	3/26 (12)
North America	1/26 (4)
South America	1/26 (4)
Practice setting	
Outpatient care	2/26 (8)
Non-academic hospital	2/26 (8)
Academic hospital	17/26 (65)
Research institution	3/26 (12)
Patient association	2/26 (8)

Supplementary figure 1. Flowchart of the consensus process for outcomes (A) and outcome measures (B).