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# Identification of Endpoints for Development of Antifibrosis Drugs for Treatment of Crohn's Disease

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**BACKGROUND & AIMS:** Intestinal fibrosis is a challenge to management of patients with Crohn's disease (CD); there is an urgent need to expedite development of antifibrosis drugs for this disease. The International Organization for the Study of Inflammatory Bowel Disease (IOIBD) aimed to identify a set of endpoints that can be used to determine efficacy of antifibrosis agents tested in clinical trials of patients with CD. **METHODS:** We conducted a systematic review to identify clinical, radiologic, biochemical, endoscopic, and composite endpoints used in assessing activity of fibrostenosing CD and response to treatment, and determined their operational properties. A panel of IOIBD experts performed a consensus process to identify the best endpoints for inclusion in clinical trials, through a 2-round, Delphi-style online survey. **RESULTS:** A total of 36 potentially relevant endpoints for intestinal fibrosis were selected and assessed. Forty-eight physicians with expertise in inflammatory bowel disease, from 5 regions (North America, Europe, Middle East, Asia/Pacific, and Latin America), participated in the Delphi consensus process. A core set of 13 endpoints (complete clinical response, long-term efficacy, sustained clinical benefit, treatment failure, radiological remission, normal quality of life, clinical remission without steroids, therapeutic failure, deep remission, complete absence of occlusive symptoms, symptom-free survival, bowel damage progression, and no disability) were rated as critical. Agreement was high among the experts. **CONCLUSIONS:** Members of the IOIBD reached expert consensus on a set of endpoints that can be used to assess antifibrosis agents in trials of patients with CD. Studies are needed to clarify methods for measuring these outcomes and validate measurement instruments.

*Keywords:* IOIBD; IBD; Fibrotic; Biomarker.

Crohn's disease (CD) is a chronic, progressive, and destructive disorder of the gastrointestinal tract,[1] characterized by transmural inflammation, a discontinuous pattern of distribution, periods of disease activity alternating with periods of remission, and the occurrence of bowel damage (such as fibrotic strictures) that is already present in up to 40% of patients at diagnosis.[2]

Inflammation and repair processes of the gastrointestinal mucosa are necessary prerequisites for the development of intestinal fibrosis in CD. Fibrosis is characterized by excessive accumulation of collagen-rich extracellular matrix, expansion of mesenchymal cells or mesenchymal-like cells, and subsequent stricture formation.[3–7] The pathophysiological mechanisms leading to intestinal fibrosis include cellular stress and increased production of inflammatory cytokines and chemokines (eg, interleukin-13 and interleukin-17),[8,9] and growth factors (eg, insulin-like growth factor,[10] platelet-derived growth factor,[11] transforming growth factor beta,[12] and basic fibroblast growth factor[13]). These mechanisms eventually lead to intestinal fibrosis and to the loss of physiological gut functions.[14,15]

Although some knowledge has been acquired regarding the pathogenesis and diagnosis of intestinal fibrosis, therapeutic management for stricturing CD remains a challenge in clinical practice.[5,16–18] Current therapies for CD aim for clinical and endoscopic remission, with the goal of preventing complications and halting the progressive course of disease; however, specific therapies aiming at preventing, or reversing, intestinal fibrosis or stricture are not currently available.[19–21] Despite immunosuppressive therapy in patients with CD in the form of steroids or immunomodulators, there was no significant decrease in the frequency of fibrostenosing complications,[22] although early use of immunosuppressants has been shown to delay intestinal

*Abbreviations used in this paper:* CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CTE, computed tomography enterography; DI, Disagreement Index; EBD, endoscopic balloon dilation; IBD, inflammatory bowel disease; IOIBD, International Organization for the Study of Inflammatory Bowel Disease; MRE, magnetic resonance enterography; TNF-α, tumor necrosis factor alpha.

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**WHAT YOU NEED TO KNOW**

BACKGROUND AND CONTEXT

Intestinal fibrosis is a challenge in Crohn's disease. There is an urgent need to expedite development of anti-fibrosis drugs for this disease and clear endpoints are needed.

NEW FINDINGS

By a systematic review and a Delphi Consensus, the authors identified 13 relevant critical endpoints that could be used in further clinical trials on anti-fibrotic drugs.

LIMITATIONS

The study's core set needs to be validated in prospective clinical trials.

IMPACT

These results may be useful for the assessment of short- and long-term efficacy and safety of future anti-fibrotic drugs in Crohn's disease.

surgery.[23] On the other hand, anti–tumor necrosis factor alpha (TNF-$\alpha$)–based therapy may slow disease progression, and potentially even reverse bowel damage in some patients,[24] but its long-term efficacy is limited for this indication.[25] Therefore, current therapy of established fibrotic strictures associated with obstructive symptoms is composed mainly of endoscopic dilatation procedures and surgical resections, and has high rates of CD recurrence.[16,26–33]

Currently, several candidate antifibrotic drugs are under investigation for indications outside of the intestine (ie, liver, lung, kidney, heart, and skin fibrosis).[5,6,34–41] Moreover, there is optimism regarding the possibility of reversal of advanced fibrosis in the intestine; the inhibition of rho kinases was shown to successfully reverse fibrosis in an animal model of chronic intestinal inflammation.[42] Optimism also comes from observations in the antifibrotic treatment of other organs, such as the reduction of skin fibrosis in patients with systemic sclerosis,[43] the improvement of skin scarring,[44] and the regression of liver fibrosis[45] and myocardial fibrosis.[46]

Given the high socioeconomic burden resulting from fibrostenotic CD, due to frequent hospitalizations and surgery,[47] there is an urgent need to expedite development of antifibrotic drugs for this indication. To achieve this aim, stakeholders from academia and the pharmaceutical/biotech industry seek a framework from which to rationally design prospective clinical trials testing antifibrotic therapies, and to identify reliable, clinically meaningful endpoints to measure disease activity and response to treatment with antifibrotic therapy. The selection of appropriate endpoints will reduce heterogeneity in outcome reporting, increase the relevance of clinical research for multiple stakeholders, and may also inform the evolution of regulatory policies.[48,49]

The purpose of the current initiative from the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) was to determine a core set of endpoints considered appropriate for clinical trials of antifibrotic therapies for CD using a 2-round Delphi-style process among international experts in the field, based on the identification of currently available endpoints measuring disease activity and response to treatment in fibrostenosing CD, and their operational properties.

## Methods

### Systematic Review of the Literature

We systematically searched the PubMed and Embase databases from their inception to June 2017. Search algorithms included *Crohn's disease* combined with *fibrosis* or *stricture*, without any language restriction. We also searched ClinicalTrials.gov and bibliographies of relevant review articles. Randomized controlled trials, clinical controlled trials, and cohort, case-control, and cross-sectional studies were considered eligible if they included adult patients ($\geq$18 years) with fibrostenosing/stricturing CD, and used well-described endpoints to measure disease activity and response to therapy. Full-text publications of potentially eligible studies were retrieved to ensure that eligibility criteria were met.

We abstracted the following data from each study: publication data, study design, number of subjects, patient characteristics, interventions, primary and secondary endpoints reported, type of endpoints used (signs/symptoms, radiographic, histological or endoscopic index, inflammatory biomarker, composite endpoint, or patient-reported outcome), their description, and timing of the assessment.

For each endpoint, we assessed the following operational properties[50]: (1) validity, the ability to measure what was intended; (2) reproducibility, the ability to produce the same or similar results in individuals on different occasions or by different observers; and (3) responsiveness, the ability to measure a change in an individual when it does occur.

The list of endpoints identified through the literature review was augmented with additional potential endpoints considered important by clinical experts, but not captured in the literature.

### Delphi Survey

We performed a consensus process among international experts on the importance of the endpoints for future clinical studies of antifibrotic therapies in patients with CD, through a 2-round, Delphi-style process[51] that was conducted through an online survey. All experts (ie, panelists) were provided with the results of the systematic review. At each step, panelists were independent (ie, blinded to the votes of others) to avoid the potential for individuals to dominate the consensus.[52]

In the first round, the panel members were presented with the complete list of endpoints and asked to rate their importance by ranking each endpoint on a scale from 1 to 9, based on the Grading of Recommendations Assessment, Development and Evaluation working group definitions.[53] Scores of 7 to 9 indicated a critical endpoint, scores of 4 to 6 indicated an important endpoint (but not critical), and scores of 1 to 3 indicated an endpoint of limited importance. We considered as "important/critical" outcomes those that are important/critical to the decision-making process. The responses of the panelists were analyzed using descriptive statistics, and a report was

prepared. In the report, the endpoints were ranked according to the median score; in case of equal median score, they were ranked according to the mean score.

In the second round, the Delphi panelists received the feedback report and were asked to rescore each endpoint on a scale from 1 to 9, as described previously. Responses from round 2 were again analyzed using descriptive statistics. The endpoints with a median score of 7 to 9 (critical), and those achieving a median score of 4 to 6 (important), were included in the set of endpoints considered as appropriate for future clinical trials of candidate antifibrotic therapies for CD. Conversely, the endpoints that achieved a median score of 1 to 3 were excluded.

The experts' agreement on the endpoints' importance was assessed with the Disagreement Index (DI), as described in the RAND/University of California Los Angeles appropriateness method.[54] The DI is based on the distribution and symmetry of the scores (across the scale from 1 to 9). A higher index indicates wider spread across the 9-point scale, whereas lower values indicate increasing consensus. If the DI exceeds 1.0, then the distribution meets criteria for extreme variation in ratings. When the DI is lower than 1.0, then there is no extreme variation (ie, there is consensus).[54]

## Results

### *Results of Systematic Review*

**Search results and description of included studies.** Figure 1 (flow diagram) summarizes the search and selection process. A total of 61 eligible studies were included[24,25,28,31,55–111] (Supplementary Table 1). The studies were of relatively small size (mean number of participants, 75; range, 9 to 438), with the vast majority (74%) being of retrospective nature. Three-quarters of the studies included only patients with CD with strictures, whereas the others included mixed populations (including 36% patients with CD with strictures, on average). Endoscopic balloon dilation (EBD) was the most commonly evaluated intervention (68%), followed by medical therapies (anti-TNF treatments, thiopurines, aminosalicylates, and corticosteroids; 20%), experimental treatments (7%), self-expandable metal stents (3%), and exclusive enteral nutrition (2%). We identified more than 20 well-described endpoints for assessing disease activity and response to therapy in fibrostenosing/stricturing disease. The endpoint definitions and their operational properties are shown in Supplementary Table 2. The endpoints are categorized into 5 groups: clinical, radiological, biochemical, endoscopic, and composite endpoints.

**Clinical endpoints.** Clinical endpoints have been well-described in the literature, and are often used for the assessment of medical therapies aiming to control inflammation. Clinical response is defined as a decrease from baseline Crohn's Disease Activity Index (CDAI) score of >70 points.[97,98] Generally, a treatment and follow-up period of 12 to 16 weeks is used to define a short-term response, whereas longer follow-up periods define a long-term clinical response. The CDAI score, and the patient-reported outcomes that are integral to it, are widely used and are part of almost all CD studies evaluating disease activity. However, these are not specific to stricturing CD, and their ability to measure a change in a patient with strictures has not been studied.

In a small retrospective cohort study, Pelletier et al[100] evaluated the effect of infliximab on symptomatic strictures of the small intestine in CD. Short-term response at week 8 was categorized as follows: complete response (total disappearance of symptoms), partial response (either the disappearance of complete obstruction with persistent intermittent obstructive symptoms, or less frequent and less severe abdominal pains), and failure (persistent or recurrent obstruction that was as severe as initially, and/or an indication for surgery within 15 days before evaluation). However, obstructive symptoms have not been clearly defined, and may therefore suffer from poor reproducibility. In this study, long-term response was evaluated at last follow-up. Peters et al[73] also proposed an evaluation of long-term clinical response at this time point, but with a very pragmatic approach, that is, treatment continuation. Unfortunately, this definition appears to lack validity, reproducibility, and responsiveness. Bouguen et al[98] evaluated long-term outcome of nonfistulizing (ulcers and strictures) perianal CD under infliximab. Twenty-nine percent of included patients had a stricturing disease, and complete clinical response was defined as a complete regression of strictures at week 4 to 12 and at the maximal follow-up after week 12. Because of its simplicity, this endpoint may be of interest for further studies. However, we should underline 2 limitations: possible interobserver variability, and restricted application to perianal CD.

Beyond clinical response, clinical remission is another well-described endpoint. In 26 patients with symptomatic bowel-stricturing CD who underwent EBD, de'Angelis et al[86] used a CDAI score under 150 for identifying those in clinical remission. The major weakness of this approach was that CDAI was not specifically developed for patients with a stricturing complication. Another observational longitudinal prospective study used the Harvey-Bradshaw Index.[65] Self-expandable metal stents are sometimes used for treating primary or anastomotic strictures. In a retrospective cohort study including 17 patients with CD with symptomatic strictures, symptom-free survival during follow-up was defined as the absence of abdominal pain after meals with or without vomiting, reduced or no stools, and reduced passage of flatus associated with distention.[92] The investigators tried to use specific symptoms of stenotic diseases, but abdominal pain can especially be related to many other conditions, likely lending poor specificity to this outcome definition. Clinical success (or clinical benefit) was intensively evaluated in patients with CD complicated by strictures, particularly in the case of EBD. It corresponds to the resolution of obstructive symptoms after the procedure,[77,78,93,107–110] the absence of subsequent surgery,[96] or both.[72,83,95,103,106] The latter definition is of interest, combining subjective and objective criteria, but this approach was not adopted in studies evaluating medical therapies. In a prospective, longitudinal study, Condino et al[88] assessed the frequency of partial or complete obstructions in 36 patients with CD after treatment with

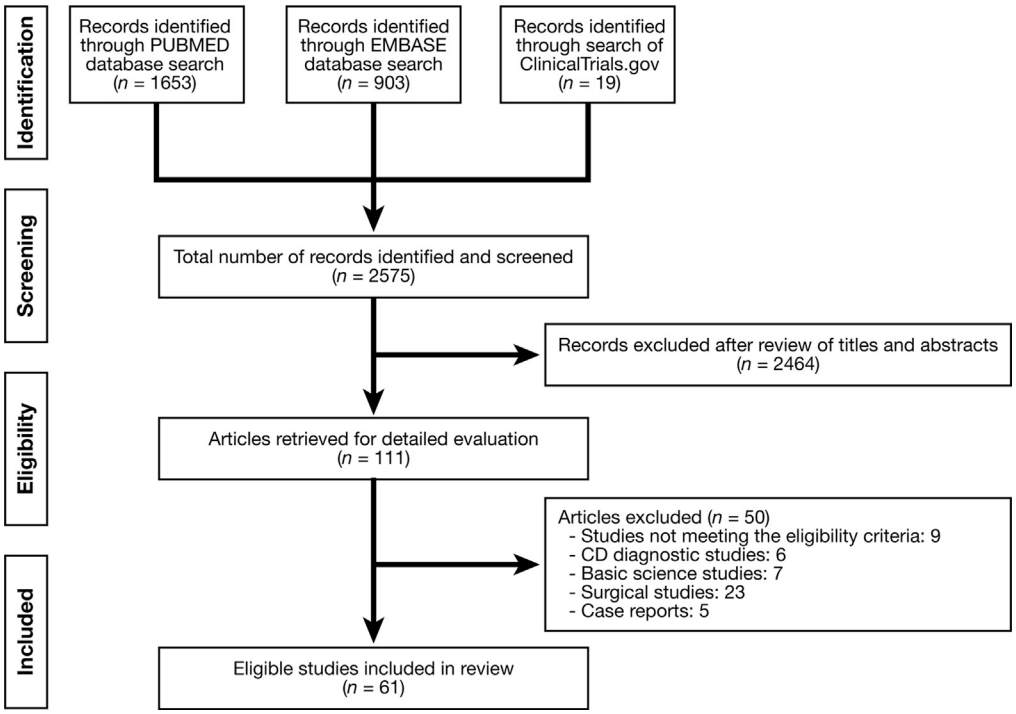


**Figure 1.** Summary of the evidence search and selection process (flow diagram).

infliximab or adalimumab. Twenty-five subjects had complications of stricture. Clinical success was evaluated at each treatment, at 6 and 12 months, and was defined as the relief of obstructive symptoms (abdominal pain, bowel distension, vomiting, no bowel movements for >24 hours), but without additional objective criteria. A similar concept was used in patients treated with stents.[94] Several studies have assessed long-term efficacy of EBD with the need for stricture-related surgical intervention during follow-up,[31,56,64,67,69,82,84,102] with or without the necessity of a new dilation session.[28,68,70,105] This concept has good face validity, but reproducibility and responsiveness are moderate, because indication of surgery or subsequent EBD widely depends on the physician's choice. In a retrospective cohort study of 53 patients with CD, 60% of whom had symptomatic strictures and were receiving medical therapy, long-term efficacy was evaluated using the outcome measure of time to relapse or surgery.[97]

**Radiological endpoints.** Endpoints based on imaging studies provide accurate and reproducible data. In a recent retrospective study, radiological response was evaluated in 150 patients with small bowel CD (35% had stricturing lesions) treated with immunomodulators, biologics, combination therapy, or budesonide.[66] All patients had pretherapy computed tomography enterography (CTE)/magnetic resonance enterography (MRE) with follow-up CTE or MRE after 6 months, or 2 CTE/MREs ≥6 months apart while on maintenance therapy. Radiological response was defined as improvement in all radiologically demonstrated strictures compared with baseline improvement defined as decreased enhancement or length of the strictures, without worsening of the other radiologically defined disease parameters of active inflammation (enhancement, length, dilated vasa recta/comb sign, perienteric inflammation [edema, phlegmon, or abscess], or fistulizing [internal penetrating] disease). This radiological endpoint is associated with low interindividual and interobserver variability; however, some items are not specific to fibrotic diseases. One potential limitation is that MRE may not be universally available. A number of studies, primarily performed in countries where gastroenterologists perform transabdominal ultrasound, have used ultrasound criteria for confirming radiologic remission in patients treated with infliximab,[101] exclusive enteral nutrition,[80] or experimental drugs.[90] These studies all used a consistent definition of radiological remission (decreased bowel wall thickness [<3 mm], decreased bowel dilation [diameter <25 mm], decreased bowel stricture [diameter >10 mm]), but the timing of the measurement varied widely (from 1 to 6 months).

**Biochemical endpoints.** This type of endpoint is potentially attractive because it can be easily repeated, with a low analytical variability. However, there are few available data about fibrosis biomarkers in CD, leading to moderate validity. In a phase I study including 15 patients with active CD (60% with CD strictures) treated with GED0301 (a smad7 antisense oligonucleotide), the authors measured several serum biomarkers of CD-related intestinal fibrosis (YKL-40, TIMP-1, Pro-MMP-1, total MMP-3, total MMP-9) at baseline and at day 180.[90] The main weakness of these biomarkers is that they have not been validated in large patient cohorts.

**Endoscopic endpoints.** In almost all studies evaluating EBD in primary or anastomotic CD strictures, the authors assessed the technical success, defined as the ability to pass the stricture with the endoscope after dilation.[31,76,81,87,91,96,99,103,104,107,111] This endpoint

incorporates all required qualities for a valuable parameter to measure response to therapy in CD strictures. However, it is typically used only in patients treated with an EBD procedure (although in principle it also could be used in patients exclusively treated with medical therapies, such as anti-TNFs or thiopurines, who have CD strictures that are within reach of a colonoscope). Hall et al[74] prospectively assessed mucosal healing in 43 patients with symptomatic small bowel CD (50% with complication of stricture) receiving immunomodulator or biological therapy. A capsule endoscopy CDAI $\leq$3.5 at week 52 was associated with a diagnosis of complete mucosal healing.

**Composite endpoints.** This heterogeneous group encompasses promising endpoints for evaluating stricturing CD activity and response to therapy. In a multicenter, prospective, observational cohort study in 97 patients with CD and symptomatic small bowel strictures, short-term response to adalimumab at week 24 was defined as treatment continuation without prohibited therapies (corticosteroids after the eighth week following inclusion, other anti-TNFs), endoscopic dilation, or bowel resection.[25] Campos et al[62] used the CD obstructive score >4 for diagnosing therapeutic failure. The Lémann index showed its ability to measure cumulative structural bowel damage in patients with CD.[112] In a prospective observational cohort study including 61 patients with quiescent small bowel CD for $\geq$3 months, receiving different medical therapies, bowel damage was confirmed in individuals with Lémann index >4.8.[55] In another study, bowel damage improvement was diagnosed if there was no increase in Lémann index >0.3.[55] This index requires further validation and is not specific to fibrotic lesions. Hall et al[74] integrated complete mucosal healing based on capsule endoscopy to the concept of deep remission. The latter endpoint was thus defined as complete mucosal healing and clinical/biochemical remission (Harvey-Bradshaw Index $\leq$5 $\pm$ C-reactive protein $\leq$5 mg/L or calprotectin $\leq$50 $\mu$g/g). We should underline the lack of specificity concerning stricturing disease. Other composite endpoints were occasionally used, such as sustained clinical benefit in patients treated with EBD and infliximab (no additional treatment, daily life nearly symptom-free, or additional treatment [except surgery] with good function in society)[89] or treatment failure (any new surgery related to inflammatory bowel disease [IBD], or hospitalizations, or penetrating complications, or need for corticosteroids or new biological).[60] However, the multiplicity of criteria in composite endpoints might reduce accuracy and reproducibility, making it difficult to apply in daily practice.

### *Results of Delphi Survey*

The initial list of endpoints identified through literature review was augmented with additional endpoints considered important by the clinical experts, for a total of 36 endpoints. A total of 48 IBD experts, among 87 members of the IOIBD (ioibd.org/members), from North America (n = 12), Europe (n = 28), Middle East (n = 2), Asia/Pacific (n = 5), and Latin America (n = 1), participated in the process, which was conducted through an online survey.

**Delphi round 1: ranking of endpoints.** The experts were presented with the complete list of endpoints (alphabetically ordered; n = 36), together with the ranking scale from 1 to 9 (Supplementary Table 3). Their responses (n = 27) were analyzed, and a feedback report was prepared. The endpoints were ranked according to the median score; in case of equal median score, they were ranked according to the mean score. Most endpoints (n = 23) were rated as critical (median scores 7–9), whereas 12 endpoints were rated as important (median scores 4–6), and 1 endpoint was considered as of limited importance (Supplementary Table 4).

**Delphi round 2: ranking of endpoints.** The feedback report was provided to the panel members, so that they could reconsider their position. They were asked to rescore each endpoint, with consideration based on the results of the first round. Forty-two IOIBD experts responded in this second round of Delphi (electronic-based questionnaire). Rating was more conservative this time, with the panel members identifying only 13 critical endpoints (namely, complete clinical response, long-term efficacy, sustained clinical benefit, treatment failure, radiological remission, normal quality of life, clinical remission without steroids, therapeutic failure, deep remission, complete absence of occlusive symptoms, symptom-free survival, bowel damage progression, and no disability). There was consensus among the experts (DI <1.0 for all 36 endpoints). Results of the rankings from the Delphi round 2 survey are shown in Table 1.

## Discussion

Intestinal fibrosis remains one of the largest clinical challenges in therapeutic management of CD. More than one-half of the patients with CD develop clinically apparent fibrostenosis throughout their disease course,[16] leading to frequent hospitalizations and surgical interventions.[47] However, current therapies for CD (ie, steroids, immunosuppressants, and biologics) may not be effective for this indication, and specific drug therapies aiming at intestinal fibrosis are not available.[19–21] Because several candidate antifibrotic drugs are currently being evaluated for other indications, and antifibrotic therapies have shown promise for reversal of advanced intestinal fibrosis in preclinical models, there is now a need to rationally design robust, prospective efficacy and effectiveness trials. Recently, the IOIBD examined potential treatment targets for IBD[113]; however, they were all focused on inflammation, whereas we need also clear targets for fibrosis.

In this work, we first conducted an extensive literature search; identified a number of potentially relevant clinical, radiological, biochemical, endoscopic, and composite endpoints measuring disease activity and response to treatment in fibrostenosing CD; and assessed their operational properties. We next developed a consensus among international IBD experts from 5 regions of the world (North America, Europe, Middle East, Asia/Pacific, and Latin America) on the importance of these endpoints, using a Delphi process. Our ultimate goal was to arrive at a set of endpoints judged

**Table 1.** Panel Members' Rankings in the Final Round of the Delphi-style Process

| Endpoints | Scores | | |
|---|---|---|---|
| | Median | Mean | DI |
| 1. **Complete clinical response**: Complete regression of strictures or complete healing of ulcers | 8 | 7.67 | 0.00 |
| 2. **Long-term efficacy**: Time to relapse or CD-related surgery | 8 | 7.62 | 0.11 |
| 3. **Sustained clinical benefit**: No additional treatment and daily life nearly symptom-free, or additional treatment (except surgery) with good function in society | 8 | 7.60 | 0.16 |
| 4. **Treatment failure**: Any CD-related surgery, or hospitalisation, or penetrating complication, or need for corticosteroids or biological drug | 7 | 6.86 | 0.26 |
| 5. **Radiological remission**: Decreased bowel wall thickness (<3 mm), decreased bowel dilation (diameter <25 mm), and decreased bowel stricture (diameter >10 mm) | 7 | 6.83 | 0.22 |
| 6. **Normal quality of life** | 7 | 6.81 | 0.37 |
| 7. **Clinical remission without steroids** | 7 | 6.76 | 0.37 |
| 8. **Therapeutic failure**: CD-related surgery, or drug discontinuation because of lack of efficacy, or loss of response, or failure to respond to dose escalation or intolerance, or drug switched to another drug because of inadequate response/loss of response | 7 | 6.74 | 0.22 |
| 9. **Deep remission**: Complete mucosal healing and clinical/biochemical remission (defined as HBI score ≤5 ± CRP ≤ 5 mg/L or calprotectin ≤50 μg/g) | 7 | 6.57 | 0.33 |
| 10. **Complete absence of occlusive symptoms**: Abdominal pain and/or nausea and/or vomiting and/or bloating and/or diet restriction after meals | 7 | 6.52 | 0.22 |
| 11. **Symptom-free survival**: Absence of abdominal pain after meals with or without vomiting, reduced or no stools, and reduced passage of flatus associated with distention | 7 | 6.52 | 0.22 |
| 12. **Bowel damage progression**: Increase in the Lémann Index >0.3 | 7 | 6.48 | 0.22 |
| 13. **No disability** | 7 | 6.43 | 0.22 |
| 14. **Radiological response**: Improvement in all radiological lesions since baseline, defined as decreased enhancement or length of disease, without worsening of other disease parameters of active inflammation (enhancement, length, dilated vasa recta/comb sign, perienteric inflammation [edema, phlegmon, or abscess], or fistulizing [internal penetrating] disease) | 6.5 | 6.36 | 0.22 |
| 15. **Being steroid-free** | 6 | 6.21 | 0.42 |
| 16. **Clinical success/benefit**: Relief of obstructive symptoms (abdominal pain, bowel distension, vomiting, no bowel movements for >24 hours) | 6 | 6.17 | 0.22 |
| 17. **No surgery for stricture** | 6 | 6.00 | 0.42 |
| 18. **Radiologic remission**: Decreased bowel thickness (<3 mm), decreased bowel dilation (diameter <25 mm), decreased bowel stricture (diameter <10 mm) | 6 | 5.98 | 0.47 |
| 19. **Clinical remission**: HBI <5 and normal CRP without steroids | 6 | 5.95 | 0.42 |
| 20. **Clinical response**: Complete (total disappearance of symptoms), partial (either the disappearance of complete obstruction with persistent intermittent obstructive symptoms or less frequent and less severe abdominal pains), failure (persistent or recurrent obstruction that was as severe as initially, and/or an indication for surgery within 15 days before evaluation) | 6 | 5.83 | 0.42 |
| 21. **Short-term success**: Drug continuation with all the following criteria: no use of a prohibited treatment, no endoscopic dilation, no bowel surgery for resection of small bowel stricture, no severe adverse events leading to drug withdrawal, and no study withdrawal whatever the reason | 6 | 5.79 | 0.47 |
| 22. **Bowel damage**: Lémann index >4.8 | 6 | 5.74 | 0.32 |
| 23. **No hospitalization for occlusive symptoms** | 6 | 5.74 | 0.52 |
| 24. **Endoscopic remission**: Ability to pass the stricture without dilation | 6 | 5.71 | 0.32 |
| 25. **US fibrotic lesions**: Small intestine contrast ultrasonography criteria for the presence of small bowel CD lesions and complications: (1) increased bowel wall thickness (>3 mm); (2) small bowel dilation, defined as a lumen diameter >25 mm; (3) bowel stricture defined as lumen diameter <10 mm, measured at the level of maximally distended loop, with or without dilation; (4) fistulas defined as hypoechoic tract with or without hyperechoic content; (5) abscess identified as roundish anechoic lesions, with an irregular wall, often presenting internal echoes and posterior echo enhancement; (6) mesenteric adipose tissue alterations and lymph nodes | 6 | 5.45 | 0.32 |
| 26. **Long-term clinical response**: Drug continuation at the end of follow-up or intended discontinuation while in remission or due to pregnancy wish | 6 | 5.26 | 0.32 |
| 27. **Complete mucosal healing**: CECDAI ≤3.5 | 6 | 5.19 | 0.85 |
| 28. **Drug discontinuation due to lack of efficacy on occlusive symptoms** | 5.5 | 5.24 | 0.32 |
| 29. **Technical success**: Ability to pass the stricture with the endoscope after dilation | 5 | 5.24 | 0.32 |
| 30. **Therapeutic failure**: CDOS <4 | 5 | 4.88 | 0.66 |
| 31. **Clinical remission**: CDAI score <150 points | 5 | 4.74 | 0.32 |
| 32. **Clinical remission**: PRO-2; CDAI | 5 | 4.50 | 0.32 |
| 33. **Clinical response**: PRO-2; CDAI | 3.5 | 3.74 | 0.22 |

**Table 1.** Continued

| Endpoints | Scores | | |
|---|---|---|---|
| | Median | Mean | DI |
| 34. **Clinical response**: Decrease from baseline CDAI score >70 points | 3 | 3.67 | 0.22 |
| 35. **Biomarker response**: Decrease of 50% in fibrotic markers (YKL-40, etc) | 3 | 3.12 | 0.22 |
| 36. **Biochemical remission**: Decreased serum YKL-40, TIMP-1, Pro-MMP-1, total MMP-3, total MMP-9 | 3 | 2.74 | 0.16 |

NOTE. The endpoints are ordered by median score; in case of equal median score, they are ordered by mean score. Scores of 7–9 indicate a critical endpoint, scores of 4–6 indicate an important endpoint, and scores of 1–3 indicate an endpoint of limited importance. The panelists' agreement on the endpoints' importance was assessed with the Disagreement Index, as described in the RAND/UCLA appropriateness method.[54] Values of less than 1.0 indicate agreement.
CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CDOS, Crohn's Disease Obstructive Score; CECDAI, Capsule Endoscopy Crohn's Disease Activity Index; DI, Disagreement Index; CRP, C-reactive protein; HBI, Harvey-Bradshaw Index; US, ultrasound.



appropriate for future trials of antifibrotic therapies for CD. We selected and voted 36 possible outcome measures for fibrosis; however, none of them is able to objectively quantify fibrosis in the gut, but they are rather outcome measures indirectly related to the clinical and structural impact of fibrosis on patients with CD. At the moment, there are no validated parameters based on clinical, endoscopic, imaging, or biological markers that can unequivocally measure the presence and the grade of fibrosis at the intestinal level. Two recent studies based on magnetic resonance imaging[114] and ultrasonography[115] have not clearly demonstrated that quantification of fibrosis is possible and reproducible by imaging techniques, and no studies have clearly demonstrated the impact of therapies in treating only fibrosis. As shown for the Lémann index,[24] at the moment, there are no validated indexes or methods to discriminate inflammation from fibrosis in patients with CD.

Overall, the results of this IOIBD initiative may lead to higher-quality clinical studies, and make it easier for the results of trials to be compared, contrasted, and synthesized as appropriate, thereby reducing waste in research.[116] Although there is no universally agreed methodological approach for selecting appropriate endpoints, a relevant systematic review demonstrated that recent studies appear to have adopted a structured approach, typically involving a systematic literature review and consensus methods (such as the Delphi process) to achieve agreement among experts[117]; methods that were used in the current study.

However, the strengths of this work should be weighed against some limitations: (1) the lack of patient involvement, which is key to ensure that the relative importance given to health outcomes reflect both a clinical and patient perspective,[49,53,117] (2) the absence of an expert radiologist from the expert panel, (3) the variability of stricture definitions used in the primary studies, (4) the high degree of nonresponse during the first round, and (5) the lack of a face-to-face meeting during the second round of Delphi.

In summary, we reached expert consensus on a set of endpoints that can be used for assessment of novel antifibrotic therapies in patients with CD strictures. Further work is needed to clarify the methods for measuring these outcomes (eg, work on definitions and parameters) and to validate measurement instruments for the assessment of outcomes.

## 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.2018.03.032.

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**Conflicts of interest**
Silvio Danese has served as a speaker, a consultant, and an advisory board member for AbbVie, Allergan, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Ferring, Hospira, Johnson & Johnson, Merck, MSD, Takeda, Mundipharma, Pfizer, Sandoz, TiGenix, UCB Pharma, and Vifor. Stefanos Bonovas is supported by FIRMAD. Anthony Lopez has received research funding from Roche, has served as consultant for Amgen, and has received lecture fees from Vifor Pharma. Gionata Fiorino has served as a consultant and Advisory Board Member for MSD, AbbVie, Takeda, Janssen, Mundipharma, Sandoz, and Pfizer. William J. Sandborn reports grants, personal fees, and nonfinancial support from AbbVie; grants and personal fees from Prometheus Laboratories, Boehringer Ingelheim, Takeda, Atlantic Pharmaceuticals, Janssen, Bristol-Myers Squibb, Genentech, and Nutrition Science Partners; and personal fees from Kyowa Hakko Kirin, Millennium Pharmaceuticals, Celgene Cellular Therapeutics, Santarus, Salix Pharmaceuticals, Catabasis Pharmaceuticals, Vertex Pharmaceuticals, Warner Chilcott, Gilead Sciences, Cosmo Pharmaceuticals, Ferring Pharmaceuticals, Sigmoid Biotechnologies, Tillotts Pharma, Am Pharma BV, Dr August Wolff, Avaxia Biologics, Zyngenia, Ironwood Pharmaceuticals, Index Pharmaceuticals, Nestle, Lexicon Pharmaceuticals, UCB Pharma, Orexigen, Luitpold Pharmaceuticals, Baxter Healthcare, Ferring Research Institute, Amgen, Novo Nordisk, Mesoblast Inc., Shire, Ardelyx Inc., Actavis, Seattle Genetics, MedImmune (AstraZeneca), Actogenix NV, Lipid Therapeutics Gmbh, Eisai, Qu Biologics, Toray Industries Inc., Teva Pharmaceuticals, Eli Lilly, Chiasma, TiGenix, Adherion Therapeutics, Immune Pharmaceuticals, Celgene, Arena Pharmaceuticals, Ambrx Inc., Akros Pharma, Vascular Biogenics, Theradiag, Forward Pharma, Regeneron, Galapagos, Seres Health, Ritter Pharmaceuticals, Theravance, Palatin, Biogen, and Western University (owner of Robarts Clinical Trials). David T. Rubin has received consulting fees or research support from AbbVie, Abgenomics, Allergan, Amgen, Celgene, Forward Pharma, Genentech/Roche, Janssen, Merck, Miraca Life Sciences, Mitsubishi, Napo Pharmaceuticals, Pfizer, Prometheus Laboratories, Salix Pharmaceuticals, Shire, Takeda, Target PharmaSolutions, and UCB Pharma. Michael A. Kamm has received research funding support from AbbVie and Ferring, and has served as a consultant in the last 2 years to AbbVie, Janssen, MSD, Takeda, Pfizer, Celgene, and Ferring. Jean-Frederic Colombel has served as consultant, advisory board member, or speaker for AbbVie, Amgen, Boehringer Ingelheim, Celgene Corporation, Celltrion, Enterome, Ferring, Genentech, Janssen and Janssen, Lilly, Medimmune, Merck, Pfizer, PPM Services, Protagonist, Second Genome, Seres, Shire, Takeda, Theradiag, Theravance Biopharma, and TiGenix. Bruce E. Sands has served as a consultant for AbbVie, Akros Pharma, Allergan, Bristol-Myers Squibb, Lyndra, Lycera, Arena Pharmaceuticals, Boehringer Ingelheim, Celgene,

EnGene, Gilead, Janssen, Lilly, MedImmune, Oppilan Pharma, Pfizer, Shire, Takeda, Target Pharmasolutions, Theravance Biopharma R&D, TiGenix, Immune Pharmaceuticals, Receptos, TopiVert Pharma, UCB, Vivelix Pharmaceuticals, Synergy Pharmaceuticals, and Salix Pharmaceuticals. Severine Vermeire has received grant support from AbbVie, MSD, Pfizer, and Takeda; received speaker fees from AbbVie, MSD, Takeda, Ferring, Dr. Falk Pharma, Hospira, Pfizer, and Tillots; and served as a consultant for AbbVie, MSD, Takeda, Ferring, Genentech/Roche, Shire, Pfizer, Galapagos, Mundipharma, Hospira, Celgene, Second Genome, and Janssen. Julian Panes has served as a speaker, a consultant, or an advisory board member for AbbVie, Biogen, Boehringer Ingelheim, Celgene, Ferring, Johnson & Johnson, MSD, Nestle, Oppilan, Pfizer, Sandoz, Takeda, Theravance, and TiGenix. Gerhard Rogler has served as a speaker, a consultant, or an advisory board member for AbbVie, Amgen, Augurix, Boehringer, Bristol-Myers Squibb, Calypso, Celgene, Falk, Ferring, Fisher, Genentech, Gilead, Index Pharmaceuticals, Janssen, MSD, Novartis, Pfizer, Phadia, Roche, UCB, Takeda, Tillots, UCB, Vifor, Vital Solutions, and Zeller. Geert D'Haens has served as advisor for AbbVie, Ablynx, Amakem, Amgen, AM Pharma, Avaxia, Biogen, Bristol Meiers Squibb, Boehringer Ingelheim, Celgene/Receptos, Celltrion, Cosmo, Covidien/Medtronics, Ferring, Dr. Falk Pharma, Eli Lilly, Engene, Galapagos, Genentech/Roche, Gilead, Glaxo Smith Kline, Immunic, Johnson & Johnson, Lycera, Medimetrics, Millenium/Takeda, Mitsubishi Pharma, Merck Sharp Dome, Mundipharma, Nextbiotics, Novonordisk, Otsuka, Pfizer/Hospira, Prometheus Laboratories/Nestle, Protagonist, Robarts Clinical Trials, Salix, Samsung Bioepis, Sandoz, Setpoint, Shire, Teva, TiGenix, Tillotts, Topivert, Versant, and Vifor; and received speaker fees from AbbVie, Biogen, Ferring, Johnson and Johnson, Merck Sharp Dome, Mundipharma, Norgine, Pfizer, Samsung Bioepis, Shire, Millenium/Takeda, Tillotts, and Vifor. Laurent Peyrin-Biroulet has received consulting fees from AbbVie, Amgen, Biogaran, Biogen, Boerhinger-Ingelheim, Bristol-Myers Squibb, Celgene, Celltrion, Ferring, Forward Pharma, Genentech, H.A.C. Pharma, Hospira, Index Pharmaceuticals, Janssen, Lycera, Merck, Lilly, Mitsubishi, Norgine, Pfizer, Pharmacosmos, Pilège, Samsung Bioepis, Sandoz, Takeda, Therakos, Tillots, UCB Pharma, and Vifor; and lecture fees from AbbVie, Ferring, H.A.C. Pharma, Janssen, Merck, Mitsubishi, Norgine, Takeda, Therakos, Tillots, and Vifor.