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Selecting Endpoints for Disease-Modification Trials in Inflammatory Bowel Disease: the SPIRIT consensus from the IOIBD

Short title: Selecting endpoints for disease-modification trials in IBD

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Abbreviations:

CD: Crohn's disease.

CT: Computed tomography.

EIM: Extra-intestinal manifestation.

EQ: EuroQol.

FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue.

IBD: Inflammatory bowel disease.

IBDQ: Inflammatory bowel disease questionnaire.

IOIBD: International Organization for the Study of Inflammatory Bowel Diseases.

MRI: Magnetic resonance imaging.

SF-36: Short Form Health Survey.

SPIRIT: Selecting Endpoints for Disease-Modification Trials.

TNF: Tumor necrosis factor.

UC: Ulcerative colitis.

UEGW: United European Gastroenterology Week.

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Abstract

Background and Aims: Inflammatory bowel diseases (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), are chronic and disabling disorders. Prospective disease-modification trials to prevent disease progression are eagerly awaited. However, disease progression is not clearly defined. The objective of the **Selecting EndPoInts foR Disease-ModIfication Trials (SPIRIT)** initiative was to achieve international expert consensus on the endpoints to be used in future IBD-disease modification trials.

Methods: This initiative under the auspices of the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) began with a systematic literature search to evaluate the current evidence on the definition of disease progression in IBD. On 22 October 2019, a consensus meeting took place during the United European Gastroenterology Week (UEGW) Congress in Barcelona, during which predefined proposed statements were discussed in a plenary session and voted on anonymously. Agreement was defined as at least 75% of participants voting for any one statement.

Results: The group agreed that the ultimate therapeutic goal in both CD and UC is to prevent disease impact on patient's life (health-related quality of life, disability, fecal incontinence), mid-term complications (encompass bowel damage in CD, IBD-related surgery and hospitalizations, disease extension in UC, extra-intestinal manifestations, permanent stoma, short bowel syndrome), and long-term complications (gastrointestinal and extra-intestinal dysplasia or cancer, mortality).

Conclusions: Recommendations on which goals to achieve in disease-modification trials for preventing disease progression in patients with IBD are proposed by the SPIRIT consensus. However, these recommendations will require validation in actual clinical studies before implementation in disease-modification trials.

Keywords: Disease severity; disease progression; Crohn's disease; ulcerative colitis.

Background and Aims

Inflammatory bowel diseases (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), are chronic and disabling disorders culminating in disease progression in many patients.¹⁻⁶ Although IBD are progressive lifelong diseases, contemporary clinical trials exclusively evaluate short-term endpoints, including clinical and endoscopic remission according to the STRIDE consensus,⁷ and not "disease modification" endpoints. As has been done in other progressive diseases, disease modification can be defined as treatments or interventions that affect the underlying pathophysiology of the disease and have a beneficial outcome on the long-term course of IBD.⁸ It requires years to accurately assess such endpoints.

The aim of current "treat-to-target" strategies is to avoid long-term bowel damage and subsequent disability by using appropriate therapy in high-risk patients, then closely monitoring and adjusting treatment according to predefined therapeutic objectives. Thus, early disease control to prevent disease progression could be critical, but prospective disease-modification trials are eagerly awaited to determine whether this approach should become routine in clinical practice (**Figure 1**).

However, there is currently no consensus on how disease progression should be defined in UC and CD trials. By contrast, in rheumatology the Outcome Measures in Rheumatology (OMERACT) initiative dating back from 2014 clearly defined disease-modification outcomes.⁹⁻¹¹ Both UC and CD are known to have an impact on patient's life and to induce specific and long-term complications, but there is a lack of consensus on which specific outcomes to consider for disease-modification trials. The objective of the Selecting Endpoints for Disease-Modification Trials (SPIRIT) initiative, under the auspices of the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD), was to

achieve international expert consensus on the endpoints to be used in future IBD-disease modification trials.

Materials and Methods

This initiative by the IOIBD comprised three steps.

First, a systematic literature search was conducted between December 2018 and July 2019 to evaluate the current evidence on the definition of disease progression in IBD, including CD and UC. The methodology is detailed in **Supplementary data**.

On 22 October 2019, a consensus meeting took place during the United European Gastroenterology Week (UEGW) congress in Barcelona and comprised 39 attendees, including 9 members of the IOIBD executive committee, 29 IOIBD members (including 9 members joining via Webex) and one fellow. The purpose of this meeting was to define: (i) the candidate factors for outcome measures in future IBD disease-modification trials; (ii) the evaluative instruments that should be used for each of these outcome measures; and (iii) the timepoint that should be chosen to assess each of these outcome measures. Proposed statements were prepared by LPB and CLB prior to the meeting, and presented according to three categories predefined based on the results of the systematic literature review: 1) impact on patient's life, 2) mid-term complications, and 3) long-term complications. The day of the meeting, the results of the systematic literature review were first presented, followed by discussion of each proposed statement in a plenary session. Each proposed statement was voted upon in an anonymous manner using a digital system. Agreement was defined as at least 75% of participants voting for one proposed statement. If a 75% agreement was not achieved, further discussion ensued which may have included amendment of voting statements where required, followed by a second round of voting if controversial. If agreement could not be reached after two rounds of voting, then the statement was definitely "excluded". Composite target statements, consisting of a combination of specific proposed targets arising from each workstream focus were developed and voted on.

In a third phase, in order to involve the patients in the development of these disease-modification outcomes, 23 patients from Nantes University Hospital, France, were asked to rate each of the 12 items selected by the experts on a visual analog scale between 0 and 10. Results are presented as the median (interquartile range, IQR). They were also asked about any important item that the experts could have overlooked.

Results

The results of the systematic literature review are presented in **Supplementary data**. They highlight notable gaps in the published evidence base, clearly demonstrating the lack of consensus on how to define disease progression in IBD, and the need for a broad consensus. The recommendations that are presented here are therefore largely based on expert opinion.

Statements for which there was agreement for CD and UC are summarized in **Tables 1 – 3** according to the category which the outcome measure belongs to (impact on patient's life, mid-term complications or long-term complications). Statements that required amendment before agreement or that were excluded (consensus of $\geq 75\%$ not achieved) are shown in **Supplementary data**.

Impact on patient's life (Table 1)

Health-related quality of life, was widely accepted by the experts (93%). Experts reached consensus on a composite endpoint made up of a disease-specific questionnaire (Inflammatory bowel disease questionnaire IBDQ-36) and a generic questionnaire (Short Form Health Survey SF-36). The complexity of such a composite endpoint was discussed but not disturbing as this outcome measure is intended for trials.

Disability was also widely accepted (92%) by the expert panel. The IBD Disability Index was chosen as the tool to assess disability in disease-modification trials,^{12,13} given that the IBD-Disk had not been much used and validated at the time of the meeting.¹⁴

At the first round of voting, 76% of the participants considered fecal incontinence as an important outcome measure to include in disease-modification trials and was further discussed. Some experts wondered if fecal incontinence was already included in health-related quality of life with the IBDQ-36. However, the panel agreed that the corresponding question in the IBDQ-36 (question 27: "how much of the time during the last 2 weeks have

you been troubled by accidental soiling of your underwear?") was inaccurate for precisely assessing fecal incontinence in IBD patients, especially since it is reversible. Then the experts adjudicated on the patients in whom fecal incontinence could be evaluated, excluding patients with isolated luminal ileal CD because this is a more unlikely cause for such a symptom, and patients with stoma, the latter being already included in surgical bowel damage. Finally, the panel voted again and accepted fecal incontinence (85%) as an outcome measure to include in disease-modification trials. The Cleveland score (or Jorge and Wexner score)¹⁵ was mostly chosen to measure this outcome (76%), as it has been raised as the most commonly adopted tool to measure fecal incontinence in IBD patients in a recent systematic review.¹⁶

Regarding the timepoint to use for assessing impact on patient's life, half of the experts voted for a time range of 6 months, while the other half voted for a 12-month interval. Thus, the expert panel agreed that we should evaluate IBD impact on patient's life every 6 to 12 months, without needing to be tailored according to duration of follow-up.

Mid-term complications (Table 2)

Bowel damage was almost unanimously voted (92%) as the first complication to incorporate in disease-modification trials. However, the expert panel agreed to restrict this outcome to patients with CD, using the Lémann index that takes into account history of intestinal resection, stricturing and penetrating lesions.⁵ All the experts agreed that the calculation of the Lémann index should be centralized in future clinical trials, and should be assessed every 12 (62%) to 24 (31%) months as it has been shown to decrease with early treatment by anti-tumor necrosis factor (anti-TNF) within the first 2 years of diagnosis.^{17,18}

IBD-related surgery was widely accepted as a complication to assess in future IBD disease-modification trials (96%). The expert panel again emphasized the difference between CD and UC. For patients with UC, the entire panel agreed that any colectomy should be

considered as an outcome measure, including colectomy with ileo-rectal anastomosis, ileal pouch-anal anastomosis with pouch, or ileostomy. For patients with CD, although it was pointed out that several IBD centers refer the patients with luminal ileal non-complicated CD to surgery, all the experts agreed to consider any CD-related surgery as an outcome measure for disease-modification trials, regardless of the type of surgery (stricturoplasty, bowel resection, definitive stoma, other), the number of surgeries, or the length of bowel resection. The expert panel agreed to also include endoscopic balloon dilation (86%) and perianal surgery (85%). The latter is often excluded from major surgery in epidemiological studies but seems important to take into account in the context of disease-modification trials. Regarding the timepoint to consider for assessing IBD-related surgery, the experts tried to answer the question “what should be the minimum duration of a clinical trial to expect a decrease in the risk of surgery?” and agreed to assess this outcome at a 24 to 36-month interval (95%).

IBD-related hospitalizations also reached a consensus to be incorporated as an outcome measure (84%), as the hospitalization rate remains high at the biologic era.¹⁹ More than half of the experts (57%) focused on the number of hospitalizations because it has been significantly reduced by the use of immunomodulators in both types of IBD.^{20,21} However, 30% voted for the length of hospital stay, often used as an indicator of the efficiency of health care utilization,^{22,23} as it has been shown to be associated with IBD severity.^{24,25} The expert panel finally agreed to consider a composite endpoint combining the total number of IBD-related hospitalizations, including hospital readmissions, and the cumulative length of hospital stay. It was also pointed out that hospitalization at diagnosis should be excluded by definition. Regarding the timepoint for assessing this outcome measure, the experts answered the question “what should be the minimum duration of a clinical trial to expect a decrease in IBD-related hospitalizations?” and agreed to assess this endpoint at a 12 to 24-month interval (76%).

The concept of disease extension did not reach a consensus at the first round of voting (65%), but when considering exclusively patients with UC, 79% agreed to incorporate disease extension in future UC-modification trials, because proximal disease extension is common in patients with proctitis or left colitis.^{26,27} The expert panel then discussed the concept of “preventing disease extension” in UC. Should it include “absence of proximal disease extension” and/or “disease regression”? Experts agreed on the exclusion of the concept of disease regression because it is still evolving and difficult to define (macroscopic or histological definition). However, it may be considered in the future with new prospective data. Thus, the entire panel decided to focus on macroscopic proximal disease extension, hence excluding patients with pancolitis (E3 according to the Montreal classification). Regarding the timepoint, the first proposed statement ranged from 6 to 36 months but all experts tended to view this time frame as too tight. Indeed, the risk of disease extension is known to be important in the first five years of UC.²⁸ After a second round of voting, the entire panel agreed to assess proximal UC extension between 2 and 5 years after diagnosis.

The existence of extra-intestinal manifestations (EIM) was first excluded by the expert panel (63%), although rather frequent in both UC and CD.²⁹ After discussion on the impact that EIM may have on therapeutic decision, and conversely, on the likelihood that some treatments may create new-onset EIM, 85% of the experts agreed for the incorporation of EIM as an outcome measure for IBD disease-modification trials, especially since it is indicative of the systemic nature of the disease. Most importantly, the experts noted that there is currently no tool for assessing EIM and agreed to consider all of them together. The time frame that was chosen to evaluate EIM ranged from 12 to 36 months (92%).

Permanent stoma (84%) and short bowel syndrome (95%), as defined by a functional small bowel length of less than 200 cm,³⁰ were added to the proposed statements by the expert panel and accepted as outcome measures to assess in disease-modification trials.

Long-term complications (Table 3)

Most experts (92%) accepted dysplasia or cancer as an outcome measure for future IBD disease-modification trials. This is, indeed, the main problem of subclinical persistent inflammation that progressively leads to conventional or non-conventional dysplasia,^{31,32} with an increased risk of digestive cancer in both UC³³ and CD.³⁴ The expert panel agreed that dysplasia and cancer will have to be distinguished. They then discussed which types of lesions are to be included and agreed to consider both gastrointestinal and extra-intestinal neoplastic lesions, notably in order to take into account treatment-related cancers. Regarding the timepoint, 86% of the experts agreed to assess this outcome at 5 years. Experts also discussed on the fact that those disease-modification trials will be the first step for chemopreventive trials assessing prevention of colorectal dysplasia and cancer, particularly in patients with IBD associated with primary sclerosing cholangitis.

Regarding mortality, the expert panel reached a consensus to incorporate this outcome in disease-modification trials at the first round of voting (83%), considering both IBD-related and non-IBD-related mortality (77%), as patients with IBD are at higher risk, among other things, of cardiovascular diseases or psychiatric comorbidities. The entire panel agreed that mortality should be assessed at 5 years in disease-modification trials.

Overall, the 12 items selected by the experts were well rated by the 23 interviewed patients, with a median over 8 on a visual analog scale between 0 and 10 for all the items (**Tables 1 – 3**). Two patients each raised an item that could have been added to the outcomes: the impact of IBD-specific treatments on daily life, and the difficulty of obtaining psychological support by persons who really know the daily management of IBD.

Finally, 94% (15/16) of the experts agreed to extrapolate the recommendations regarding “mid-term complications” from adults to children, with the addition of linear growth. Recommendations regarding the impact on patient’s life will obviously require an adjustment to children because they need specific instruments to measure “patient-reported outcomes”. Similarly, “long-term complications”, encompassing dysplasia/cancer and mortality, are not adapted to pediatric studies, especially the timepoint that was used to assess them in adults (5 years), and will require specific adjustments to be relevant to children.

Discussion

It is time to move beyond the STRIDE consensus and determine which endpoints should be assessed in those trials in order to prevent disease progression, as has been done in rheumatology with the OMERACT initiative. In osteoarthritis the core outcomes measurement set comprises life impact, pathophysiological manifestations and death,¹⁰ and has been implemented in disease-modification trials.³⁵ This was a major turning point in rheumatology but was hitherto lacking in IBD. The REACT1 trial was the forerunner of IBD disease-modification trials,³⁶ but consensus on disease-modification outcomes is still eagerly awaited.

The 12 outcome measures presented here are based on a combination of published evidence but mostly on expert opinion. Since the attendees represented a number of different countries, this agreement incorporated international input on the topics considered. The group agreed that the ultimate therapeutic goal in both CD and UC is to prevent disease impact on patient's life (health-related quality of life, disability, fecal incontinence), mid-term complications (bowel damage in CD, IBD-related surgery and hospitalizations, disease extension in UC, extra-intestinal manifestations, permanent stoma, short bowel syndrome), and long-term complications (gastrointestinal and extra-intestinal dysplasia or cancer, mortality). This latter recommendation is in line with the IBD Cancer and Serious Infection in Europe (I-CARE) study, a prospective, observational cohort study designed to assess the neoplastic and infectious risk in patients using immunosuppressants or biologics.

This consensus is just a starting point to design disease-modification trials. The next step will be to validate this core set in cohort studies and real-life studies, to assess the potential applicability of such outcomes to clinical practice and "real-life" patients, before implementing it in future disease-modification trials that will evaluate if an early use of highly effective treatment in patients with severe disease or who are at high risk for disease

progression, subject to a tight monitoring of clinical, biological, endoscopic and even radiological or histological aspects, may decrease the impact of IBD on patient's life and the risk of disease complications, and potentially avoid neoplastic complications and mortality in the long term (**Figure 2**).

In conclusion, following an international consensus and a comprehensive literature review, recommendations on goals to achieve in future disease-modification trials for preventing disease progression in patients with IBD are now available. These include endpoints about impact on patient's life, mid-term complications and long-term complications for both UC and CD, that define the treatment target and the frequency of assessment to reach this target. However, these recommendations are mostly based on expert opinion due to significant gaps identified in the systematic literature review, and will have to be validated in real-world clinical studies before implementing them in disease-modification trials.

Table 1. Three outcome measures to use in IBD disease-modification trials by the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) regarding impact on patient's life.

Proposed statement	Voting results		
	No. of ballots	Percentage votes at last ballot (n/N)	Patients' rating on a 0-10 VAS, median (IQR)
1. Health-related quality of life	1	93 (28/30)	10 (8-10) (n=23)
• Tool: Combination of IBDQ 36 + SF-36	2	85 (17/20)	
2. Disability	1	92 (23/25)	8 (5-10) (n=23)
• Tool: IBD Disability Index	1	83 (24/29)	
3. Fecal incontinence	2	85 (17/20)	8 (6-10) (n=23)
• Tool: Jorge and Wexner (Cleveland score)	1	76 (13/17)	
Timepoint: 6 to 12 months		100 (24/24)	
	1	50 (6 mo.) / 50 (12 mo.)	

Abbreviations: IBD, Inflammatory bowel disease; IBDQ-36, Inflammatory bowel disease questionnaire (36 questions); IQR, Interquartile range; mo., months; SF-36, Short Form Health Survey 36; VAS, Visual analog scale.

Table 2. Seven outcome measures to use in IBD disease-modification trials by the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) regarding mid-term complications.

Proposed statement	Voting results		
	No. of ballots	Percentage votes at last ballot (n/N)	Patients' rating on a 0-10 VAS, median (IQR)
1. Bowel damage in CD	1	92 (24/26)	8 (6.5-10) (n=23)
<ul style="list-style-type: none"> • Tool: Lémann index • Timepoint: 12 to 24 months 	1	83 (10/12)	
	1	93 (24/26)	
	1	62 (12 mo.) / 31 (24 mo.)	
2. IBD-related surgery	1	96 (24/25)	8 (7-10) (n=22)
<ul style="list-style-type: none"> • Tool for UC: any colectomy • Tool for CD: <ul style="list-style-type: none"> ○ CD-related surgery ○ Endoscopic balloon dilation ○ Perianal surgery • Timepoint: 24 to 36 months 	1	100 (24/24)	
	1	100 (11/11)	
	1	86 (18/21)	
	1	85 (17/20)	
	1	95 (19/20)	
	1	50 (24 mo.) / 45 (36 mo.)	

3. IBD-related hospitalizations	1	84 (21/25)	8 (7-9.75) (n=22)
• Tool: number of hospitalizations + cumulative length of hospital stay	1	87 (20/23) 57 (number) / 30 (length)	
• Timepoint: 12 to 24 months	1	76 (19/25) 28 (12 mo.) / 48 (24 mo.)	
4. Disease extension in UC	1	79 (15/19)	8 (7-10) (n=21)
• Tool: macroscopic proximal disease extension (excluding patients with pancolitis)	1	100 (19/19)	
• Timepoint: 2 to 5 years	2	100 (21/21) 19 (2 y.)/52 (3 y.)/29 (5y.)	
5. Extra-intestinal manifestations (all considered together)	2	85 (17/20)	9 (5.5-10) (n=23)
• Timepoint: 12 to 36 months	1	92 (23/25) 32 (12 mo.)/32 (24 mo.)/28 (36 mo.)	
6. Permanent stoma	1	84 (16/19)	8 (6-10) (n=23)
7. Short bowel syndrome	1	95 (18/19)	8 (7-9.75)

(n=22)

Abbreviations: CD, Crohn's disease; IBD, Inflammatory bowel disease; IQR, Interquartile range; mo., months; UC, Ulcerative colitis; VAS, Visual analog scale; y., years.

Table 3. Two outcome measures to use in IBD disease-modification trials by the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) regarding long-term complications.

Proposed statement	Voting results		
	No. of ballots	Percentage votes at last ballot (n/N)	Patients' rating on a 0-10 VAS, median (IQR)
1. Dysplasia or cancer (all considered together)	1	92 (22/24)	9 (7-10) (n=23)
• Timepoint: 5 years	1	83 (20/24)	
2. Mortality	1	83 (20/24)	8 (6-10) (n=21)
• Tool: both IBD-related and non-IBD-related mortality	1	77 (17/22)	
• Timepoint: 5 years	1	100 (22/22)	

Abbreviations: IBD, Inflammatory bowel disease; IQR, Interquartile range; VAS, Visual analog scale.

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Figure legends

Figure 1. Concept of the SPIRIT consensus.

As has been done for deep remission with the STRIDE consensus in order to achieve best possible remission in the short term, the SPIRIT consensus aims at achieving international expert consensus on the endpoints to be used in future IBD-disease modification trials in order to change the disease course in the long term.

Figure 2. Concept of the “therapeutic window of opportunity” in early inflammatory bowel disease and summary of the outcome measures retained by the SPIRIT consensus to be used in future IBD disease-modification trials.

^a: Transmural healing may be the ultimate therapeutic goal in CD; ^b: Histological healing may be the ultimate therapeutic goal in UC.

Abbreviations: CD, Crohn’s disease; CRP, C-reactive protein; FC, Fecal calprotectin; IBD, Inflammatory bowel disease; UC, Ulcerative colitis.

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