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Evolution of Eligibility Criteria in Inflammatory Bowel Disease Clinical Trials: A Clinical Trial Databank Analysis

An Outtier[1,2] | Rosanne Janssens[3] | Liese Barbier[3] | João Sabino[1,2] | Bram Verstockt[1,2] | Séverine Vermeire[1,2] | Isabelle Huys[3] | Marc Ferrante[1,2]

[1]Department of Gastroenterology and Hepatology, University Hospitals Leuven, Leuven, Belgium | [2]Translational Research in Gastrointestinal Disorders, Department of Chronic Diseases and Metabolism, KU Leuven, Leuven, Belgium | [3]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium

Correspondence: Marc Ferrante (marc.ferrante@uzleuven.be)

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ABSTRACT

Background: Eligibility criteria in clinical trials have been criticised for being overly restrictive without clinical justification.

Objective: We aimed to investigate the types, evolution, and current status of eligibility criteria in clinical trials for inflammatory bowel diseases (IBD).

Methods: We performed a clinical trial databank search on clinicaltrials.gov, and included all Phase 3 placebo-controlled randomised-controlled trials (RCTs) investigating biologics or small molecules as induction therapy for moderate-to-severe Crohn's disease (CD) and ulcerative colitis (UC). Eligibility criteria were analysed both quantitatively and qualitatively.

Results: Fifty-nine RCTs were identified between the year 2000 and 2022 (30 for CD and 29 for UC). The median (interquartile range) number of eligibility criteria was 44 (38–49), and did not significantly change over the studied time period ($p = 0.26$). Qualitative analysis showed that common patient populations, such as older patients, therapy refractory patients, patients with comorbidities, prior malignancies, unclassified IBD type, ulcerative proctitis, stricturing and fistulizing CD, as well as patients with an ostomy, were often excluded. Heterogeneity in eligibility criteria across the different IBD clinical trials was found, such as for disease activity measurement, dosage of concomitant medication, wash-out period of advanced therapies, and laboratory tests.

Conclusion: The median number of eligibility criteria for IBD RCTs did not significantly change over time. The eligibility criteria are however restrictive and complex, limiting the generalisability of efficacy and safety outcomes in daily practice when drugs are approved. Future research is needed to investigate the impact of broadening eligibility criteria to better encompass real-world practice.

1 | Introduction

Randomised controlled trials (RCTs) are considered the gold standard to study the treatment effect of new investigational medicinal products. The study population of an RCT is defined based on the specific eligibility criteria (EC) mentioned in the protocol. Eligibility criteria consist of both inclusion and exclusion criteria; where inclusion criteria are requirements

Abbreviations: 5-ASA, 5-aminosalicylic acids; AEs, adverse events; APTT, activated partial thromboplastin time; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; EC, eligibility criteria; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; IBD-U, inflammatory bowel disease unclassified; IMP, investigational medicinal product; IOIBD, International Organisation of Inflammatory Bowel Disease; IQR, interquartile range; PGA, Physician Global Assessment; PRO2, two-component patient-reported outcome; RCT, randomised controlled trial; SES-CD, simple endoscopic score for Crohn's disease; TB, tuberculosis; UC, ulcerative colitis; UP, ulcerative proctitis.

Summary

- Summarise the established knowledge on this subject
  - Eligibility criteria (EC) of randomised controlled trials (RCTs) have been criticised for being overly restrictive, thereby excluding multiple patients, without clinical justification.
  - Overly restrictive EC may result in findings that do not correspond to the population that will ultimately use the medicine after regulatory approval.
  - Only 31.1% of inflammatory bowel disease (IBD) patients are eligible to participate in such an RCT.
  - There is a lack of research and insights regarding the evolution and current status of EC in IBD clinical trials.
- What are the significant and/or new findings of this study?
  - The median number of ECs per IBD clinical trial was 44 with a median of 10 inclusion criteria and 33 exclusion criteria, and did not significantly change over time.
  - Common patient populations, such as older patients, therapy refractory patients, patients with comorbidities, prior malignancies, unclassified IBD type, ulcerative proctitis, stricturing and fistulizing CD, as well as patients with an ostomy, were often excluded.
  - EC in IBD clinical trials are restrictive and complex, limiting the generalisability of efficacy and safety outcomes in daily practice when drugs are approved.

that must be met for patients to be included in the trial, and exclusion criteria are characteristics that disqualify potential study subjects [1]. Such criteria may include factors such as age, medical history, current health status, as well as previous and concomitant medication.

However, ECs have been criticised for being overly restrictive, thereby excluding multiple patients, without clinical justification [2]. Strict ECs are used to ensure a homogenous study population for accurate and optimal measurement of the treatment effect, to protect the study subjects' safety, and for commercial interests [3]. Furthermore, many Phase 3 trials adopt the restrictive EC used in their corresponding Phase 1 and Phase 2 trials. Overly restrictive EC may result in findings that do not correspond to the population that will ultimately use the medicine after regulatory approval [4]. Treating physicians are therefore confronted with uncertainties regarding clinical use in real-world practice, and will not know whether a drug will be effective and/or safe for a specific patient.

For inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), many new drugs with different modes of action are currently being developed and investigated in RCTs [5]. However, previous research has shown that only 31.1% of IBD patients are eligible to participate in such an RCT. Patients would have been excluded because they had stricturing or penetrating CD, took high doses of steroids, had comorbidities or prior exposure to (multiple) advanced therapies, or received topical therapies [6]. Nevertheless, those patient subgroups are also in need of IBD treatment and could receive such treatments in the real-world once the new drug is approved by the regulatory authorities. The use of strict EC has inevitably led to decreasing enrolment rates in IBD clinical trials in recent years. From 1998 to 2020, the average enrolment rate in moderate-to-severe UC decreased from 0.32 to 0.12 patients per site per month, whereas the average recruitment rate in moderate-to-severe CD decreased from 0.65 to maximum 0.08 patients per site per month [7].

While many points of critique regarding EC have been raised by stakeholders involved in IBD clinical trial development and evaluation, there is a lack of research and insights regarding the evolution and current status of EC in IBD clinical trials [6, 8–14]. Such insights are however needed to address the problem of restrictiveness and complexity and formulate stakeholder-specific solutions to address these. Therefore, this study aimed to provide an overview of the EC implemented in IBD clinical trials and specifically addresses the following research questions: (i) what is the number of EC used in IBD clinical trials and how has this number evolved over time, and (ii) what are the types of EC used in IBD clinical trials and how have these changed over time?

2 | Materials and Methods

2.1 | Clinical Trial Selection and Eligibility Criteria Collection

We performed a clinical trial databank search in January 2023 on clinicaltrials.gov using the terms ‘ulcerative colitis’ and ‘Crohn's disease’, and filtering for interventional, Phase 3 and industry sponsored studies. We focussed on placebo-controlled RCTs investigating biologics or small molecules as induction therapy for moderate-to-severe IBD. Full EC lists were identified and collected from the protocol of the concerned study or through clinicaltrialsregister.eu. We accessed the protocols through either clinicaltrials.gov, our own database at the IBD unit of UZ Leuven, or by requesting them directly from the sponsor.

2.2 | Eligibility Criteria Quantification and Categorisation

Eligibility criteria were quantified based on the numbering provided in the inclusion and exclusion criteria list of the protocols. Qualitative content analysis was performed to generate EC categories and analyse the EC content between the different clinical trials and over time.

2.3 | Statistical Analysis

Descriptive statistics were utilised to summarise the characteristics of the evaluated protocols. Continuous variables were summarised as medians with interquartile ranges (IQR). Simple linear regression was used to test the association between time and number of ECs. All reported *p*-values were two-sided. A numerical *p*-value less than 0.05 was considered statistically significant. Statistical analyses were performed using Prism version 8 (GraphPad Software, San Diego, USA).

3 | Results

3.1 | IBD Clinical Trial Characteristics and Number of Eligibility Criteria

We identified 59 Phase 3 RCTs, 29 for UC and 30 for CD. The year of study initiation ranged from 2000 until 2022 (Table 1). We could not find the full EC list for 3 CD clinical trials and therefore excluded them from the analysis (C87031, ELN100226-CD307 and INTREPID). The median (IQR) number of ECs per trial was 44 (38–49) with a median of 10 (9–11) inclusion criteria and 33 (29–39) exclusion criteria. There was no significant change in the number of ECs over time ($p = 0.26$) (Figure 1). Figure 2 shows the distribution of the number of inclusion and exclusion criteria and the year of study start.

3.2 | Eligibility Criteria Categories

3.2.1 | Patient Characteristics

Twenty-two (39.3%) clinical trials included paediatric (≥ 12 years old) or adolescent (≥ 16 years old) patients. The inclusion of this younger patient population has only been observed in IBD clinical trials that initiated in 2015 or later. These patient populations mostly had to meet additional criteria regarding minimum weight, body mass index, or Tanner stage. Twenty-four (42.9%) clinical trials had no upper limit of age for inclusion, but the other clinical trials did have an upper limit of age, ranging from 75 to 80 years old.

Most (94.6%) clinical trials required a minimum duration of IBD diagnosis before the patient could be enroled in the clinical trial, ranging from 3 to 6 months. Histopathological confirmation of the disease was necessary in 44 (78.6%) IBD clinical trials.

Patients with severe, progressive, or uncontrolled comorbidities were usually excluded. Nine (16.1%) clinical trials (8 UC trials and 1 CD trial) specifically excluded patients with primary sclerosing cholangitis, regardless of the liver test results.

Infections, mainly tuberculosis, hepatitis B and C, human immunodeficiency virus infection and gastrointestinal infections (e.g., *Clostridioides difficile*), were frequently part of the exclusion criteria. Other infections that were exclusionary in some of the reviewed IBD clinical trials were listeriosis, histoplasmosis, coccidioidomycosis, hepatitis *A*, hepatitis *E*, corona virus infection, cytomegalovirus colitis, history of recurrent herpes zoster, history of disseminated herpes zoster or herpes simplex and opportunistic infections.

Two-thirds (62.5%) of the IBD clinical trials allowed inclusion of patients with prior malignancies on the condition that they did not occur in the past 5 or 10 years. All other trials except one (ENACT-1) did not allow patients with prior malignancies. Nearly all IBD clinical trials (96.4%) did however make an exception for patients with treated cutaneous squamous cellular carcinomas or basocellular carcinomas. Patients with unresected colonic adenomas were not allowed to participate, and sometimes (in 32.1% of trials) resected colonic dysplasia lesions were exclusionary for the patient to be enroled.

Women who were trying to conceive, pregnant, or nursing were not allowed in any of the trials. Some trials (55.4%) also excluded men who planned to father a child while being enroled. Double-barrier contraception was required in a minority of the trials (10.7%).

An overview of the exclusion criteria used concerning patient characteristics across the different IBD clinical trials is listed in Table 2.

3.2.2 | Disease Activity

Until 2017, disease activity in the UC clinical trials was measured using the total Mayo score. From 2018 onwards, the total Mayo score shifted to the modified Mayo score, eliminating physician global assessment.

For the CD clinical trials, clinical disease activity was measured using the Crohn's Disease Activity Index (CDAI) until 2011. Afterwards, clinical disease activity was measured using either a combination of the CDAI and/or two-component Patient-Reported Outcome (PRO2) or using the PRO2 only. Endoscopic disease activity assessment was required from 2015 onwards through the Simple Endoscopic Score for Crohn's disease (SES-CD).

An overview of the inclusion criteria used concerning disease activity across the different IBD clinical trials is shown in Table 3.

3.2.3 | Disease Phenotypes

Patients with IBD type unclassified (IBD-U), an ostomy, pouch, isolated upper gastrointestinal involvement of CD, and short bowel syndrome were excluded from all IBD clinical trials.

Ulcerative proctitis (UP) was excluded in all but two recent UC clinical trials (ELEVATE UC 52 and 12). Definitions of proctitis varied from disease 'limited to the rectum' to disease limited to 10, 15 or 20 cm from the anal verge.

Strictures were not allowed in CD clinical trials if they were either symptomatic, impassable, or caused prestenotic dilatation. One clinical trial (ACCENT I) did not allow any kind of stricture. Intra-abdominal and peri-anal abscesses were also excluded. The inclusion of CD patients with fistulas varied and depended on the fistula's location (enterocutaneous, internal or perianal), whether it was actively draining, and if a seton was in place or surgery was required. Eleven (40.7%) CD clinical trials also required sufficient remaining bowel for entry in the clinical trial, defined as no ileorectal anastomosis, not ≥ 2 or 3 resections, not > 2 missing segments, ≥ 3 segments remaining or > 25 cm of colon still in place.

3.2.4 | Concomitant and Prior Medication

As concomitant or prior medication, 5-aminosalicylic acids and steroids were allowed in all clinical trials, but the requirements for

TABLE 1 | Characteristics of inflammatory bowel disease clinical trials.

	Ulcerative colitis						
	Mode of action	**Drug**	**Protocol**	**ClinicalTrials.gov ID**	**Year study start**	**Year study stop**	**Number of EC**
Biologicals	Anti-TNFα	Infliximab	ACT 1	NCT00036439	2002	2007	58
			ACT 2	NCT00096655	2002	2007	58
		Adalimumab	ULTRA 1	NCT00385736	2006	2009	34
			ULTRA 2	NCT00408629	2006	2010	33
		Golimumab	C0524T16	NCT00488774	2007	2009	53
			C0524T17	NCT00487539	2007	2010	53
	Inhibit T-cell activation	Abatacept	IM101-108	NCT00410410	2006	2009	49
	Anti-integrin	Vedolizumab	GEMINI I	NCT00783718	2009	2012	38
		Etrolizumab	HICKORY	NCT02100696	2014	2020	65
		Ontamalimab	FIGARO UC 301	NCT03259334	2017	2020	42
			FIGARO UC 302	NCT03259308	2017	2020	44
	Anti-MMP9	Andecaliximab	TRIUMPH	NCT02520284	2015	2016	31
	Anti-IL-(12/)23	Ustekinumab	UNIFI	NCT02407236	2015	2021	52
		Risankizumab	INSPIRE	NCT03398148	2018	2023	36
		Mirikizumab	LUCENT 1	NCT03518086	2018	2024	45
		Guselkumab	QUASAR	NCT04033445	2019	Ongoing	56
			ASTRO	NCT05528510	2022	Ongoing	51
	Anti-IL36-receptor	Spesolimab	BI1368-0005	NCT03482635	2018	2020	30
Small molecules	JAK-inhibitor	Tofacitinib	OCTAVE	NCT01458951	2012	2015	46
		Filgotinib	SELECTION 1	NCT02914522	2016	2020	40
		Upadacitinib	U-ACHIEVE	NCT02819635	2018	2021	50
			U-ACCOMPLISH	NCT03653026	2018	2021	50
		Izencitinib	RHEA	NCT03758443	2019	2021	38
		Ivarmacitinib	RSJ10135	NCT05181137	2021	Ongoing	35
	S1P receptor modulator	Ozanimod	RPC01-3101	NCT02435992	2015	2020	48
		Etrasimod	ELEVATE UC 52	NCT04176588	2019	Ongoing	45
			ELEVATE UC 12	NCT03996369	2020	2021	45
	miR-124 upregulator	Obefazimod	ABTECT-1	NCT05507203	2022	Ongoing	34
			ABTECT-2	NCT05507216	2022	Ongoing	34
Crohn's Disease							
Biologicals	Anti-TNFα	Infliximab	ACCENT I	NCT00207662	2000	2005	30
		Adalimumab	CHARM	NCT00077779	2003	Unknown	37
			GAIN	NCT00105300	2004	Unknown	37
		Certolizumab Pegol	C87085	NCT00552058	2008	2009	39
			C87031[a]	NCT00152490	2003	2005	NA
	Anti-integrin	Natalizumab	ENACT-1	NCT00032799	2001	2003	19
			ELN100226-CD307[a]	NCT00078611	2004	2005	NA
		Vedolizumab	C13007	NCT00783692	2008	2012	40
			C13011	NCT01224171	2010	2012	39
		Etrolizumab	BERGAMOT	NCT02394028	2015	2021	69

(Continues)

TABLE 1 | (Continued)

	Ulcerative colitis						
	Mode of action	**Drug**	**Protocol**	**ClinicalTrials.gov ID**	**Year study start**	**Year study stop**	**Number of EC**
		Ontamalimab	CARMEN CD 306	NCT03566823	2018	2020	49
			CARMEN CD 305	NCT03559517	2018	2020	49
	Inhibits T-cell activation	Abatacept	IM101-084	NCT00406653	2006	2009	51
	Anti-IL-(12/)23	Ustekinumab	UNITI 1	NCT01369329	2011	2013	39
			UNITI 2	NCT01369342	2011	2014	39
		Risankizumab	ADVANCE	NCT03105128	2017	2021	39
			MOTIVATE	NCT03104413	2017	2021	37
		Guselkumab	GALAXI	NCT03466411	2018	Ongoing	49
			GRAVITI	NCT05197049	2022	Ongoing	49
		Brazikumab	INTREPID[a]	NCT03759288	2018	2023	NA
		Mirikizumab	I6T-MC-AMAM	NCT03926130	2019	2023	48
Small molecules	CCR9 antagonist	GSK1605786 A	SHIELD-1	NCT01277666	2010	2013	38
	SMAD7 antisense oligonucleotide	Mongersen	GED-0301-CD-002	NCT02596893	2015	2018	41
			GED-0301-CD-003	NCT02974322	2017	2018	43
	JAK-inhibitor	Filgotinib	DIVERSITY 1	NCT02914561	2016	2022	40
		Upadacitinib	U-EXCEED	NCT03345836	2017	2021	48
			U-EXCEL	NCT03345849	2017	2022	48
	S1P receptor modulator	Ozanimod	RPC01-3201	NCT03440372	2018	Ongoing	54
			RPC01-3202	NCT03440385	2018	2023	54
		Etrasimod	CULTIVATE	NCT04173273	2020	Ongoing	32

Abbreviations: CCR9, chemokine receptor 9; EC, eligibility criteria; ID, identification; IL, interleukin; JAK, Janus kinase; miR-124, microRNA-124; MMP, matrix metalloproteinase; NA, not applicable; S1P, sfingosine-1-phosphate; TNF, tumour necrosis factor.
[a]As a full list of eligibility criteria was not available for this trial, it was excluded from further analyses.

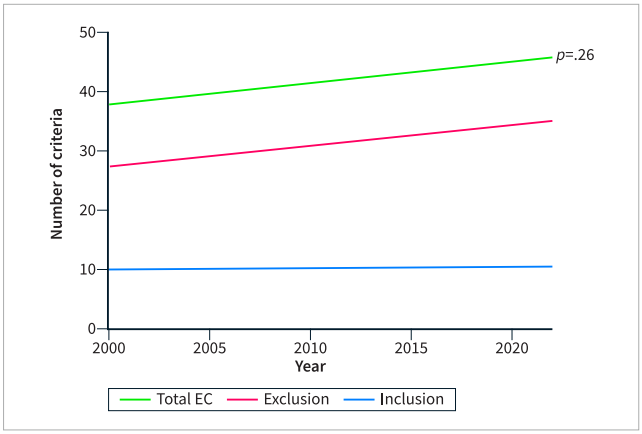

FIGURE 1 | Evolution in the number of eligibility criteria (EC) in inflammatory bowel disease clinical trials over time.

maximum dose, duration of treatment, and duration of stable dosage varied across the different studies. Twelve (21.4%) clinical trials did not allow immunomodulators as concomitant medication. Rectal therapies with 5-aminosalicylic acids and steroids were not allowed in any of the UC trials. Previous use of biologics and/or small molecules was allowed, but with a mandatory washout period (ranging from 2 weeks to 1 year) or undetectable serum levels. Since 2015, a cap on the number of previously used biologics and/or small molecules was occasionally added. Other concomitant medications were not allowed if they could interact with the metabolism of the investigational medicinal product.

3.2.5 | Laboratory Evaluations

Blood tests to check for eligibility were required during the screening period, including haematology, renal function, hepatic function, albumin and activated partial thromboplastin time (APTT). The different tests required and the corresponding cut-offs varied across the different IBD clinical trials (Table 4).

The most relevant changes in EC types over time are highlighted in Figure 3.

4 | Discussion

Previous research in the field of clinical trial EC has shown that the number of EC continues to rise [15, 16]. In thoracic oncology clinical trials, the median number of ECs significantly increased from 21 to 46 over a 30 year time period [16]. Our results,

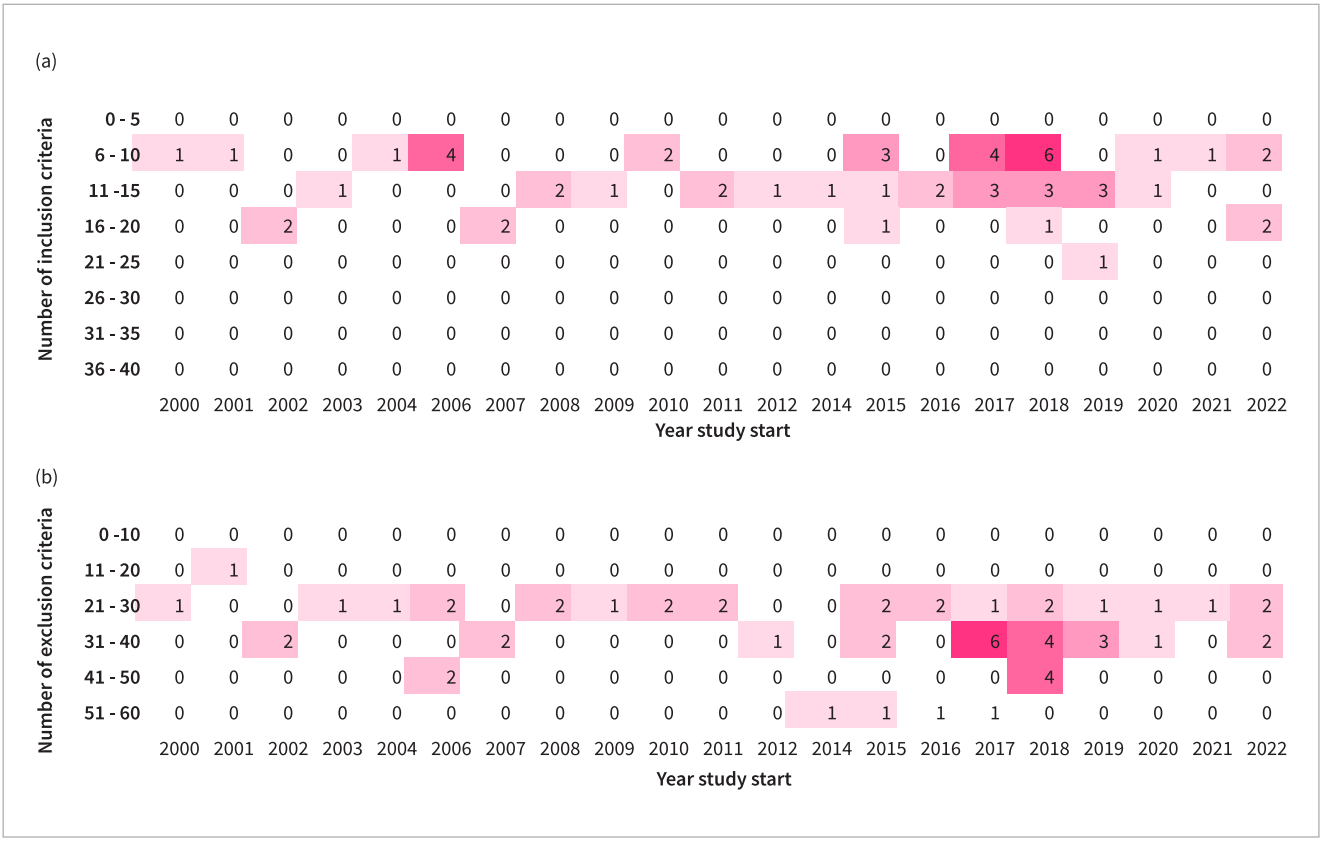

FIGURE 2 | Heatmap of the number of inclusion (a) and exclusion (b) criteria in inflammatory bowel disease clinical trials and year of study start.

however, did not show any significant increase in the number of ECs in IBD clinical trials in the last 20 years, although this has been suggested [8].

Our analysis showed that ECs used in IBD clinical trials are restrictive. Common patient populations are excluded by using criteria for patient characteristics, disease activity, disease phenotype, prior and concomitant medication and laboratory tests. Ha et al. showed earlier that only 31.1% of IBD patients with moderate-to-severe disease activity encountered during routine clinical practice would be eligible to participate in an RCT of biologics [6]. Vieujean et al. showed that only 38.7% of IBD patients with symptomatic disease, for whom a change of treatment was deemed to be required, were offered an RCT by their treating IBD physician. Reasons related to EC were the presence of comorbidities, prior exposure to multiple biologics, and isolated proctitis [17].

Almost two-thirds of IBD clinical trials reviewed in this study used an upper age limit of 75 or 80 years old for inclusion, which should be questioned given today's ageing population [18]. Indeed, patients aged 65 or older are the fastest-growing subpopulation of people with IBD due to both an ageing population of previously diagnosed cases and newly diagnosed elderly-onset cases [19]. Our findings confirm previous research showing that older adults are frequently excluded from IBD clinical trials because of their chronological age but also because of comorbidities, a history of dysplasia or cancer, and prior exposure to IBD treatments [10]. The assessment of frailty and functional capacities seems to be a better approach than screening solely by age to stratify the risk of adverse events.

Two-thirds of the reviewed IBD clinical trials allowed the inclusion of patients with prior malignancies, but on the condition that they did not occur in the past 5 or 10 years. However, a meta-analysis suggested that anti-TNF therapy, conventional immunosuppressant therapy, or combination immunosuppression are not associated with an increased risk of cancer recurrence in patients with chronic immunologic diseases [20]. Nevertheless, a careful discussion with the treating oncologist, taking into account the natural history of cancer, histologic type and stage, time from diagnosis, and course of underlying chronic inflammatory disease, should take place before enrolling in a clinical trial with immunosuppressive drugs.

The EC for disease activity has become more objective over time; for UC, the total Mayo score was replaced by the modified Mayo score in 2018, eliminating the physician global assessment. For CD, endoscopic disease activity was required since 2015. However, the currently used disease activity scoring systems are outdated and do not fully capture the complexity and severity of the disease [21]. Also, the definitions of moderate-to-severe IBD used in clinical trials are often not applied in clinical practice when determining the need for advanced therapies.

We also observed that the number of previously used biologics and/or small molecules was occasionally capped in the eligibility criteria in IBD clinical trials since 2015. Sponsors want to

TABLE 2 | Overview of exclusion criteria concerning patient characteristics.

Age	Lower limit		12 yo or 16 yo or 18 yo
	Upper limit		75 yo or 80 yo or no upper limit
IBD diagnosis	Less than 3, 4 or 6 m		
Comorbidities	Renal		
	Hepatic (primary sclerosing cholangitis)		
	Haematologic		
	Endocrine		
	Pulmonary		
	Cardiac		
	Neurologic		
	Psychiatric		
	Others		
Infections	*Mycobacterium tuberculosis*	Active	Untreated and sometimes treated
		Latent	Untreated and sometimes treated
	Hepatitis B virus	Active	
	Hepatitis C virus	Untreated	
	Human immunodeficiency virus	Positive	
	Gastrointestinal	Untreated	
	Others		
Malignancies	Prior		5 or 10 y or never
	Current		
Colonic adenomas	Unresected and sometimes resected		
Reproduction/Reproductive health	Trying to conceive		
	Pregnancy		
	Nursing		

Abbreviations: IBD, inflammatory bowel disease; m, months; y, years; yo, years old.

TABLE 3 | Overview of inclusion criteria concerning disease activity.

UC	Total mayo score	Between 6 and 12	AND	Endoscopy subscore	≥ 2
	2000–2017			(Stool frequency	≥ 1)
				(Rectal bleeding	≥ 1)
				(Physician global assessment	≥ 2)
	Modified mayo score	Between 4 or 5 and 9	AND	Endoscopy subscore	≥ 2
	2018–2022			(Rectal bleeding	≥ 1)
CD	CDAI	Between 220 and 400, 450 or 480			
	2000–2022				
	PRO2	Stool frequency	≥ 4 or 3.5		
	2012–2022	AND/OR			
		Abdominal pain	≥ 2		
		OR			
		Total	≥ 14		
	SES-CD	≥ 6 or 7 (or ≥ 3[a])			
	2015–2022	≥ 3 or 4 for isolated ileal disease			

Abbreviations: CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; PRO-2, two-component patient-reported outcome; SES-CD, simple endoscopic score for Crohn's disease; UC, ulcerative colitis.
[a]Only in ADVANCE protocol.

TABLE 4 | Cut-offs used for laboratory tests in inflammatory bowel disease clinical trials.

		Most strict cut-off	Least strict cut-off	
Liver	AST	> 1.5 × ULN	> 3 × ULN	
	ALT	> 1.5 × ULN	> 3 × ULN	
	AP	> 1.5 × ULN	> 3 × ULN	
	Total bilirubin	> 1.5 × ULN or ≥ 2 mg/dL	≥ 3 × ULN	Except Gilbert's syndrome
	Direct bilirubin	> 1.5 × ULN or ≥ 1 mg/dL		
Kidney	Creatinin	> 1,5 × ULN or > 1.4 mg/dL	> 2 × ULN or > 1.7 mg/dL	
	eGFR	< 40 mL/min	< 30 mL/min	
Haematology	Haemoglobin	< 9 g/dL	< 7.5 g/dL	
	WBC count	$< 3.5 \times 10^9$/L	$< 2.5 \times 10^9$/L	
	Neutrophils	$< 2.0 \times 10^9$/L	$< 1.0 \times 10^9$/L	
	Lymphocytes	$< 0.8 \times 10^9$/L	$< 0.5 \times 10^9$/L	
	Platelets	$< 100 \times 10^9$/L or $> 1000 \times 10^9$/L	$> 1200 \times 10^9$/L	
Albumin		< 2.0 g/dL		
APTT		> 1.5 × ULN		

Abbreviations: ALT, alanine aminotransferase; AP, alkaline phosphatase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; ULN, upper limit normal; WBC, white blood cell.

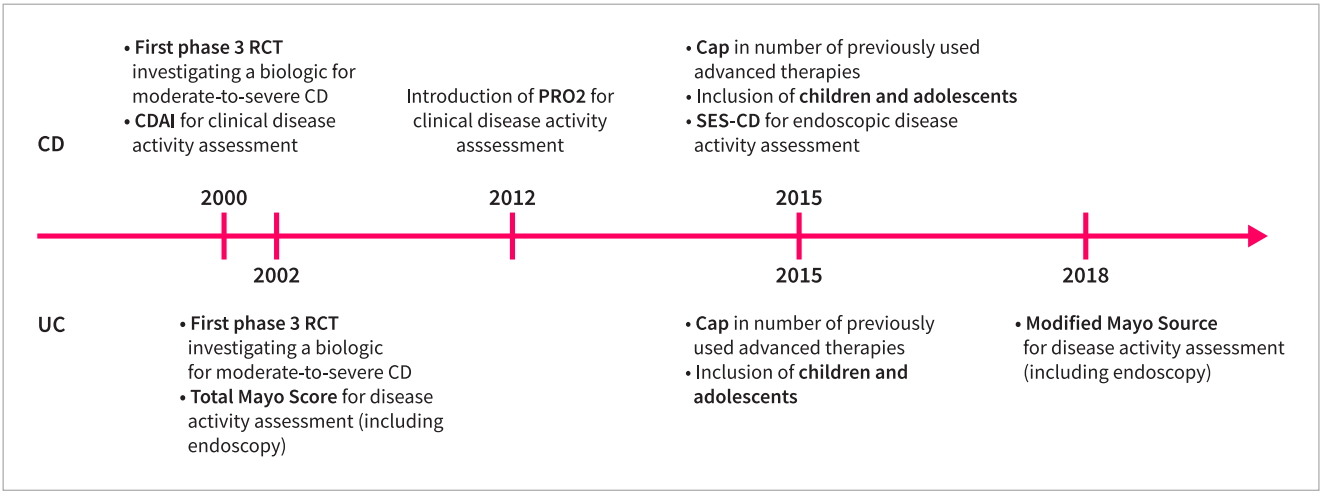

FIGURE 3 | Evolution of types of eligibility criteria in inflammatory bowel disease (IBD) clinical trials over time. CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; PGA, physician global assessment; PRO2, two-component patient-reported outcome; RCT, randomised controlled trial; SES-CD, simple endoscopic score for Crohn's disease; UC, ulcerative colitis.

avoid including highly refractory patients, probably less likely to respond to the study drug. However, because the medical armamentarium in IBD is becoming larger, the added value of a new drug only benefiting the more therapy-responsive patient population becomes questionable. New modes of actions or a combination of existing agents which can provide a meaningful benefit beyond the already existing armamentarium should be explored. Also, patients tend to prefer a commercially available drug over an RCT to avoid the risk of receiving placebo, but this results in more therapy refractory patients that would consider a study drug in an RCT.

Certain disease phenotypes were usually excluded from IBD clinical trials. IBD type unclassified is a case of uncertain diagnosis, with the majority of IBD-U cases evolving to a definite diagnosis of UC over time [22]. Since most biologics and small molecules have proven efficacy in both UC and CD, it should be appropriate to include IBD-U patients in UC clinical trials. Ulcerative proctitis patients have also been excluded from UC clinical trials because of the belief that UP is more refractory to response. Real-world data does however show comparable clinical outcomes in this patient population [23]. Also, two UC clinical trials investigating etrasimod showed comparable efficacy outcomes between the overall study population and the proctitis subpopulation [24]. Stricturing and penetrating CD might prevent a correct measurement of disease activity and increase the risk of hospitalisation and surgery [25]. However, CD patients with asymptomatic strictures, fistula's without the presence of abscesses, and missing colonic segments, are not believed to compromise the efficacy and safety outcomes of a new study drug and should therefore be considered for inclusion in CD clinical trials [14].

Besides the EC being restrictive, we also observed that EC in IBD clinical trials has become more complex. Since 2012, disease activity in CD clinical trials was measured using either a combination of the CDAI and PRO2 or using only PRO2. More heterogeneity is found in the allowed maximum dose, time since start and time on stable dose for concomitant medications, wash-out periods of biologics and small molecules, and required blood tests and their corresponding cut-offs. These small but important differences might lead to confusion among investigators and thus risk more screening failures. Moreover, the recommendations for concomitant medication, including the wash-out periods of advanced therapies, that are used in IBD clinical trials, are not part of routine clinical practice and limit patient recruitment.

Efforts should be made to broaden and homogenise the EC in IBD clinical trials. The Food and Drug Administration formulated a guidance on broadening EC in clinical trials to ensure that the study population better reflects the patient population likely to use the drug in clinical practice [3]. Also, the American Gastroenterological Association performed a roundtable meeting with different stakeholders involved in IBD clinical trial design and proposed solutions for inclusion of patients traditionally excluded from clinical trials [26]. The International Organisation for the Study of Inflammatory Bowel Disease formulated recommendations to broaden clinical trial eligibility that were found to be both appropriate and feasible [14]. Nevertheless, these recommendations are not legally binding and thus implementation by the industry remains a challenge. Also, the effect of broadening EC on efficacy and safety outcomes should be investigated to evaluate feasibility.

A limitation of this research is the inconsistency seen in the numbering of EC across the protocols. Some protocols gave more or less numbered criteria to express the same message. Next, the rationale of the EC is usually not mentioned in the protocols, which makes it difficult to interpret whether these ECs are justified. Another limitation is the selection of only Phase 3 placebo-controlled trials, biasing the study population towards a more homogeneous population. Nevertheless, we conducted a thorough analysis using expert knowledge and practical experience, collaborating with a broad IBD study team and utilising the study protocols available on our own IBD platform.

5 | Conclusion

This study showed that the median number of eligibility criteria for IBD clinical trials did not significantly increase in the last 20 years. The eligibility criteria are however restrictive and complex, limiting the generalisability of efficacy and safety outcomes to the actual patient population. Future research is needed to investigate the impact of broadening EC in IBD clinical trials.

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Conflicts of Interest

Marc Ferrante—Research support: AbbVie, Amgen, Biogen, Janssen, Pfizer, Takeda and Viatris. Speaker's fees: AbbVie, Amgen, Biogen, Boehringer Ingelheim, Falk, Ferring, Janssen-Cilag, Lamepro, MSD, Mylan, Pfizer, Sandoz, Takeda and Truvion Healthcare. Consultancy fees: AbbVie, Boehringer Ingelheim, Celgene, Celltrion, Eli Lilly, Janssen-Cilag, Medtronic, MSD, Pfizer, Samsung Bioepis, Sandoz, Regeneron, Takeda and Thermo Fisher.

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Bram Verstockt—Research support: Pfizer; Speaker's fees: Abbvie, Biogen, Chiesi, Falk, Ferring, Galapagos, Janssen, MondayNightIBD, MSD, Pfizer, R-Biopharm, Takeda and Truvion. Consultancy fees: Alimentiv, Applied Strategic, Atheneum, Bristol Myers Squibb, Guidepont, Ipsos, Janssen, Progenity, Sandoz, Sosei Heptares and Takeda.

An Outtier, Rosanne Janssens, Liese Barbier and Isabelle Huys declare no conflicts of interest.

Data Availability Statement

Data underlying this article will be shared indefinitely upon reasonable request to the corresponding author. The data will be shared through a secure file transfer system for person-to-person email communication.

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