Assessing the Uptake of Core Outcome Sets in Randomized Controlled Trials for Inflammatory Bowel Disease: A Cross-Sectional Study

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To ensure transparency and reproducibility, our data and manuscript were uploaded to Open Science framework (OSF). Any changes to the protocol, will also be specified and uploaded on OSF. https://osf.io/s8zxw/

Abstract

Background
Increasing prevalence and significant medical expenses associated with Inflammatory Bowel Disease (IBD) necessitate high-quality clinical research to evaluate treatment effectiveness. Randomized control trials (RCTs) provide robust evidence, but the diversity of outcomes used in these trials poses challenges in summarizing outcomes for systematic reviews. Core Outcome Sets (COS) were established to improve the comparability of outcomes across studies. The aim of this study is to examine the uptake of the COS for IBD within clinical trials.

Methods
This cross-sectional analysis involved screening ClinicalTrials.gov for RCTs evaluating outcomes in patients with IBD. We extracted information on the four outcome domains — (1) symptoms, function, and quality of life; (2) disutility of care; (3) healthcare utilization; and (4) survival and disease control — and trial characteristics. Extraction was performed in a masked, duplicate manner.

Results
The initial search identified 3,205 trials from ClinicalTrials.gov, and after exclusions, the final sample included 177 clinical trials for analysis. The uptake of COS over time was not statistically significant. The most frequently reported outcomes were change in bowel symptoms (88.1%, 156/177) and pain or discomfort (83.1%, 147/177). In contrast, no trial reported on colorectal cancer, only 1% (2/177) reported overall survival, and 8% (15/177) reported cause of death.

Conclusion
Our study revealed no increase in adherence to COS in IBD clinical trials, before or after the publication of the IBD COS. We recommend that trialists make efforts to implement COS in clinical trials to improve the standardization across studies in the field of IBD.

Key Words: Inflammatory Bowel Disease, Core Outcome sets, and ClinicalTrials.gov

Introduction

Inflammatory bowel disease (IBD) – consisting of Crohn's disease and ulcerative colitis – currently affects 4.9 million adults worldwide.[1] Furthermore, the incidence of this disease is increasing with over 70,000 new cases diagnosed each year.[2] With in increasing incidence, cost associated with care has risen over time. From 1996 to 2016, the annual U.S. health care spending on IBD increased from $6.4 billion to $25.4 billion and is projected to increase even further.[3] Additionally, a 2020 study showed that patients with IBD spend three times as much in direct cost, and more than twice as much in out-of-pocket costs compared to non-IBD patients.[4] Given the increasing prevalence and significant medical expenses accrued by patients with IBD, it is vital that clinical research assessing the effectiveness of IBD treatments be of the highest quality.

One challenge with IBD research is that the unclear pathogenesis and multifactorial nature has resulted in the development of a variety of interventions.[5] Treatment options are typically established through their success in randomized controlled trials (RCTs). RCTs can be compiled into systematic reviews that summarize outcomes in a more concise, relevant format that physicians use as a guide for clinical practice. [6,7] However, there is a variety of outcomes used in clinical trials, which may lead to difficulty summarizing outcomes in systematic reviews. The lack of standardization of outcomes leads to measurements that are not comparable and limits progression of therapeutic advancement.[8] In an effort to overcome the variability in outcomes being reported in IBD research, Kim *et al*. published a core outcome set (COS) in 2018.[9]

A COS is a standardized set of minimum outcomes specific to a disease or set of conditions that should be measured and reported in all clinical trials.[10] These sets are developed through consensus meetings with invested parties – physicians, patients, and trialists – that agree upon outcomes which are both clinically and academically relevant. The consistent use of COSs by RCTs will lead to more comparable outcomes that are easily synthesized into reliable evidence for clinicians to use in their practices.[10] In a study looking at COS uptake in rheumatoid arthritis, the use of COS proved to minimize the difference and range of outcomes measured in the field, and ensured that relevant outcomes were being reported.[11] Presently, no study has analyzed the implementation of COS in RCTs assessing IBD interventions. Therefore, the purpose of our study is to analyze the uptake of COS by IBD clinical trials before and after its time of publication.

Methods

Reproducibility and Study Design

Prior to study start, a pilot test of the search strategies, inclusion criteria, and data extraction materials was performed. In an effort to ensure inclusive reporting of our findings, we adhered to the PRISMA 2020 checklist.[12] Our methodology was uploaded to Open Science Framework to establish transparency and reproducibility of data.[13] Our protocol was submitted to the Institutional Review Board, and it was determined that our study did not involve human subjects, in accordance with 45 CFR 46.102 (d) and (f) the US Department of Health and Human Services' Code of Federal Regulations.[14]

Search Strategy

We identified the COS developed by Kim *et al.* in 2018 through the Core Outcome Measures in Effectiveness Trials (COMET) Initiative COS database for uptake analysis of outcomes.[15] The COMET Initiative serves as an online database for COSs in order to aid and encourage the uptake of COSs in all fields of medicine.[15] To identify phase III/IV RCTs involving IBD, we used the ClinicalTrials.gov database, an electronic clinical trial registry. ClinicalTrials.gov automatically searches for synonyms that are specific to certain conditions and diseases, and we have included these search terms in Supplemental File 1. We applied the following filters to our search: "conditions: inflammatory bowel disease", "study type: interventional studies", "phase: 3 and 4", "date: 03/28/2013 to 06/26/2023," and no restrictions regarding recruitment status. Only phase III/IV clinical trials were considered because this study follows Kirkham's methodology which is specific to interventional studies.[11] Trials from 2013-2023 were examined in order to assess the difference in COS uptake in five years pre COS publication and the five years post COS publication.

Training

Prior to screening and extraction, all investigators completed training on the purposes and methodology of COS development and use. To further promote reliable data extraction, training consisted of group discussion and review of the COMET Initiative handbook.[16] COS development training videos and presentations were provided by the COMET Initiative COS tutorial website.[17]

Screening/Eligibility Criteria

Criteria for RCT study inclusion consisted of the following: subjects are patients with IBD, study was registered five years prior to publication of the COS to the search date on June 26, 2023, and assessed the effectiveness or efficacy of interventions. Any trial failing to meet the criteria listed prior, such as those not exclusively focused on IBD, non-randomized trials, those focused on drug pharmacokinetics/pharmacodynamics, those focused on diagnostic test accuracy, and single-group assignment trials, were excluded from the study. We compiled all RCTs that met inclusion criteria into a Google Sheet for screening. Two investigators (AS, AK) in the initial screen independently assessed clinical trial registries in a masked, duplicate fashion to determine inclusions. Afterwards, both investigators reconciled inclusion/exclusion study decisions, defaulting to a third investigator (TM) if a consensus could not be reached.

Data Extraction

Two authors (AS, AK) extracted the general study characteristics and comprehensive COS uptake of included trials in a masked, duplicate fashion via a pilot-tested Google Form. Characteristics were as follows: year of trial start date, National Clinical Trial number, trial continent affiliation(s), whether the trial was registered before/after publication of COS, recruitment status, phase of trial, funding type, enrollment number, trial duration, and intervention type. Outcome measures were included in the Google Form, as defined by the authors of the COS, which can be seen in . In addition, authors recorded the type of measurements used, if available. In cases where a trial included "adverse events" as an outcome,

we categorized the corresponding COS outcome of "occurrence and impact of complication from an IBD intervention" as a "yes". The first five RCTs within the sample were used for training, where two investigators (AS, AK) extracted data independently, discussing and resolving any discrepancies. The remaining extraction was conducted in the same fashion, with reconciliation occurring upon completion. For training and remaining extraction, a third investigator (TM) was consulted to resolve discrepancies.

inflammatory; inflamed; inflammatories

inflammatory bowel disease; Inflammatory Bowel Diseases; bowel diseases inflammatory; IBD - inflammatory bowel disease; disease inflammatory bowel; Idiopathic chronic inflammatory bowel disease

bowel; Intestinal; Gut; Intestine bowel disease; Intestinal Diseases;

bowel diseases; Enteropathy; Intestinal Disease; intestinal disorder; intestinal disorders; disease intestinal; bowel disorders disease.

Diseases; Disorders; disorder; Diagnosis; condition; disease type

Supplemental 1.

Table 1. Core Outcomes Identified by Kim et al.

Outcome	Measurement	Timing	Source of Data
Symptoms, Functions, and Quality of Life	Tracked the following measurements using the IBD-Control Questionnaire (Change in Bowel Symptoms, Missing Planned Activities, Night Symptoms, Pain or Discomfort, Energy and Fatigue, Feel Anxious or Depressed, Overall Control over IBD, Weight, and Fistula Symptoms*)	Baseline and 6-monthly	Patient Reported
Disutility of Care	Steroid Use; Occurrence of Complication from an IBD Intervention	Baseline and Annual Follow-Up	Clinician Reported
Healthcare Utilization	Time Spent in Hospital	Baseline and Annual Follow-Up	Clinician Reported
Survival and Disease Control	Presence of Anemia	Baseline and 6-monthly	Clinician Reported
	Disease Activity and Remission	Baseline and 6-monthly	Patient and Clinician Reported
	Colorectal Cancer	Baseline and Annual Follow-Up	Clinician Reported
	Overall Survival	Baseline and Annual Follow-Up	Clinician Reported
	Cause of Death	Baseline and Annual Follow-Up	Clinician Reported

Supplemental 2.

Data Analysis

Descriptive statistics were employed to identify the characteristics of the trials in our sample. Our primary analysis involved an interrupted time series to assess the adoption of the IBD COS in trials before and after its publication. Using this analysis, our aim was to evaluate the relationship between the percentage of COS adherence over time. For each trial, we calculated the percentage of adherence to the COS- the number of COS outcomes measured in relation to the number of outcomes in the published COS- which we will define as the "COS-defined outcomes". Additionally, we computed the mean percentage of COS outcome completion for each month during a one-year period following the COS publication. After the COS publication, a one-year period was allowed for uptake. After the data point calculations, the ITSA command in STATA [Stata/BE 17.0 (StataCorp, LLC, College Station, TX)], R (version 4.2.1), and RStudio were used for the analysis. The Newey West method was employed to estimate standard errors. Secondly, we used one-way ANOVAs to assess the effects of 'Funding Type', 'Recruitment Status', and 'Continent' on the variation of "COS-defined outcomes". A Pearson correlation analysis was used to determine the relationship between 'Enrollment Number' and the percent of COS outcomes measured. We uploaded all statistical analysis approaches, original data, and final reconciled data to OSF.

Results

Trial Inclusions and Exclusions

Our search of ClinicalTrials.gov identified 3,205 records. After filtering by wrong trial phase and wrong date, 360 trials remained for screening. Following trial screening, 183 additional trials were excluded because they did not meet inclusion criteria. Our final sample consisted of 177 clinical trials for data extraction (Figure 1).

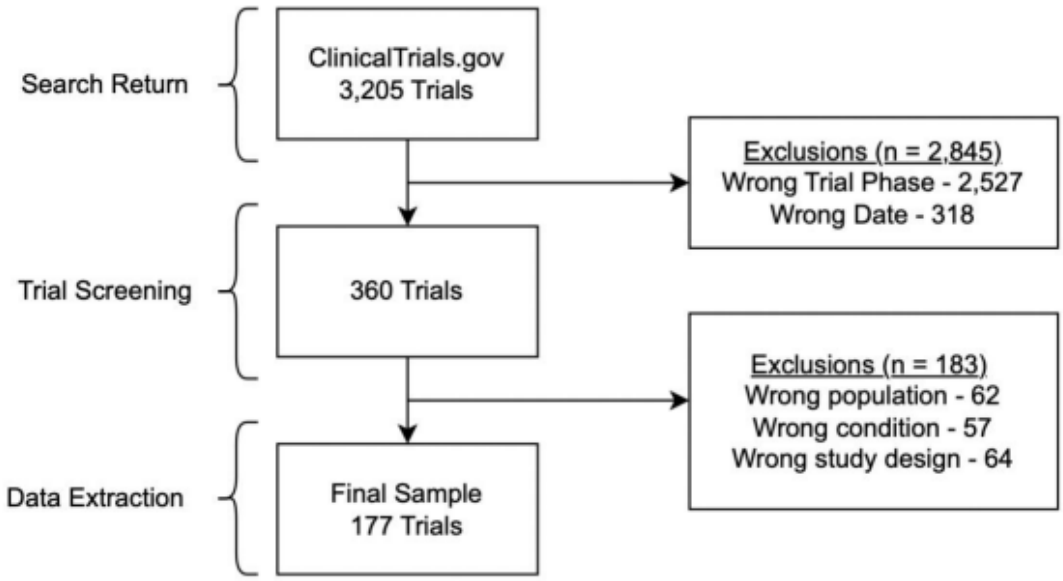

Figure 1: Figure 1 represents our PRISMA Flow diagram which demonstrates the systematic review process followed in this project. The initial search of ClinicalTrials.gov identified 3,205 records. After filtering by wrong trial phase and wrong date, 360 trials remained for screening. Following trial screening, 183 additional trials were excluded because they did not meet inclusion criteria. The final sample consisted of 177 clinical trials for data extraction.

Trial Characteristics

The median duration of the clinical trials in our sample was 38 months. A portion of the (75/177; 42.37%) of the trials were conducted over multiple continents. The recruitment status of the trials were primarily either completed (56/177; 31.64%) or currently recruiting (43/177; 24.29%), with only 12.43% (22/177) having an unknown status. The majority of interventions tested were biologics (64/177; 36.16%) followed by multiple interventions (51/177; 28.81%). Only two trials (2/177;1.13%) solely used corticosteroids as an intervention. In addition, 71.75% (127/177) were phase 3 trials and only 28.25% (50/177) were phase 4. Further, 52.54% (93/177) of the trials were sponsored by industry while only 1.69% (3/177) had a private sponsor. Additional information regarding trial characteristics can be found in Table 1.

Table 1. Trial Characteristics

Characteristic	**N = 177**
Year, n (%)	
2018	28 (15.82)
2016	23 (12.99)
2017	21 (11.86)
2019	21 (11.86)
2022	16 (9.04)
2014	15 (8.47)
2015	14 (7.91)
2020	14 (7.91)
2021	11 (6.21)
2023	8 (4.52)
2013	6 (3.39)
Phase, n (%)	
3	127 (71.75)
4	50 (28.25)
Continent, n (%)	
Multiple	75 (42.37)
Europe	41 (23.16)
Asia	34 (19.21)

Characteristic	N = 177
North America	20 (11.29)
Africa	3 (1.69)
Australia	3 (1.69)
South America	1 (0.56)
Recruitment Status, n (%)	
Completed	56 (31.64)
Recruiting	43 (24.29)
Unknown	22 (12.43)
Terminated	21 (11.86)
Active, but No Recruiting	17 (9.60)
Not Yet Recruiting	10 (5.65)
Withdrawn	6 (3.39)
Enrolling by Invitation	1 (0.56)
Suspended	1 (0.56)
Funding Type, n (%)	
Industry	93 (52.54)
Multiple Without Industry	30 (16.95)
Hospital	24 (13.56)
University	14 (7.91)
Multiple With Industry	13 (7.34)

Characteristic	N = 177
Private	3 (1.69)
Enrollment Number, Median (IQR)	196 (84 – 482)
Trial Duration in Months, Median (IQR)	38 (26 – 64)
Type of Intervention, n (%)	
Biologics	64 (36.16)
Multiple	51 (28.81)
Other	42 (23.73)
Immunosuppressant	13 (7.34)
Aminosalicylates (ASA)	5 (2.82)
Corticosteroids	2 (1.13)

Analysis of COS Uptake

Our analysis began five years prior to the publication of our COS (March 2013), at which outcome measurement completion was approximately 40%. Prior to the publication of the COS, data showed a monthly decrease of 0.002% in the use of IBD core outcomes (p=0. 99, 95 % CI = [-0.42, 0.42]). Following the COS publication, there was a monthly decrease of 0.25% (p= 0.07, 95% CI = [-0.52, 0.02]) in "COS-defined outcomes." All data in Figure 2 and Figure 3 was shown to be statistically non-significant. 'Change in bowel symptoms' (88.14%; 156/177), 'pain or discomfort', (83.05%; 147/177) and 'disease activity and remission' (82.5%; 146/177) were the most frequently reported outcomes. In contrast, no trial measured 'colorectal cancer', 2 trials (1.13%; 2/177) reported 'overall survival', and 15 trials (8.47%; 15/177) reported 'cause of death' (Table 2).

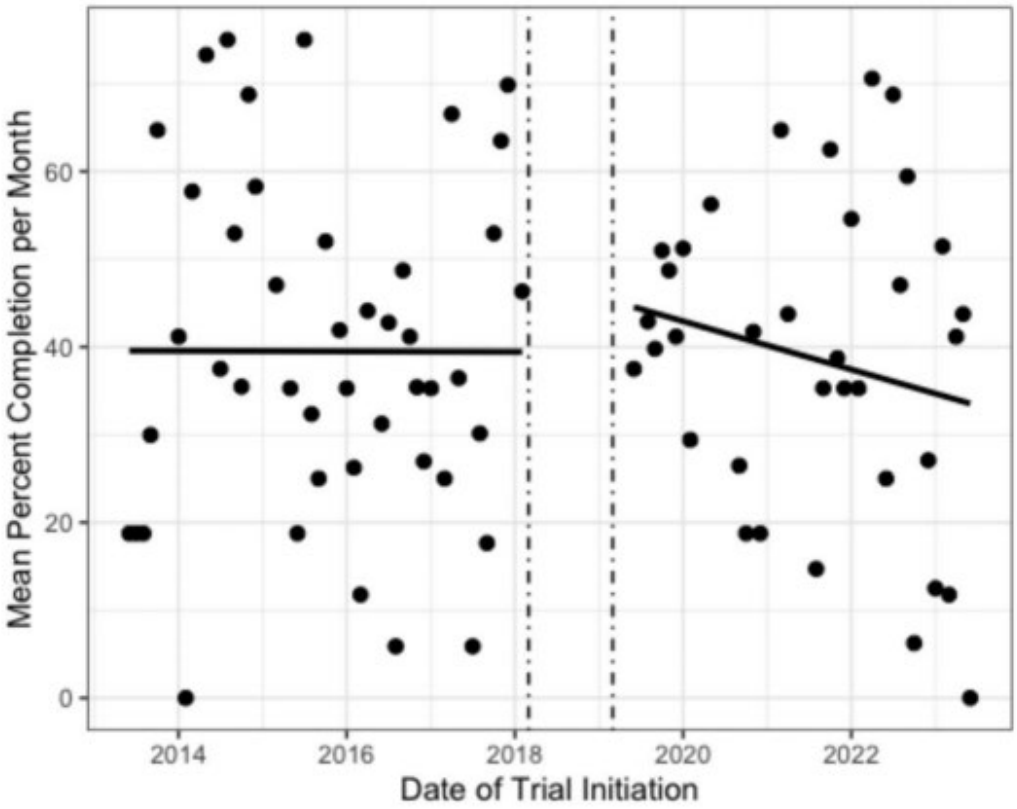

Figure 2: Figure 2 represents a visual presentation of the adoption of the COS by IBD clinical trials. A one-year grace period was included to account for the uptake of the COS.

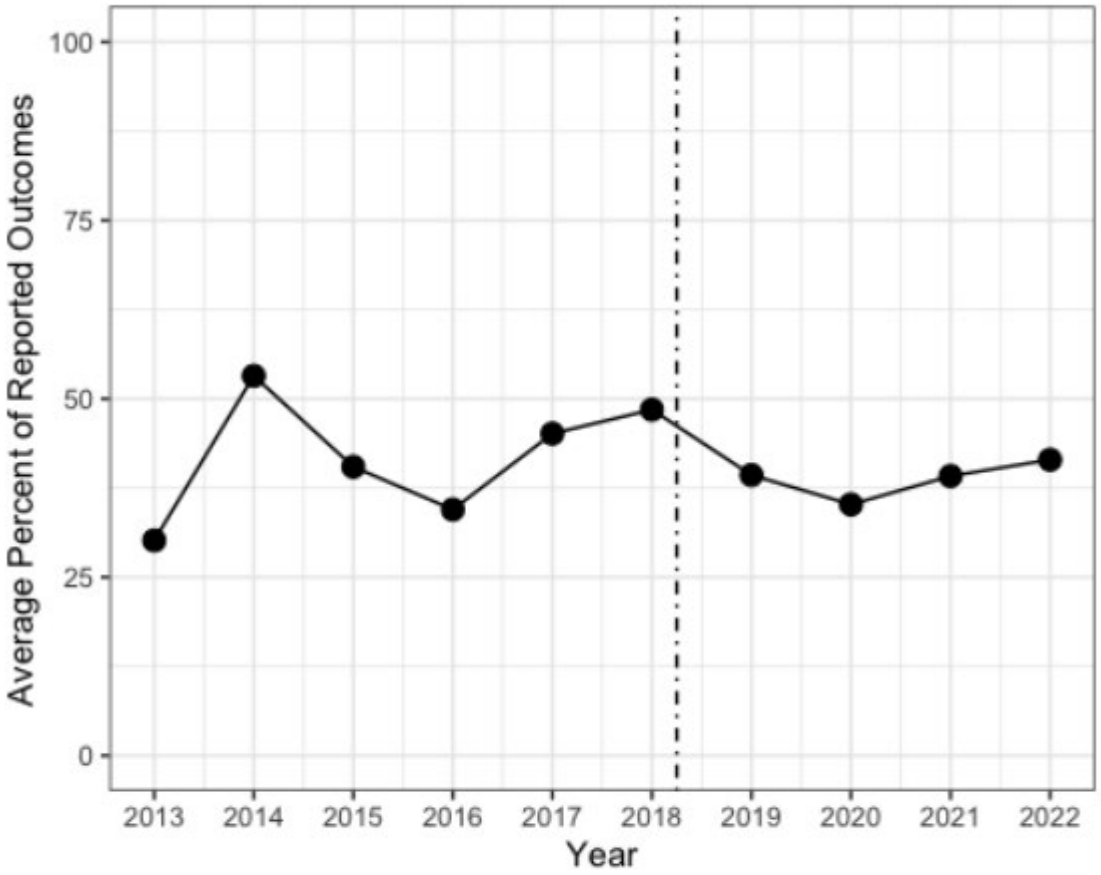

Figure 3: Figure 3 displays the mean percentage of outcome measures in trials per year.

Table 2. Frequency of Outcome Set Uptake

Domain	**Outcome Set Item**	**N = 177**
Symptoms, Function, and Quality of Life	Change in Bowel Symptoms, n (%)	
	Yes	156 (88.14)
	No	21 (11.86)
	Missing Planned Activities, n (%)	
	Yes	76 (42.94)
	No	101 (57.06)
	Night Symptoms, n (%)	
	Yes	57 (32.20)
	No	120 (67.79)
	Pain or Discomfort, n (%)	
	Yes	147 (83.05)
	No	30 (16.95)
	Energy and Fatigue, n (%)	
	Yes	75 (42.37)
	No	102 (57.63)
	Feel Anxious or Depressed, n (%)	
	Yes	78 (44.06)
	No	99 (55.93)
	Overall Control Over IBD, n (%)	

Domain	Outcome Set Item	N = 177
	Yes	109 (61.58)
	No	68 (38.42)
	Weight, n (%)	
	Yes	94 (53.11)
	No	83 (46.89)
Symptoms, Function, and Quality of Life (Crohn's)	Fistula Symptoms, n (%)	
	Yes	19 (21.8)
	No	68 (78.2)
	Not Applicable	90
Disutility of Care	Steroid use, n (%)	
	Yes	64 (36.16)
	No	113 (63.84)
	Occurrence and Impact of Complication From an IBD Intervention, n (%)	
	Yes	69 (38.98)
	No	108 (61.02)
Healthcare Utilization	Time Spent in Hospital, n (%)	
	Yes	43 (24.29)
	No	134 (75.71)
Survival and Disease Control	Presence of Anemia, n (%)	

Domain	Outcome Set Item	N = 177
	Yes	57 (32.20)
	No	120 (67.79)
	Disease Activity and Remission, n (%)	
	Yes	146 (82.49)
	No	31 (17.51)
	Colorectal Cancer, n (%)	
	No	177 (100.00)
	Overall Survival, n (%)	
	Yes	2 (1.13)
	No	175 (98.87)
	Cause of Death, n (%)	
	Yes	15 (8.47)
	No	162 (91.53)

Relationship Between Trial Characteristics and Outcome Measurement

A significant effect was observed for 'Continent' ($F=4.79$, $p= <0.001$, $\eta2 =0 .14$) and 'Funding Type' ($F=3.37$, $p=0.01$, $\eta2=0.09$). In contrast, 'Recruitment Status' ($F=1.82$, $p=0.08$, $\eta2=0.08$) showed no significant effect on "COS-defined outcomes." The effect sizes ($\eta2$) showed that approximately 5% of the variation in the COS was attributed to the differences in 'Continent' and 'Recruitment Status', whereas approximately 6% was attributed to the differences between 'Funding Type.' In addition, we conducted a Pearson correlation analysis between 'Enrollment Number' and percentage of outcomes measured and found a statistically significant, positive correlation ($r=0.24$, $t=3.24$, $p<0.001$). Results from the ANOVAs and correlation analysis can be found in Table 3.

Table 3: ANOVA and Pearson Correlation Analysis

Characteristic	**N = 177**[1]	***F*-statistic**[2]	**p-value**[2]	**(η^2)**[2]
Continent		4.79	<0.001	0.14
Africa	33.09 (19.50)			
Asia	28.09 (18.38)			
Australia	37.87 (13.09)			
Europe	38.66 (22.03)			
Multiple	48.84 (22.04)			
North America	44.49 (15.22)			
South America	5.88 (NA)			
Funding Type		3.37	0.01	0.09
Hospital	36.73 (22.86)			
Industry	46.32 (22.36)			
Multiple With Industry	34.47 (17.83)			
Multiple Without Industry	30.37 (19.79)			
Private	54.04 (11.92)			
University	42.91 (15.61)			
Recruitment Status		1.82	0.08	0.08
Active, but No Recruiting	46.47 (19.60)			
Completed	47.45 (21.81)			
Enrolling by Invitation	41.18 (NA)			
Not Yet Recruiting	35.15 (22.49)			
Recruiting	37.40 (21.51)			
Suspended	68.75 (NA)			
Terminated	40.72 (21.37)			
Unknown	30.98 (21.06)			
Withdrawn	43.01 (23.37)			

Characteristic	*t*-statistic[3]	p-value[3]	(r)[3]
Enrollment Number	3.24	0.001	0.24

[1]Mean (SD)

[2]One-way ANOVA, η^2

[3]Pearson Correlation Coefficient

Discussion

Our findings indicate that the release of the COS for IBD in 2018 has made no significant effect on the uptake of outcomes in registered RCTs. In reference to the characteristics of the trials analyzed in this review, there was a significant difference between the different continents in which Trials were published in and the uptake of COS; therefore, this could mean that the IBD COS, and its importance are more known in different parts of the world. Amongst the IBD COS, the most frequently measured outcomes were 'bowel symptoms', 'pain or discomfort', and 'disease activity and remission' with over 80% of trials measuring these domains. In contrast, three outcomes were measured in less than 10% of the RCTs, including 'colorectal cancer' not being measured in any trials. These findings were consistent both before and after the publication of the IBD COS. Ultimately, our results show poor IBD COS uptake by clinical trialists, suggesting potential barriers in COS use.

A previous study by Hughes *et al.* has suggested that the lack of COS uptake by trialists may be due to time or resource constraints.[18] Further explorations into COS uptake by Matvienko-Sikar *et al.* found that trialist's own preferences for outcomes and lack of knowledge about the existence of COSs were considered barriers to adequate uptake.[19] Additionally, practical challenges such as added complexity and costs for trialists could limit COS uptake.[20]
In this review specifically, there was a positive Pearson correlation between the enrollment number and the percentage of outcomes measured; which could elude to larger clinical trials (with larger budgets) producing more strong reproducible data.[11] To overcome finical and other constraints that come with implementation of the COS, it may be beneficial for trialists to have a plan for COS implementation at the onset of their study. To address these barriers, Williamson *et al*. proposed that COS publishers may promote implementation by increasing the dissemination and understanding of their COS and establishing a strategy during the early stages of its development.[21] Further, the authors found that 84% of the COS publishers in their sample planned to promote the uptake of COS, however the majority did not promote their study after the publication.[21] By giving trialists a roadmap on how to implement their COS, publishers can increase the uptake of their agreed upon outcomes in future clinical trials, ultimately preventing the omission of important outcomes altogether.

Our study found that no clinical trials measured all the core outcomes in the COS established for IBD. Poor use of the IBD COS can hinder progress made in the field of IBD.[22] Additionally, no RCTs measured the outcome of 'colorectal cancer'. This finding is concerning because patients with Crohn's disease or ulcerative colitis have an increased risk for developing colorectal

cancer.[23] The Crohn's and Colitis Foundation stresses the importance of screening among this population, further indicating the importance of measuring this outcome in clinical trials.[23] It is possible trialists were monitoring their patients for colorectal cancer; however, not reporting what screening took place or the number of patients that developed cancer may affect study transparency. The risk of developing colon cancer is an important factor when physicians are considering potential interventions for IBD. Furthermore, given the debilitating nature of IBD, trialists must account for domains affecting all aspects of patient health, not only GI-associated outcomes.

Nearly 90% of our trials reported 'bowel symptoms' and over 80% reported 'pain or discomfort', yet many trials failed to measure outcomes regarding patients' health-related quality of life. For example, less than 60% of the included trials in our sample measured 'anxiety and depression', 'night symptoms', 'missing planned activities', 'energy and fatigue', or 'occurrence/impact of complication of an intervention'. Proper measurement of these outcomes is needed, as IBD is not diagnosed by one single test, but rather a combination of physical exam, symptoms, blood tests, and procedures.[24] In addition, IBD has one of the highest economic burdens among gastrointestinal disorders.[25] Stark *et al.* demonstrated that productivity loss due to disability was one of the main contributors to the financial burden of a patient with IBD.[26] If IBD is in fact associated with increased healthcare costs for patients, measuring how treatment influences patients' health-related quality of life is warranted. Acknowledging the importance of quality-of-life related outcomes and promoting their implementation by trialists may improve overall patient-centered care.

Strengths and Limitations

Our study has several strengths. First, we ensured inclusiveness by considering all IBD RCTs registered on ClinicalTrials.gov, which is a globally recognized and reliable source for accessing registered trials.[27] Second, to uphold methodological rigor, investigators received data extraction training and conducted the study in a masked, duplicate fashion in accordance with the Cochrane Collaboration Guidelines.[28] Third, we uploaded our extraction form, data sheet, and protocol to Open Science Framework, an open-source repository that promotes transparency in research.[29] Despite being methodologically rigorous, our study is not without limitations. Our initial systematic search may not have yielded all relevant clinical trials. We only used ClinicalTrials.gov to screen for trials but some may have been missed as we did not use international trial registries as well. In addition, the IBD COS was released in 2018 and our study analyzed trials five years before and after the publication of the COS. With the year of this study being 2023, it is possible that inadequate time for COS uptake could limit our data points.

Conclusion

Our study revealed there were no noticeable patterns in the adherence to COS in IBD clinical trials, both before and after the publication of the IBD COS. Notably, the only consistent outcomes across the trials were 'bowel symptoms', 'pain or discomfort', and 'disease activity and remission'. Future research studies should emphasize the evaluation of quality-of-life outcomes to better understand the impact of interventions; especially because IBD treatments are not all curative and can be far from optimal.[5] Future research could also be done in regards to the knowledge of IBD COS, and barriers that prevent trialist from adhering to all core outcomes.

By better integrating COS into their research, trialists can enhance the standardization and comparability of outcomes across studies in the field of IBD.

References

1. Wang R, Li Z, Liu S, Zhang D. Global, regional and national burden of inflammatory bowel disease in 204 countries and territories from 1990 to 2019: a systematic analysis based on the Global Burden of Disease Study 2019. *BMJ Open*. 2023;13(3):e065186.

2. What is Inflammatory Bowel Disease (IBD)? Crohn's & Colitis Foundation. Accessed July 13, 2023. https://www.crohnscolitisfoundation.org/campus-connection/what-is-ibd

3. Singh S, Qian AS, Nguyen NH, et al. Trends in U.S. Health Care Spending on Inflammatory Bowel Diseases, 1996-2016. *Inflamm Bowel Dis*. 2022;28(3):364-372.

4. Park KT, Ehrlich OG, Allen JI, et al. The Cost of Inflammatory Bowel Disease: An Initiative From the Crohn's & Colitis Foundation. *Inflamm Bowel Dis*. 2020;26(1):1-10.

5. Lee SH, Kwon JE, Cho ML. Immunological pathogenesis of inflammatory bowel disease. *Intest Res*. 2018;16(1):26-42.

6. Hariton E, Locascio JJ. Randomised controlled trials - the gold standard for effectiveness research: Study design: randomised controlled trials. *BJOG*. 2018;125(13):1716.

7. Akobeng AK. Understanding randomised controlled trials. *Arch Dis Child*. 2005;90(8):840-844.

8. Liao Z, Quintana Y. Challenges to Global Standardization of Outcome Measures. *AMIA Jt Summits Transl Sci Proc*. 2021;2021:404-409.

9. Kim AH, Roberts C, Feagan BG, et al. Developing a Standard Set of Patient-Centred Outcomes for Inflammatory Bowel Disease-an International, Cross-disciplinary Consensus. *J Crohns Colitis*. 2018;12(4):408-418.

10. COMET initiative. Accessed July 13, 2023. https://www.comet-initiative.org/

11. Kirkham JJ, Clarke M, Williamson PR. A methodological approach for assessing the uptake of core outcome sets using ClinicalTrials.gov: findings from a review of randomised controlled trials of rheumatoid arthritis. *BMJ*. 2017;357:j2262.

12. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med*. 2021;18(3):e1003583.

13. Magee T, Jones G, Magana K, Fitzgerald K, Modi J, Ward S. OSF. Accessed July 13, 2023. https://osf.io/s8zxw/

14. Office for Human Research Protections (OHRP). 2018 Requirements (2018 Common Rule). HHS.gov. Published March 7, 2017. Accessed July 7, 2023. https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/revised-common-rule-regulatory-text/index.html

15. Kim AH, Roberts C, Feagan BG, et al. Developing a standard set of patient-centred outcomes for inflammatory bowel disease—an international, cross-disciplinary consensus. *J Crohns Colitis*. 2018;12(4):408-418.

16. COMET Initiative. Accessed March 22, 2023. https://www.comet-initiative.org/

17. COMET initiative. Accessed July 12, 2023. https://www.comet-initiative.org/Resources/COSTutorial

18. Hughes KL, Clarke M, Williamson PR. A systematic review finds Core Outcome Set uptake varies widely across different areas of health. *J Clin Epidemiol*. 2021;129:114-123.

19. Matvienko-Sikar K, Avery K, Blazeby JM, et al. Use of core outcome sets was low in clinical trials published in major medical journals. *J Clin Epidemiol*. 2022;142:19-28.

20. Williamson PR, Altman DG, Blazeby JM, et al. Developing core outcome sets for clinical trials: issues to consider. *Trials*. 2012;13:132.

21. Williamson PR, Barrington H, Blazeby JM, et al. Review finds core outcome set uptake in new studies and systematic reviews needs improvement. *J Clin Epidemiol*. 2022;150:154-164.

22. Sahnan K, Tozer PJ, Adegbola SO, et al. Developing a core outcome set for fistulising perianal Crohn's disease. *Gut*. 2019;68(2):226-238.

23. The risk of colorectal cancer in Crohn's disease and ulcerative colitis patients. Crohn's & Colitis Foundation. Accessed July 14, 2023. https://www.crohnscolitisfoundation.org/what-is-ibd/colorectal-cancer

24. Inflammatory bowel disease: Symptoms, treatment & diagnosis. Cleveland Clinic. Accessed July 17, 2023. https://my.clevelandclinic.org/health/diseases/15587-inflammatory-bowel-disease-overview

25. Pakdin M, Zarei L, Bagheri Lankarani K, Ghahramani S. The cost of illness analysis of inflammatory bowel disease. *BMC Gastroenterol*. 2023;23(1):21.

26. Stark R, König HH, Leidl R. Costs of inflammatory bowel disease in Germany. *Pharmacoeconomics*. 2006;24(8):797-814.

27. CTG labs - NCBI. Accessed July 19, 2023. https://www.clinicaltrials.gov

28. Chapter 5: Collecting data. Accessed July 19, 2023. https://training.cochrane.org/handbook/current/chapter-05

29. Foster ED, Deardorff A. Open Science Framework (OSF). *J Med Libr Assoc*. 2017;105(2):203.

30. Bautista-Molano W, Navarro-Compán V, Landewé RBM, Boers M, Kirkham JJ, van der

Heijde D. How well are the ASAS/OMERACT Core Outcome Sets for Ankylosing Spondylitis implemented in randomized clinical trials? A systematic literature review. *Clin Rheumatol*. 2014;33(9):1313-1322.

31. Center for Drug Evaluation, Research. Clinical development programs for drugs, devices, and biological products for the treatment of rheumatoid arthritis (RA). U.S. Food and Drug Administration. Published May 6, 2020. Accessed July 14, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-development-programs-drugs-devices-and-biological-products-treatment-rheumatoid-arthritis

32. EMA. Clinical investigation of medicinal products used in the treatment of osteoarthritis - Scientific guideline. European Medicines Agency. Published September 17, 2018. Accessed July 14, 2023. https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-used-treatment-osteoarthritis-scientific-guideline

33. Kirkham JJ, Gorst S, Altman DG, et al. Core Outcome Set-STAndards for Reporting: The COS-STAR Statement. *PLoS Med*. 2016;13(10):e1002148.

34. Ma C, Panaccione R, Fedorak RN, et al. Development of a core outcome set for clinical trials in inflammatory bowel disease: study protocol for a systematic review of the literature and identification of a core outcome set using a Delphi survey. *BMJ Open*. 2017;7(6):e016146.

35. Dubinsky MC, Collins R, Abreu MT, International Organization for the Study of Inflammatory Bowel Diseases (IOIBD). Challenges and Opportunities in IBD Clinical Trial Design. *Gastroenterology*. 2021;161(2):400-404.