

Review article: randomised controlled trials in inflammatory bowel disease—common challenges and potential solutions

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Summary

Background: Recruitment rates for Crohn's disease and ulcerative colitis clinical trials continue to decrease annually. The inability to reach recruitment targets and complete trials has serious implications for stakeholders in the inflammatory bowel disease (IBD) community. Action is required to ensure patients with an unmet medical need have access to new therapies to improve the management of their IBD.

Aims: Identify challenges contributing to recruitment decline in IBD clinical trials and propose potential solutions.

Methods: PubMed and Google were used to identify literature, regulatory guidelines and conference proceedings related to IBD clinical trials and related concepts. Data on IBD clinical trials conducted between 1989 and 2020 were extracted from the Trialtrave database.

Results: Key aspects that may improve recruitment rates were identified. An increasingly patient-centric approach should be taken to study design including improvements to the readability of key trial documentation and inclusion of patient representatives in trial planning. Placebo is unappealing to patients; approaches including platform trials should be explored to minimise placebo exposure. Non-invasive imaging, biomarkers and novel digital endpoints should continue to be examined to reduce the burden on patients. Reducing the administrative burden associated with trials via the use of electronic signatures, for example, may benefit study sites and investigators. Changes implemented to IBD trials during the COVID-19 pandemic provided examples of how trial conduct can be rapidly and constructively adapted.

Conclusions: To improve recruitment in Crohn's disease and ulcerative colitis trials, the IBD community should address a broad range of issues related to clinical trial conduct.

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1 | INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) comprise the main phenotypes of inflammatory bowel disease (IBD). These diseases represent chronic disorders that cause inflammation of the gastrointestinal tract and are characterised by phases of remission and relapse. The aetiology of IBD is unknown; however, in genetically predisposed individuals, there appears to be an intestinal mucosal immune reaction to environmental factors, with the gut microbiota playing a central role as a trigger.¹ IBD is increasing in incidence and presents heterogeneously, carrying a substantial burden of symptoms which include bloody diarrhoea, faecal incontinence, urgency, fatigue, pain, skin lesions, ocular manifestations such as uveitis, and increased risk of cancer.²⁻⁴ IBD also markedly impacts health-related quality of life.⁵

Despite the availability of a range of treatment options for IBD, gaining a satisfactory outcome for all patients in clinical practice remains elusive with existing therapies typically exhibiting maintenance remission rates of approximately 30%-40%.⁶⁻¹¹ Therefore, there remains an unmet medical need in IBD. This unmet medical need in combination with a greater understanding of the pathological basis of IBD has led to an exponential rise in the number of compounds in clinical development for this disease over the last three decades.^{12,13} Consequently, the number of IBD clinical trials being initiated continues to increase annually. Specifically, the number of CD clinical trials initiated each year more than doubled between 1999 and 2019 while the number of UC clinical trials increased 10-fold during the same time period (Figure 1).

While this increased number of compounds and trials portends potentially favourable therapeutic developments for patients with IBD, it also contributes to difficulties in timely recruitment for

clinical trials.¹² As patient recruitment is often the rate-limiting step in the route to the approval of new therapies, failure to enrol patients quickly or in sufficient numbers have been identified as leading causes of clinical trial discontinuation.¹⁴ Several factors contribute to difficulties with recruitment including patient concerns regarding placebo assignment, specific issues associated with study attributes/design, and an increase in the number of approved treatment options.^{12,15} As a result, the average recruitment rate in clinical trials for CD decreased from 0.65 to 0.10 patients per site per month between 1998 and 2018, while a decrease from 0.32 to 0.13 patients per site per month has been observed over a similar time period in clinical trials for moderate-to-severe UC.¹²

The inability to reach recruitment targets and the subsequent failure of trials to complete has serious implications for all stakeholders in the IBD community including patients, research institutions, investigators and industry sponsors. Patient recruitment is, therefore, a key challenge for the IBD community and action is required to ensure that potential medicines for IBD continue to have the opportunity to be evaluated in a sufficient and practical manner. In this paper, we will discuss some key challenges related to IBD clinical trial conduct and recruitment from the viewpoint of stakeholders in Europe. We will also explore how these challenges may be addressed, based on the authors' personal experiences as investigators for industry-sponsored clinical trials.

2 | METHODOLOGY

A descriptive review was conducted using PubMed and Google to identify literature, regulatory guidelines and conference proceedings in English related to IBD clinical trials. Specifically, scientific

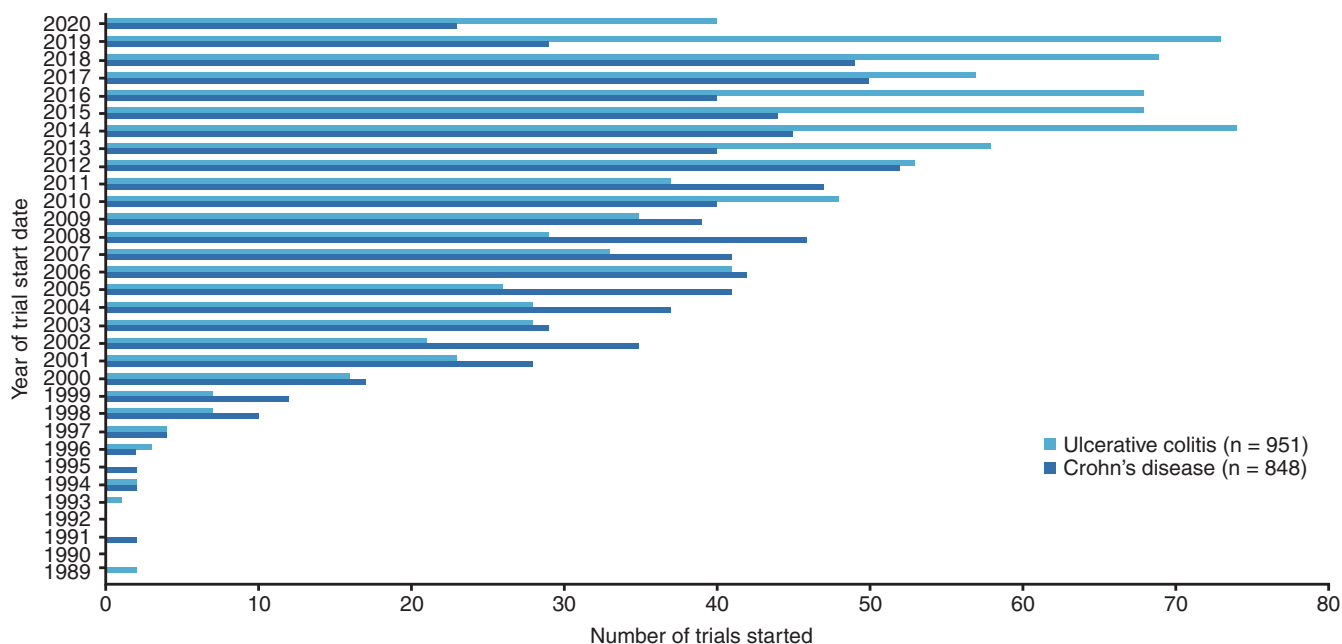


FIGURE 1 Number of Crohn's disease and ulcerative colitis clinical trials initiated annually based on data obtained from the Trialstrove database. All trials with an "actual start date" listed were included

literature was identified using PubMed. Google searches were used to find resources held on websites (eg, Guidance from the Food and Drug Administration) and further information on initiatives that were not well described in the literature, such as IDEA-FAST (Identifying Digital Endpoints to Assess Fatigue, Sleep and Activities in daily living in Neurodegenerative disorders and Immune-mediated inflammatory diseases), which was identified by the authors. Date ranges were not specified during PubMed searches. However, the most recent data was prioritised wherever possible; the legitimacy of each journal was evaluated prior to inclusion of a publication in the reference list. The PubMed search included the following key terms, used alone and in combination, to identify relevant literature: accrual, biomarker, Crohn's disease, clinical research, clinical study, clinical trial, consent, COVID-19, design, diagnosis, endoscopy, endpoint, extraintestinal manifestation, faecal calprotectin, incentive, inflammatory bowel disease, intestinal ultrasound, management, master protocol, monitoring, motivation, non-invasive, outcome, participation, pathogenesis, patient-centred, patient information, patient perspective, patient preference, placebo, quality of life, randomised controlled trial, recruitment, remote monitoring, shared decision making, telemedicine, therapy, trial, ulcerative colitis." Data on IBD clinical trials conducted between 1989 and 2020 were extracted from the Trialtrave database (<https://citeline.informa.com>).

3 | IDENTIFYING AND ADDRESSING CHALLENGES IN IBD CLINICAL TRIALS

3.1 | Geographical expansion and an increasing number of sites

To address the challenges associated with patient recruitment, the number of sites and countries involved in IBD clinical trials has increased markedly over the last three decades (Figures 2 and 3). Enrolment has shifted to areas outside North America and Western Europe, which reflects trends in rising IBD incidence worldwide (Figure 4).¹⁶ While expansion to additional sites and countries presents a short-term solution, it is resource- and time-consuming as a multiplicity of regulatory requirements must be addressed in a host of jurisdictions. Furthermore, expansion to multiple sites and countries may not always lead to increases in patient recruitment. For example, in countries where the infrastructure for the care of patients with IBD is relatively centralised, there may be an increased number of screen failures in patients from peripheral centres. With this in mind, it is particularly important for sponsors to explore additional ways to improve recruitment rates in the coming years. At all sites, regardless of whether they are new to research or how many patients are enrolled, it is important for sponsors to put mitigation strategies in place that ultimately support recruitment. Such strategies could include tailored training and proactive identification of

obstacles at sites that would impact trial conduct. Such additional support can ensure that screening is completed effectively, that the quality of data obtained is high, and that sites conclude the trial with a positive overall perception of the experience.

3.2 | Patient centricity in IBD clinical trials

Many patients remain unaware of opportunities to participate in clinical trials.¹⁷ However, both sponsors and organisations such as the Center for Information and Study on Clinical Research Participation (<https://www.ciscrp.org/about-us/>) are working to educate and inform the public about clinical research. In addition, it remains to be seen how coronavirus disease (COVID-19), which has put clinical trials in the spotlight internationally, will impact recruitment and patient perceptions of clinical trials. This increased awareness of clinical trials among the general public could be beneficial for recruitment in IBD clinical trials. Aside from this, a more patient-centred approach should be explored to improve recruitment. It is important to address the reasons patients participate in trials and to go beyond quick-fix options such as financial incentives which are ethically contentious and have a mixed impact on the willingness of patients to participate.^{18,19}

For patients with IBD who are aware of clinical research opportunities, fear and misunderstanding tend to be barriers to participation.¹⁸ This is consistent with patient attitudes reported in other disease areas in which uncertainty about the clinical trial process, potential risks and the impact of the trial on daily life can be a barrier.^{19,20} As physicians represent an important source of information for patients regarding clinical trials, engaging referring physicians and securing their support in communicating with potentially eligible patients about clinical trials are important factors in addressing patients' concerns and positively impacting patients' willingness to participate.^{18,21}

A patient's understanding of a trial has been shown to impact their likelihood of participation.^{19,22,23,24,25} Therefore, providing both patients and physicians with innovative and effective educational tools, including those supporting shared decision-making, may help facilitate recruitment. Ideally, such tools should be evaluated by patients and physicians for effectiveness prior to use. It is important to consider the format of educational tools for patients as the way in which information is provided can impact patient perceptions.²⁶ Currently, sponsors are producing a range of materials for patients in local languages to assist in recruitment and retention within their trials. However, key trial documentation, such as the informed consent form, remains technical and laden with complex scientific terminology.^{27,28} Wherever possible, educational materials and trial documentation should be simplified to ensure greater understanding. This consideration should also be applied to any verbal information transfer between patients and healthcare providers.

Sponsors may also want to consider the impact of providing patient-friendly materials following trial completion; not only to

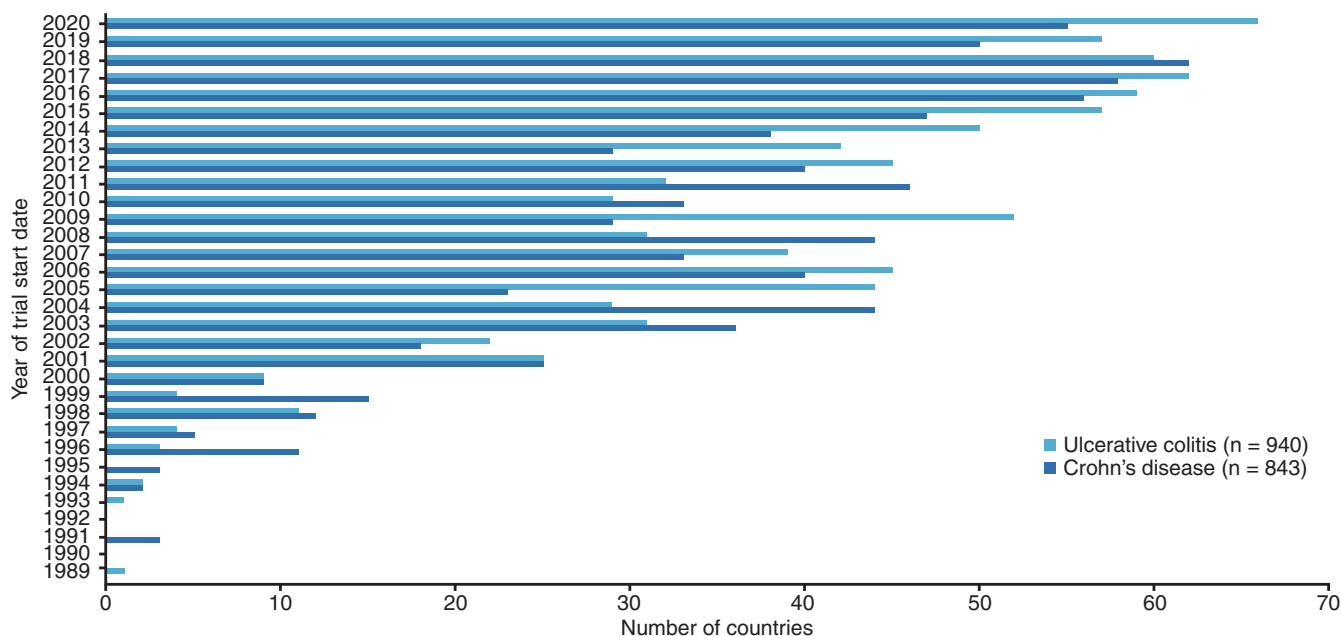


FIGURE 2 Average number of countries involved in Crohn's disease and ulcerative colitis clinical trials per year based on data obtained from the Trialtrave database. All trials with an "actual start date" and "country" listed were included

participants but in a publicly accessible location. An overwhelming majority of participants want to be informed about the results of the trial in which they have participated.²⁹ Furthermore, a large proportion of patients (68%) would choose not to participate in future clinical trials if they did not receive such a summary.³⁰ Openly sharing trial results in patient-friendly language increases clinical trial transparency, potentially reducing fear and misunderstanding related to participation both for new patients and those previously involved in trials.

The use of shared decision-making tools is an avenue that sponsors may wish to explore to increase recruitment rates. These tools are usually designed for situations where there is uncertainty about the best treatment option. They can be used before and during consultation to provide information about the potential risks and benefits of each treatment option.³¹ Patients exposed to decision aids report feeling more knowledgeable, allowing them to make more informed decisions.³² Such tools can include brochures as well as audio-visual media and specific interaction training of medical personnel.

Materials that specifically focus on patient concerns surrounding clinical trials, including safety and the rationale for inclusion of a comparator such as placebo are also important.¹⁸ In addition, patients may be more inclined to participate if they understand that participation could provide them with more regular access to high-quality medical care.¹⁸ Educating patients about the general benefit of increasing the number of treatment options available and the role of clinical trials in the drug approval process could also help to support enrolment as altruism and contributing to research is a key factor in trial participation for many patients.^{21,33,34,35}

An additional consideration for the development of patient-facing materials is that patients in the IBD community represent a heterogeneous group and individual patient demographics can impact their likelihood to participate in clinical trials. Patients with poor quality of life are most likely to participate in trials and patients taking part in clinical trials report indicators of more severe disease such as IBD-related hospitalisations or IBD-related surgery.³⁶ Materials for clinical trials must therefore be tailored carefully to the demographic and socioeconomic status of the patients that the trial aims to enrol. In general, patients or their representative associations should assist in the development of patient-facing materials to encourage the creation of effective documentation.

Patients are key stakeholders in the clinical trial process. As part of a patient-centric approach, sponsors should explore innovative ways to support patients considering trial participation. The I-SPY-2 trial provided a blueprint for such an approach; site coordinators were trained by patient advocates regarding how best to conduct conversations with recently diagnosed patients about their potential options in a clinical trial. I-SPY-2 also used a unique two-step consent process, with consent required for both screening and treatment, which makes trials more approachable for patients.³⁷ Another consideration, if permitted by regional ethics assessments, could include reasonable compensation for patients' time and effort whenever their participation goes beyond what is typically required per the standard of care for their illness. In addition, giving patient advocates an opportunity to provide their input during trial planning would be an effective way to tailor IBD clinical trials to patients' needs and mitigate certain issues related to the running of the trial, thereby impacting recruitment.³⁸ Sponsors are beginning to explore how they

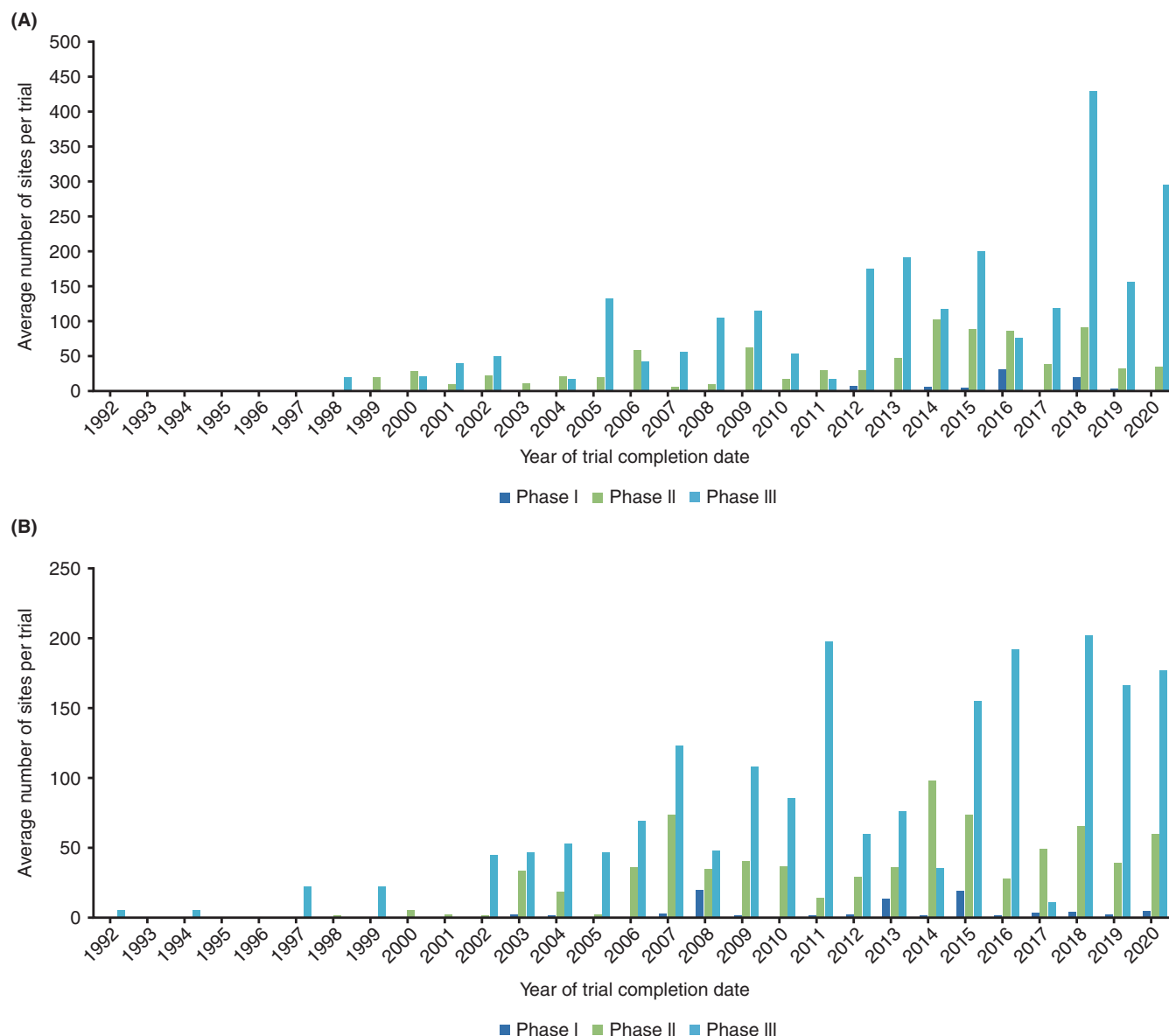


FIGURE 3 Average number of sites per (A) Crohn's disease (n = 283) and (B) Ulcerative colitis (n = 353) clinical trial by year based on data obtained from the Trialstro database. All trials with an "actual primary completion date" listed were included. Phase I/II, II/III, IV trials and trials with phase listed as "other" were excluded

can include patients in trial steering committees, which have already been implemented in some EU-funded academic initiatives. It is important for sponsors to develop frameworks within which they can work effectively and compliantly with patients. The European Patients' Academy on Therapeutic Innovation, an initiative comprising over 30 groups including patient organisations, universities and pharmaceutical companies, has created guidance for patient involvement in industry-sponsored clinical research.³⁹ The INVOLVE initiative from the National Institute of Health Research in the United Kingdom also provides resources to support patient engagement in clinical research. Such guidance serves as a foundation for the development of IBD-specific guidelines.

3.3 | The impact of study design on patient recruitment in IBD clinical trials

Fear of receiving placebo is one of the main barriers to participation in IBD clinical trials^{15,40} and evidence suggests that lowering the chance of receiving placebo would lead to a small but significant increase in recruitment.¹⁵ However, the use of placebo offers a host of benefits including the potential to observe treatment effects with a smaller sample size, resulting in fewer patients being exposed to investigational treatment.⁴¹ Furthermore, patients receiving placebo rarely participate without background therapy as the majority of IBD trials allow 5-aminosalicylic acid and a stable dose of corticosteroids as a minimum at baseline. The importance

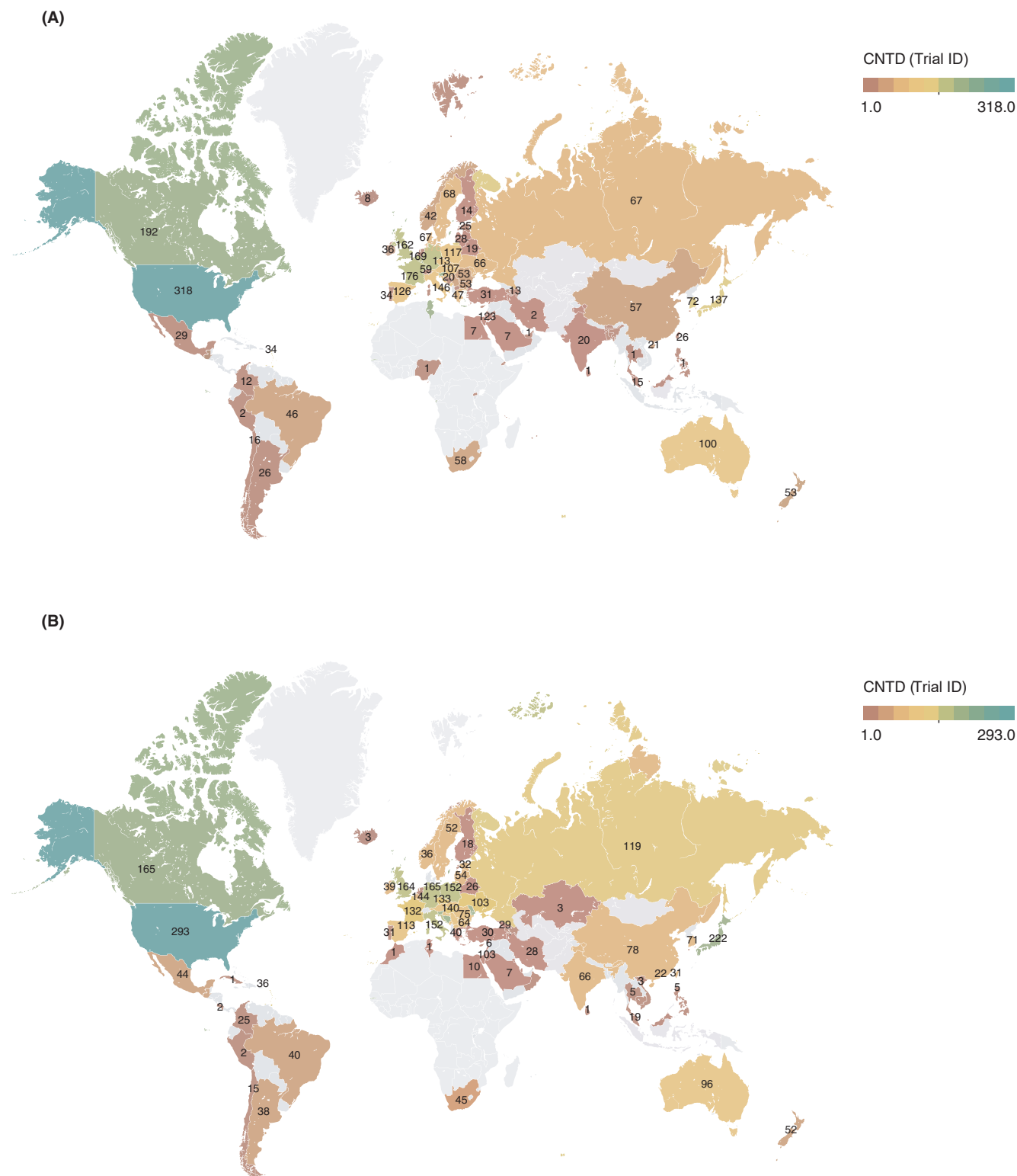


FIGURE 4 Global distribution of (A) Crohn's disease ($n = 843$) and (B) ulcerative colitis ($n = 940$) clinical trials based on data obtained from the Trialtrave database. All trials with an "actual start date" and "country" listed were included

of placebo in trial design is also affected by several factors, including the phase of the trial.⁴⁰ Placebo-controlled trials are of particular importance early in the clinical development programme and, while some might argue they are perhaps less relevant in phase

III, placebo remains important for monitoring and assessing the frequency of adverse events.⁴⁰

From a regulatory perspective, the position of the European Medicines Agency Committee for Medical Products for Human Use

is that, where ethical and feasible, a placebo control arm should be included in the pivotal trial(s) used to support the marketing authorisation application.⁴¹

The more widespread use of study designs with an active comparator, using a therapy marketed for the treatment of IBD, has been proposed to address the ethical concerns regarding allocation of patients to placebo. However, active comparator studies typically require significantly larger population sizes than placebo-controlled trials. The impact of this is a more costly trial which can take longer to recruit and a larger number of patients exposed to an investigational therapy.⁴¹

Platform trials using master protocols can be used to assess multiple treatments in parallel. Such studies share patients, investigators, central laboratories and other study resources which enables patients to be screened simultaneously for multiple studies and shared across therapeutic agents with different enrolment requirements.¹² Studies can share investigator training platforms and protocols may continue even after a candidate exits, so new agents can be added while the protocol is ongoing without the need to create an entirely new, free-standing trial.¹² Typically, in such studies, a reduced number of patients are required (similar to multiple ascending dose phase I studies in which placebo groups are pooled) in comparison with standard trial designs leading to an overall reduction in the number of placebo patients. In addition, significantly shorter trial durations reduce the amount of time patients spend on placebo.³⁷

To conduct a master protocol study, extensive pre-trial statistical simulation is required. Pre-trial statistical simulation evaluates the operating characteristics of a clinical trial under multiple scenarios, for example with inclusion of interim analyses or subgroups. This evaluation allows key stakeholders to understand the advantages and limitations of different designs on the study prior to execution.⁴² Master protocols, and particularly platform trials, provide potential advantages in efficiency and flexibility and have the potential to revolutionise drug development if the methodological and operational challenges can be overcome.⁴³ The ongoing I-SPY-2 trial is an example of a successful platform trial; median trial durations for therapies included in the platform have been more than halved compared with standard phase II trials (18 months vs 40 months). Furthermore, therapies that successfully “graduate” the I-SPY-2 trial have both an 85% predicted probability of success in phase III trials and require far fewer patients than standard phase III trials.³⁷

3.4 | Endpoint selection in IBD clinical trials

Clinical trials are becoming increasingly complex due to factors such as novel patient-reported outcomes, a greater number of endpoints and more specific eligibility criteria. Between 2002 and 2012, the total number of eligibility criteria in phase III trials increased from 31 to 50, the total number of endpoints from 7 to 13, and the total number of procedures from 106 to 157.⁴⁴ IBD clinical trials reflect this general increase; in particular, multiple efficacy endpoints are currently used due to a lack of consensus regarding disease activity

and severity.⁴⁵ Such increased complexity leads to substantial commitments of time and resources from patients, investigators, clinical trial sites and sponsors. Initiatives such as Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) of the International Organisation for the Study of Inflammatory Bowel Diseases are developing evidence- and consensus-based recommendations that, in the future, may lower the burden on stakeholders by identifying the most important endpoints for IBD clinical trials.⁴⁶

Despite an increase in the use of alternative endpoints, endoscopy remains an important objective measure of disease severity in IBD.⁴⁷ Indeed, the European Medicines Agency guidelines on the development of new medicinal products for the treatment of CD and UC state that co-primary endpoints should focus on the proportion of patients with symptomatic remission and with endoscopic remission.^{48,49}

Furthermore, high rates of placebo response (on symptom-driven endpoints) are a common phenomenon in IBD clinical trials.⁵⁰⁻⁵² Trials in which endoscopy is used to identify and enrol patients with more active disease (a more stringent criterion of Ulcerative Colitis Disease Activity Index endoscopy subscore ≥ 2 for study entry vs ≥ 1 for study entry) are associated with significantly lower placebo response rates than trials enrolling patients with less active disease (odds ratio 2.44, 95% confidence interval 1.16-5.15, $P = 0.019$ for Ulcerative Colitis Disease Activity Index endoscopy subscore ≥ 1 vs ≥ 2). Endoscopy at study entry also appears to be a better tool for assessing active disease than symptom-based criteria.⁵²

Despite the utility of endoscopy, its burden on the patient is a major hurdle in clinical trial recruitment. The requirement for repeated endoscopies in IBD clinical trials is a significant challenge for patients due to the invasive nature of the procedure.^{53,54} Indeed, fewer endoscopies has been identified as a factor that could make clinical trials more attractive to patients, ultimately increasing recruitment rates.¹⁵ Validation of alternative assessment measures in place of repeated endoscopy, including use of other imaging modalities and biomarker measurements, should therefore be prioritised.⁵⁵

Intestinal ultrasound is a non-invasive imaging modality with high acceptability among patients with IBD compared to endoscopy and other imaging modalities.^{53,56,57} Intestinal ultrasound is also well correlated with endoscopy.⁴⁶ Data on intestinal ultrasound for monitoring treatment response in UC are promising but limited, with most studies performed in single centres with special expertise in using the technique.⁵⁸⁻⁶⁰ Results from the multicentre TRansabdominal Ultrasonography of the bowel in Subjects with IBD To monitor disease activity with UC study suggest that intestinal ultrasound is a useful monitoring tool for UC. In the study, the percentage of patients with an increased bowel wall thickness in the sigmoid or descending colon decreased significantly after 2 weeks of treatment intensification and remained low at week 6 and 12, with normalisation of bowel wall thickness and clinical response after 12 weeks of treatment showing high correlation ($P < 0.001$).⁶¹ Evidence from multiple studies also supports the use of intestinal ultrasound in the management of CD and utility of the technique is already recognised in the European Crohn's and Colitis Organisation and European

Society of Gastrointestinal and Abdominal Radiology Guideline for Diagnostic Assessment.^{62,63} Altogether, intestinal ultrasound is recognised as a valuable tool with potential for improvement of the management of IBD and its development as a tool for both diagnosis and monitoring treatment response should be a priority for the IBD community.⁶²

As intestinal ultrasound remains underused in many countries, a coordinated approach will be required to implement its use into both clinical practice and clinical trials. A framework for the establishment of intestinal ultrasound in clinical practice has been proposed and a training curriculum has been developed by The International Bowel Ultrasound Group; both the framework and training curriculum will help build momentum to support the use of this technique.⁶² Furthermore, the recommended outcomes for disease modification trials recently proposed by the Selecting endpoints for disease-modification trials initiative are focused on regression of impact on patient life and disease complications. These outcomes have a reduced reliance on endoscopy and include many variables measurable by intestinal ultrasound.

Faecal biomarkers, including faecal calprotectin^{64–67} may supplement endoscopy and provide a non-invasive way to assess and diagnose IBD and therefore be more acceptable to patients than endoscopy.^{68,69} Faecal calprotectin has been shown to correlate with endoscopic disease activity in both CD and UC.⁴⁶ However, debate remains regarding the predictive capability and optimal cut-off ranges of faecal calprotectin, in addition to variability in the values observed based on the method used.^{46,47,70} Considering these limitations, faecal calprotectin may become valuable as part of a composite score that includes other measurements. In recent years, faecal calprotectin has been used as an experimental endpoint in IBD clinical trials.^{8,11,71} Such studies will shed further light on the potential of faecal calprotectin and it is recommended that trials incorporate faecal calprotectin as an endpoint accordingly.

There are ongoing projects to develop objective patient-reported outcomes, which include IDEA-FAST by the European Innovative Medicines Initiative.⁷² IDEA-FAST supports the development of digital technologies to measure the global burden of chronic disease, independent from organ- or indication-specific symptoms in a range of disease areas, including autoimmune and inflammatory conditions. IDEA-FAST aims to identify digital endpoints for fatigue and sleep disturbance that will provide a more sensitive, reliable measure of the severity and impact of these symptoms in a real-life setting. This will be achieved by identifying the characteristics of fatigue and sleep disturbance and the digital endpoints that could quantify them, selecting the digital devices and technologies that could measure and record these symptoms, and designing a secure digital management platform to support the acquisition, storage and analysis of these data.⁷² In addition to gaining new insights into the mechanisms behind fatigue and sleep disturbance, projects like IDEA-FAST are examples of novel ways to improve the reliability and dynamic range of patient-reported outcomes, and so speed up the development of new treatments for chronic diseases.⁷²

3.5 | Lessons learned from clinical trials conducted during the COVID-19 pandemic

The COVID-19 pandemic has presented a unique situation for the clinical trial community. Energy and resources have been focused on the rapid establishment of COVID-19 clinical trials resulting in many existing non-COVID-19 studies being temporarily paused (either a complete pause or a pause in some activities) and/or having to adapt their processes.⁷³ Such adaptations, which aim to prioritise safety for patients and healthcare teams amidst the pandemic, have impacted all aspects of trial function including gaining consent and recruiting patients into trials, data collection and management and intervention delivery.⁷³ Importantly, lessons learned from the management of patients with IBD during the COVID-19 pandemic have the potential to improve the conduct of future IBD clinical trials in a way that may positively impact patient recruitment.^{74,75}

Novel approaches to conducting trials during the COVID-19 pandemic have been supported by regulatory agencies including the US Food and Drug Administration (FDA). The FDA recommended that, as patients may not be able to come to the investigational site for protocol-specified visits, sponsors should evaluate whether alternative methods for safety assessments (eg phone contact, virtual visit, alternative location for assessment, including local laboratories or imaging centres) could be implemented, and be sufficient to assure the safety of patients.⁷⁵

While a variety of new strategies such as home delivery of medications have been adopted during the pandemic, telemedicine has been particularly useful. If applied more widely in IBD clinical trials, telemedicine may significantly minimise the time investment required from patients. This would likely have an impact on recruitment; recruitment rates have been shown to increase as the time required by patients decreases.¹⁵ Therefore, sponsors should think critically during protocol development about where telemedicine approaches could be included. For example, patients could be offered the option to perform a visit from home (via telephone or video conferencing) instead of requiring a trip to the hospital. If telemedicine could be paired with offsite monitoring (eg at-home faecal calprotectin testing), it would drastically reduce patient burden while increasing patient safety. From a patient perspective, the use of mobile technologies for remote collection of data is strongly preferred to traditional in-person trial visits.⁷⁶ This reflects sentiment in the IBD patient population where remote and telemedicine approaches in both clinical trials and clinical practice are seen as a favourable alternative to in-person visits outside of pandemic restrictions, even during flares.^{77,78}

3.6 | Reducing the administrative burden of IBD clinical trials

Clinical trials are associated with a substantial administrative burden which can place a significant financial burden on clinical trial sites that may not be recovered. Methods to reduce the administrative burden of clinical trials mainly involve changes to administrative procedures and documentation. An important step that should be implemented

as widely as possible is the use of electronic signatures for trial documentation. The use of electronic sources and archiving should also be considered. Acceptance of electronic signatures will circumvent the need for paper documentation and the associated circulation of the documentation between sponsors, clinical research organisations, investigators and local regulatory authorities. Electronic signatures would be suitable for most trial documentation including protocol signature pages, protocol amendments and documents provided to local or central institutional review board/independent ethics committees. Electronic signatures on informed consent forms which must be signed by patients, investigators and sometimes by independent witnesses may prove to be more difficult to complete electronically than other documentation. Regulatory factors may also impact the feasibility of using electronic signatures on informed consent forms. However, this option should be examined by sponsors.

Additional steps for reducing administrative burden involve the use of innovative web-based tools and patient-centred apps which could streamline data collection and minimise the time and resource investments required from all stakeholders. Furthermore, the use of the same software across different clinical trial programmes and sponsors, and a single-password approach to access all clinical trial systems on the vendor level would be beneficial. Simplified documentation and self-loading serious adverse event forms are further examples of how time investment may be minimised for both patients and clinical trial sites. In addition, consolidated and clear communication with investigators may reduce the impact on the investigators' time.

A lack of time on the part of physicians, both for the identification of ongoing trials and the patients that would be suitable for inclusion, is another major hurdle to trial recruitment.⁷⁹⁻⁸¹ Reducing the administrative burden on physicians would allow them to more efficiently screen patients and perform clinical trial duties.

A series of initiatives and tools are already being explored and developed by the research community to reduce the administrative burden on physicians and therefore enhance trial recruitment. These tools include open access search and analytical tools for electronic health records⁸² and the Feasibility And Recruitment System for Improving Trial Efficiency (FARSITE) software tool.⁸³ FARSITE consists of an anonymous database of patient records that can be searched by trial stakeholders to identify suitable patients. The physician caring for the patient is then contacted to ask whether they agree if the patient is a suitable candidate for screening. The Scottish Research Register (SHARE) is a register of patients who have consented to be contacted about opportunities to participate in research. Their electronic health records are stored in a database which can be searched by the SHARE team which contacts the patient about a suitable study. Patients interested in participation are then linked directly to the trial team removing the burden on physicians to identify patients.⁸⁴

Commercial products are also available that focus on lifting the administrative burden from physicians and they should continue to be explored and used by sponsors where feasible. Such services provide project management teams that for example, bridge the gaps between patient referral and site follow-up where many patients are lost and perform administrative tasks such as transfer of medical

records. Patient facilitators are also used to remove patient barriers to participation such as scheduling conflicts and lack of transportation to trial sites. Some commercial options also use networks of speciality physicians to identify high-quality patients for screening which greatly reduces screen failures. In some cases, physicians in these networks are reimbursed for time spent finding patients and reviewing their records. While ethical concerns exist around payments for these services,⁸⁵ compensating clinical trial referrals could be an effective way to overcome recruitment barriers due to the time-intensive nature of referrals.⁸⁶

4 | FUTURE PERSPECTIVES AND CONCLUSIONS

As long as an unmet medical need remains for patients with IBD, trials will be required to ensure the safety and efficacy of potential new therapies. Therefore, as recruitment for IBD trials becomes progressively more difficult, stakeholders in the community must take action to ensure trial conduct remains feasible.

This review has proposed a range of solutions that may be implemented to improve recruitment in IBD clinical trials. However, the proposals are not exhaustive and additional issues such as the increasing patient population size required for the conduct of trials should continue to be explored and addressed by stakeholders. While several of the solutions proposed can be implemented relatively easily, others (such as the use of master protocols) will require commitment and cooperation from stakeholders. Furthermore, it is time to put the patient at the centre of trial conduct, including through participation in the trial design process and by taking a thoughtful approach to incentivising patients. The COVID-19 pandemic ignited innovation in trial conduct and made it clear that implementing novel approaches does not need to be complicated. In the longer-term, additional factors have the potential to impact recruitment. These could include the use of big data, multi-omics and biomarkers, and we must continue to reevaluate their potential for improvement of trial conduct and recruitment.^{87,88}

We implore the IBD trial community to take steps towards implementing new strategies, including those explored here, to potentially improve recruitment rates for IBD trials and ultimately, bring new treatment options to patients as quickly and safely as possible.

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