Moving towards more patient-centred clinical trials in IBD

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Declining recruitment rates in inflammatory bowel disease (IBD) trials have resulted in calls to modify the conduct of trials in IBD in order to make them more efficient and patient centred. Here, we propose a number of potential modifications.

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Randomized clinical trials (RCTs) have had a pivotal role in supporting advances in inflammatory bowel disease (IBD) care. However, concerns are growing surrounding the ability to deliver future trials in IBD. The rising number of investigational agents undergoing late-phase assessment has increased the demand for trial participants. Conversely, the increased availability of licensed treatments has reduced clinical equipoise and reduced the incentive for trial participation. Increasingly rigorous trial schedules have also increased the burden of trial participation. The globally declining recruitment rates to IBD trials predates the coronavirus disease 2019 (COVID-19) pandemic[1,2], but concerns about declining recruitment rates have been magnified during this event. These concerns have resulted in calls to modify the conduct of trials in IBD in order to make them more efficient and patient centred[3].

During the COVID-19 pandemic, IBD trial activity has reduced majorly, even across sites with historically high levels of research involvement[4]. In response, suggestions were made for modifications to trials including considerations for remote visits, possible alternatives to endoscopic investigation and strategies to minimize steroid exposure. Although these modifications were proposed to be temporary, they might also offer some longer-term solutions to the ongoing difficulties of IBD trials[5].

Informed consent is a critical process in RCTs and has typically occurred during face-to-face clinical visits. This practice reflects existing regulatory requirements for handwritten, dated and signed consent forms, as well as physician and patient familiarity with counselling during an in-person visit. During the COVID-19 pandemic, clinicians have become increasingly familiar with remote consultation and, at the same time, trial sponsors have had to consider the possibility of electronic consent (e-consent). This change has been associated with high levels of participant satisfaction, particularly when user-friendly interfaces are used and where participant requirements are clearly presented. The benefits of e-consenting also include widening access and opportunities to more individuals, including those living in remote settings and those who have difficulty attending clinic visits. The merits of e-consenting, however, will need to be considered on a trial-by-trial basis, and it will be appropriate for the consent process of RCTs to retain the opportunity for patients to have a detailed discussion with physicians. Nevertheless, we suggest that these discussions are possible within a remote consultation, affording the opportunity to reflect on treatment schedules and potential risks without the inconvenience (and perhaps indirect pressure) of an in-person visit.

Historically, when few treatments were available for IBD, the demand for more effective interventions was clear and trial participants were regarded as the ‘lucky few’. Nowadays, with a growing number of licensed treatment options, it has become increasingly important to consider the convenience of therapies as well. Indeed, patient preferences have been highlighted as one of the key drivers behind subcutaneous and oral drug development programmes. Additionally, research has now shown that patients are more likely to participate in RCTs that have limited or no placebo interventions and where there is also a possibility of open-label extension to active treatments[6]. For both ethical and scientific reasons, we feel that sponsors should consider trial designs with active comparator arms alongside new treatments.

Again, the COVID-19 pandemic has accelerated a global shift towards telemedicine and virtual health-care provision. This change has caused some apprehension among sponsors, as many trial schedules have historically mandated face-to-face assessments to ensure accuracy of data collection. Nonetheless, evidence from the pandemic has shown that it is possible to conduct predominantly virtual consultations and still ensure accurate, remote data collection[4].

A key criticism of many current IBD trial schedules is that they are overly burdensome for patients, resulting in negative effects on both recruitment and retention. In this regard, we advise early engagement with patient and public involvement representatives, to improve patient acceptability of trial designs. In particular, the collection of biological samples and monitoring of biological parameters has previously been seen as a necessity for

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patients to attend hospital clinics. However, technologies to enable home testing for blood and stool samples, used alongside results extracted from routinely collected health data (RCHD), offer substantial promise and the opportunity for change. Although the concept of using RCHD for RCT follow-up might seem unrealistic given the many challenges surrounding data access, evidence is increasing that these challenges can be overcome[7], and we believe that integrating systems to allow the use of RCHD should be a priority area of focus in the field.

Patient-reported outcome measures are increasingly being used for RCTs in IBD. Alongside patient-reported outcome measures, endoscopic assessment has emerged as a critical objective end point, given the increasing evidence of association with longer-term outcomes[8]. Conversely, patients with IBD have consistently identified that the need for endoscopy, and especially the need for multiple endoscopies, is a factor that would decrease their likelihood of participation in research[6,9]. This challenge is a difficult one to overcome and we note the recent SPIRIT consensus recommendations, which suggest that noninvasive measures might be considered an appropriate, future, objective end point in IBD[10]. Despite widespread acknowledgement for the benefits of noninvasive tests such as faecal calprotectin, ultrasound or MRI, these measures are not recognized by regulators as suitable end points for registration of trials owing to a lack of validation. Even in early-phase trials, the precedent for using these modalities as a primary outcome measure is limited. A crucial aspect for progression in the field will be to generate validated, quantitative data from noninvasive modalities correlating with endoscopic findings, such that these noninvasive targets could be adopted as co-primary end points in future trials.

The number of potential therapeutic options for IBD is growing, and RCTs remain the gold-standard method of assessment for efficacy and safety. However, there is an increasing recognition that IBD trials need to become more patient centred, and we have proposed a number of potential modifications. For some of these, such as e-consenting and remote data collection, the technology and infrastructure is already well developed, and what is required is a shift in the stance of sponsors. Other changes, such as the increased use of active comparators, will require greater shifts away from traditional trial designs but are absolutely deliverable. Further development of noninvasive end points to satisfy regulators will require considerable effort, but should be an area of priority in this next era of improvement for RCTs in IBD.

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