



Viewpoint

# Clinical Trials [and Tribulations]: The Immediate Effects of COVID-19 on IBD Clinical Research Activity in the UK

Nurulamin M. Noor,<sup>a,b,c,e</sup> Ailsa L. Hart,<sup>d</sup> Peter M. Irving,<sup>e,f</sup> Subrata Ghosh,<sup>g</sup> Miles Parkes,<sup>a,b</sup> Tim Raine<sup>a</sup>

<sup>a</sup>Department of Gastroenterology, Addenbrooke's Hospital, Cambridge University Hospitals NHS Trust, Cambridge, UK  
<sup>b</sup>Department of Medicine, University of Cambridge School of Clinical Medicine, Cambridge, UK  
<sup>c</sup>Medical Research Council Clinical Trials Unit, University College London, London, UK  
<sup>d</sup>St Mark's Hospital, IBD Unit, Harrow, London, UK  
<sup>e</sup>IBD Centre, Guy's and St. Thomas' NHS Foundation Trust, London, UK  
<sup>f</sup>School of Immunology and Microbial Sciences, King's College London, London, UK  
<sup>g</sup>Institute of Translational Medicine, NIHR Biomedical Research Centre, University of Birmingham, Birmingham, UK

Corresponding author: Dr Tim Raine, MB BChir PhD, Department of Gastroenterology, Addenbrooke's Hospital, Cambridge University Hospitals NHS Trust, Hills Road, Cambridge CB2 0QQ, UK. Tel.: +441223 245151; email: [tim.raine@addenbrookes.nhs.uk](mailto:tim.raine@addenbrookes.nhs.uk)

## Abstract

There have been immediate and profound impacts of SARS-CoV-2 and COVID-19 on health care services worldwide, with major consequences for non COVID-19 related health care. Alongside efforts to reconfigure services and enable continued delivery of safe clinical care for patients with IBD, consideration must also be given to management of IBD research activity. In many centres there has been an effective shutdown of IBD clinical trial activity as research sites have switched focus to either COVID-19 related research or clinical care only. As a result, the early termination of trial programmes, and loss of potentially effective therapeutic options for IBD, has become a real and worrying prospect. Moreover, in many countries research activity has become embedded into clinical care—with clinical trials often providing access to new therapies or strategies—which would otherwise not have been available in standard clinical pathways. This pandemic has significant implications for the design, conduct, analysis, and reporting of clinical trials in IBD. In this Viewpoint, we share our experiences from a clinical and academic perspective in the UK, highlighting the early challenges encountered, and consider implications for patients and staff at research sites, sponsors, research ethics committees, funders, and regulators. We also offer potential solutions both for now and for when we enter a recovery phase from the pandemic.

**Key Words:** Clinical trials; COVID-19; SARS-CoV-2

## 1. Introduction

There has been a rapid and coordinated IBD-specific consensus to tackle some of the clinical challenges from severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] causing coronavirus disease 2019 [COVID-19].<sup>1–3</sup> Whereas there has been an appreciation of the clinical impact,<sup>4</sup> there is limited literature on the impact of infectious disease outbreaks on IBD research activity. There are likely

to be many lessons to learn for the IBD community to overcome the challenges of the COVID-19 period, and enable preparedness for future epidemics or pandemics. We offer here our perspective on the nature of the challenges that must be overcome and lessons that must be learned, drawing in particular upon data from a survey of leading IBD trial centres in the UK. In an accompanying article in *JCC*, colleagues at the International Organization for the study of

IBD [IOIBD] have provided useful guidance regarding ongoing clinical trial conduct, which serves to complement many of the findings and solutions offered in this Viewpoint.<sup>5</sup>

## 2. Progress before COVID-19

Recent progress in IBD clinical research has resulted in an impressive pipeline of medications new to registration or in early- or late-phase clinical trials.<sup>6</sup> Given the clear association between sites with greater research activity and better clinical outcomes,<sup>7–10</sup> clinical care has become intertwined with trial provision across many centres—often providing access to new therapies or strategies that would otherwise not be available in standard clinical pathways.<sup>11</sup>

The ‘success’ of agents from early stage through to regulatory approval has been dependent on clinical trials recruiting sufficient numbers of patients to be adequately powered to draw informed conclusions.<sup>12</sup> However, enrolment to interventional trials—particularly those with a placebo arm—is a difficult and often underestimated task, with a need for equipoise, detailed informed consent discussions, delivery of care to trial protocols, reporting on patient safety, and performing a variety of procedures, with collection of samples and data points often with prolonged follow-up.<sup>13</sup> Even before the SARS-CoV-2 period, and in the context of growing numbers of licensed treatments, there had been increasing concerns about declining recruitment to trials in IBD globally.<sup>14</sup>

Lower than expected enrolment gives rise to many potential problems. These include: the need for trial sponsors to seek and gain approvals and extensions from ethics committees, regulators, and funders; protocol amendments which, if substantial, can be costly and time consuming to enact as well as affecting the validity or perceived validity of final trial results<sup>15</sup>; and a delay or cessation of development programmes for potentially promising interventions.<sup>16</sup> Indeed, difficulties in patient recruitment were cited as a major reason behind the decision not to proceed with phase III trial investigation for apremilast, an oral inhibitor of phosphodiesterase 4—despite promising efficacy signals in a phase II trial for ulcerative colitis [NCT02289417].<sup>17</sup>

In the context of the SARS-CoV-2 pandemic, there has been a widespread shutdown of IBD clinical research activity as research sites have focused on COVID-19 related research and/or provision of core elements of clinical care only.<sup>18</sup> Accordingly, the early termination of programmes, and the loss of further potentially effective treatments for IBD, have become a real and worrying prospect.

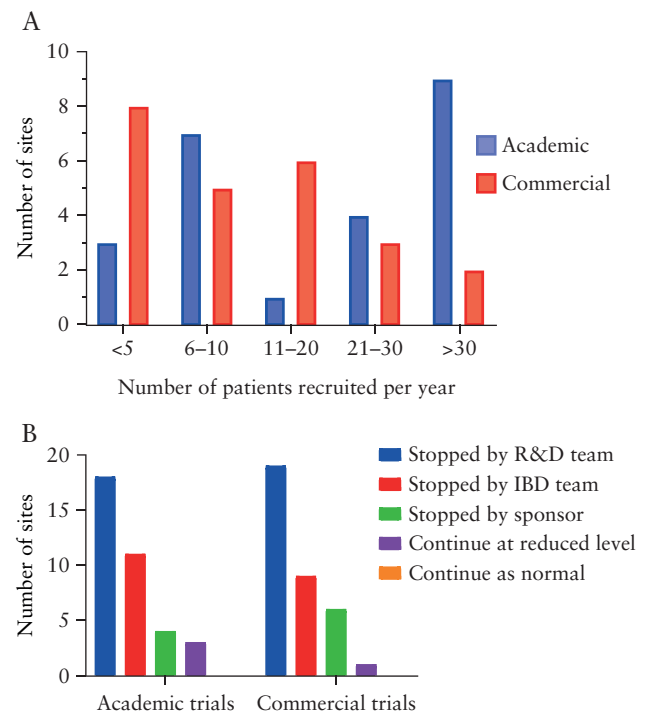
## 3. Impact on trial recruitment

To assess the impact of SARS-CoV-2 on IBD-specific trial activities, we surveyed consultant gastroenterologists at 25 centres across the UK—collectively responsible for over 700 estimated patients recruited into IBD clinical trials in the 12 months preceding onset of the SARS-CoV-2 pandemic [Figure 1A]. The majority of sites surveyed reported a halt to recruitment across both academic [investigator-initiated] and commercial [industry-sponsored] trials [Figure 1B]. The main driver appears to have been guidance from local research and development [R&D] departments. However, there are likely to have been many factors driving decisions for each trial and in many instances the R&D team, local IBD team, and sponsors will have aligned in recommending a halt to recruitment. Although no sites reported enrolment as normal, some sites which retained the capacity and capability to do so, reported ongoing recruitment to trials but at a reduced rate.

The regulatory approach taken in the UK is broadly typical of other European countries: the UK National Institute for Health Research has suspended a new site set-up for research activities,<sup>19</sup> and for those sites already set up, considerations can broadly be categorised into those for potential new participants and those for patients already participating in clinical trials. For these two groups, the Health Research Authority governing health research in the UK,<sup>20</sup> and the Medicines and Healthcare products Regulatory Agency [MHRA] regulating clinical trials in the UK,<sup>21</sup> have issued comprehensive guidance.

For each trial and each patient, careful consideration of the relative benefits and risks of research participation is required.<sup>22</sup> This includes the risk of exposure to SARS-CoV-2 during attendance at, or travel to, any required clinical encounters. Other factors include the availability of licensed treatments, and of such assessments as can be made of the potential relative efficacy of these compared with trial medications. Likewise, the safety profile of licensed treatments and trial medications should be considered, often in the context of limited safety information for new therapeutics, and should be continually reassessed with respect to what is known about risks of COVID-19.

Additionally, sites have to assess the practicality of being able to deliver clinical trial activity. Here commitments to existing trial participants must take priority over enrolment of new patients. For many sites it is impractical to continue new recruitment given the decreased availability of research staff. This finding is supported by our



**Figure 1.** Recruitment of patients to IBD clinical trials before COVID-19 and impact of SARS-CoV-2 on clinical trial enrolment. [A] Interventional clinical trial recruitment to both academic and commercial clinical trials the 12 months preceding the COVID-19 period. [B] Impact of SARS-CoV-2 on enrolment to IBD research activities demonstrated across academic and commercial clinical trials. Multiple answers could be selected from each site to indicate multiple drivers for recruitment decisions. Results from survey of research active inflammatory bowel disease [IBD] sites across the UK [ $n = 25$ ].

observation of high rates of redeployment for research nurses and research fellows to alternative clinical duties [Figure 2A].

Existing trial participants who are considering ongoing research participation are in general more likely to have demonstrated benefit from trial participation and safely tolerated the medication under investigation, hence shifting considerations for both risks and benefits when compared with licensed alternatives. This is not the case for new patients, who must often also consider the risk of placebo randomisation, with the ensuing possibility for lack of disease control.

Any failure of disease control is not only associated with obvious morbidity but there is potentially an increased risk of COVID-19 in the context of active IBD. The TREAT registry has demonstrated that patients with active IBD are at higher risk of developing serious infections,<sup>23</sup> and there does appear to be an increased association between active IBD and serious viral infections.<sup>24</sup> It is reassuring that, to date, no significant increases in COVID-19 presentation among patients with IBD have been reported compared with the general population, even in areas of high prevalence for COVID-19.<sup>25</sup> Nevertheless, a recent Italian study,<sup>26</sup> and early findings from the global IBD-SECURE registry,<sup>27</sup> suggest that active disease is indeed a risk factor for adverse outcomes with COVID-19 in IBD. Thus the key goal, as ever, must be to control active disease using the safest strategy available.<sup>1,2</sup>

#### 4. Impact on trial continuation

A key decision for each trial is whether to continue, pause, or formally halt recruitment. This may vary according to trial stage.

##### 4.1. Phase I trials

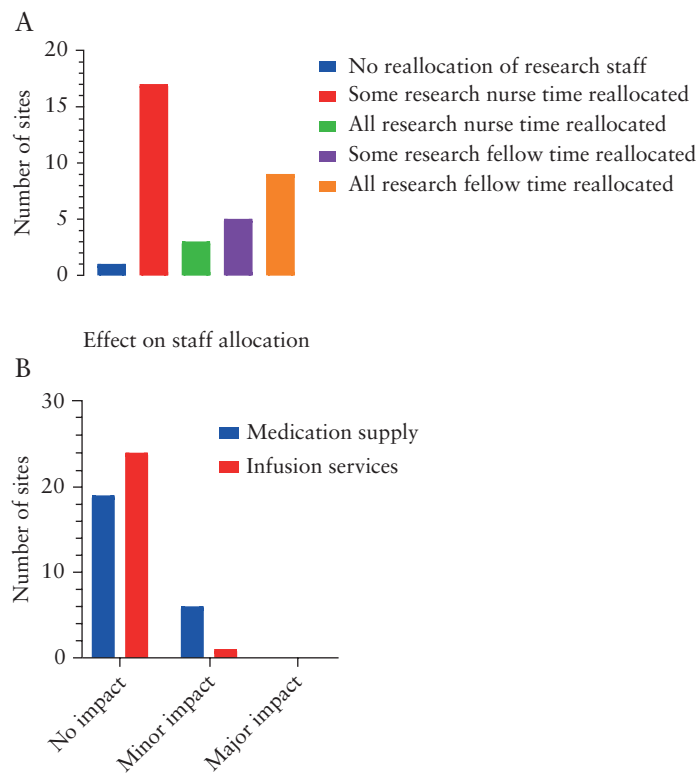
Phase I trials of potential therapeutics typically enrol healthy volunteers and the main outcome of interest is safety.<sup>28</sup> Given there is unlikely to be clinical benefit for healthy volunteers taking part in such trials, and the potential risks associated with both the clinical encounters and the therapeutic under investigation, we would strongly advise stopping phase I trial activity for potential IBD therapies during the SARS-CoV-2 pandemic.

##### 4.2. Phase II trials

Phase II trials typically assess dose response and early signals of efficacy.<sup>28</sup> Here the potential risks from any novel immunosuppressive agents and dosing uncertainties are greater than in later-phase clinical trials. There are also appropriate concerns regarding randomisation to placebo, the requirement of many protocols for a stable dose of steroid medications or slow tapering of steroid doses, and lesser use of open-label extension programmes in the phase II trial setting. Given these observations, for patients where there are well-established clinical care pathways and licensed treatment options available, phase II trial enrolment will require special justification in the present climate.

##### 4.3. Late-phase trials

For phase III trials assessing efficacy of interventions, open-label extension, and post-registration trials, as well as strategy trials, considerations will differ. Given risks from active inflammation, and the potential lack of efficacious and safe alternatives for many patients, the balance of benefit and risk may be shifted in favour of



**Figure 2.** Impact of SARS-CoV-2 on research staff availability, medication supply, and infusion services. [A] Reallocation of research staff in response to SARS-CoV-2, including some or all of time for research nurses and/or research fellows allocated to clinical activities. Multiple answers could be selected for each individual site to indicate effect on research nurses and/or fellows. [B] The impact of SARS-CoV-2 on trial medication supplies and on ability to deliver infusions for participants enrolled within clinical trials for inflammatory bowel disease [IBD]. Results from survey of research active IBD sites across the UK [ $n = 25$ ].

trial participation. In particular, high-dose steroids are actively discouraged in the context of COVID-19,<sup>1,2</sup> and elective IBD surgery has effectively been cancelled or severely curtailed in many centres. Outpatient IBD care may thus be combined with ongoing trial provision and access to novel medications, paradoxically, may be needed more than ever.

For clinical trials of investigational medicinal products [CTIMPs] where a formal temporary halt is felt appropriate by sponsors on safety grounds, an urgent discussion with the regulators should take place to determine if a substantial amendment should be submitted.<sup>21</sup> It is important to note that many research ethics committees have been inundated with applications from COVID-19 specific trials as well as amendments to trials as a consequence of SARS-CoV-2. Although in many countries ethics committees have agreed to fast-track such amendments, resumption of trial activities following subsequent application is difficult to predict, and it will be important that ethics committees treat future applications to restart activity with an equal degree of priority.

## 5. Impact of COVID-19 on trial conduct

### 5.1. Trial treatment and access to medications

For patients on IBD therapies who are in remission, in most cases treatment should continue, including the continuation of infusion services and investigational medications.<sup>1,2</sup> For sites unable to provide care as per trial protocols, discussion with trial sponsors is advised.<sup>20</sup> Reassuringly, access to trial medications and trial infusion services across sites we surveyed have so far been maintained or only minimally affected [Figure 2B]. For instances where infusion services for trial medications come under pressure locally, then appropriate potential solutions include moving these infusions to ‘clean, non COVID-19 sites’.

It remains important for sites to plan ahead with appropriate stock to ensure treatment continuation in case of distribution failure. We would advise discussions with sponsors regarding supply of trial-specific therapies. For non-invasive treatments, delivery direct to the homes of participants by trial sponsors should be explored and indeed is being encouraged by regulators such as the MHRA.<sup>21</sup> For trials using established clinical therapies such as strategy trials, we note commendable collaborative efforts to minimise disruptions to medication supply, such as the industry single point of contact [i-SPOC] system. This system allows pharmaceutical companies to report directly to the European Medicines Agency [EMA], in parallel to national authorities, so that shortage of medications can be anticipated and mitigated well in advance of problems occurring.<sup>29</sup>

### 5.2. Trial follow-up and procedures

In an attempt to reconcile the need for continued follow-up and to minimise risks from clinical contact, there has been a mass shift to telemedicine and virtual clinics as initially demonstrated by colleagues in China.<sup>25</sup> This extends to clinical trial visits, and the majority of UK sites we surveyed have switched either to virtual visits or to a mixture of virtual and face-to-face visits [Figure 3A]. Nevertheless, for many trial protocols, in-person visits remain critical, especially where physical observations and measurements are required. In this regard, endoscopic IBD assessment during the SARS-CoV-2 era represents a particular challenge.<sup>30</sup>

A total of 15 of the 25 sites we surveyed reported halting all endoscopy and imaging for research activities [Figure 3B], reflecting urgent consensus guidance for endoscopy services that only emergency

or essential procedures take place.<sup>31</sup> However, endoscopic assessment is increasingly critical to IBD trial conduct, with a recognition that endoscopic outcomes are well correlated with longer-term clinical outcomes.<sup>32</sup> This tension requires early discussions between trial sponsors and research sites. There is an onus on sponsors to consider amendments to minimise risk to both patients and staff through the use of alternative non-invasive endpoints such as faecal calprotectin. Reassuringly, regulatory agencies such as the EMA have issued guidance that a proportionate approach will be taken to considering such protocol deviations and amendments if required.<sup>33</sup>

Many IBD trial teams have also moved to ‘critical data collection only’. We highlight the variation between sites for definition of ‘critical data collection’ and contrast this with data that will be collected during this period [Figure 3C]. In our survey, both clinical symptom scores and questionnaires were consistently rated as ‘critical data collection’ and items that sites would continue to collect.

The detection of SARS-CoV-2 ribonucleic acid [RNA] in different clinical specimens,<sup>34</sup> including from stool samples,<sup>35</sup> raises questions about collection and transport of samples, although the clinical significance of virus detection, differing viral loads, and the consequences for transmission are still unclear.<sup>36</sup> Home calprotectin testing,<sup>37</sup> and point of care calprotectin testing, are both promising strategies<sup>38</sup> which sponsors could consider incorporating into trial protocols. In this regard, we strongly advise patient and public involvement/engagement to inform decisions about both ongoing trial participation and which aspects of trial schedules and sample collection would be feasible from a patient perspective.

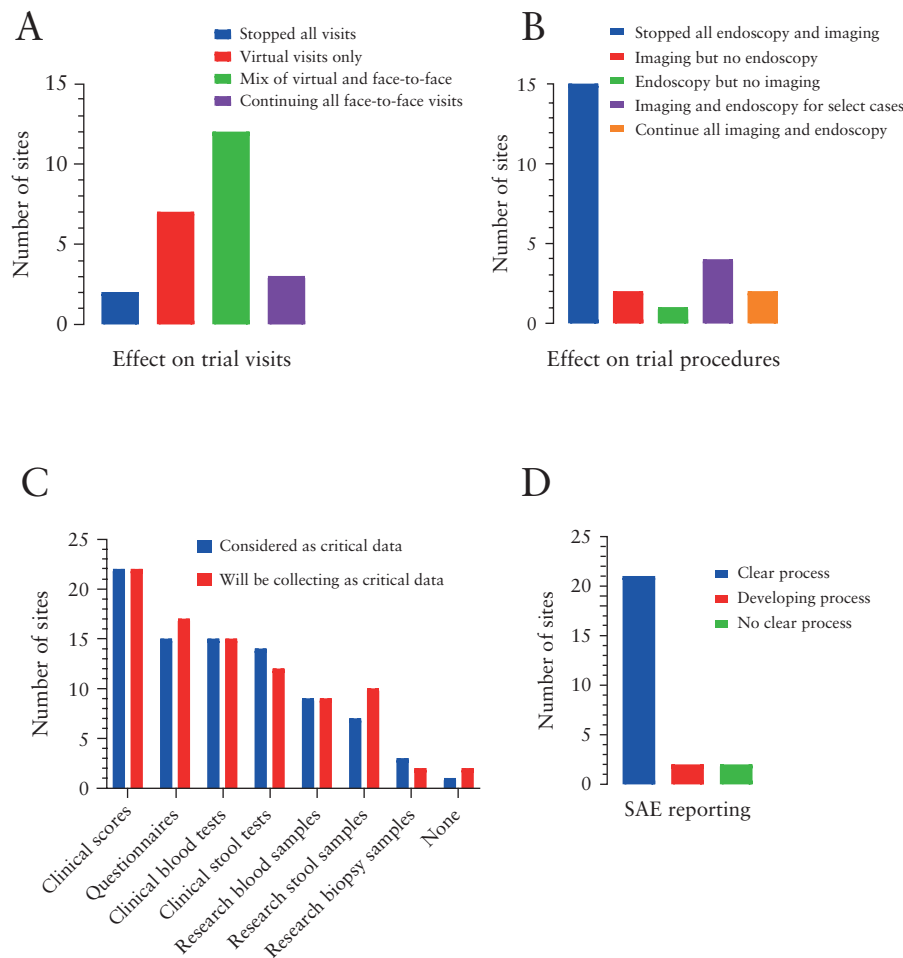
To facilitate and minimise burden on trial sites, sponsors should consider which aspects of protocols can be amended to ensure safety of participants and staff, while still preserving trial integrity. Given the reallocation of research staff time, the onus is on sponsors to reduce administrative burden for sites, including reduced frequency of data queries and moving to remote monitoring of trials. Commendably, the UK MHRA has already demonstrated such pragmatism by stopping all but essential trial inspections during this period.<sup>21</sup>

In considering protocol amendments, the hierarchy of endpoints for each trial must be considered. For example, where endoscopic or imaging findings are secondary or exploratory outcomes, sponsors may have to accept missing procedures and employ statistical methods to handle these missing data.<sup>39</sup> Conversely, if the primary endpoint is endoscopic or radiological, then investigators have to balance their obligations for ensuring preservation of trial validity,<sup>40</sup> against resources and risks to both patients and staff. The ability to collect data will vary by data type, by patient, by site, and by time—hence considerable flexibility will need to be allowed in protocol amendments following the principle that some data collection is always better than no data collection. In particular, for patients with active disease, the benefits of clinical tests to ensure safety likely outweigh potential risks. However, for patients in remission, the risks of clinical contact and providing samples particularly for exploratory research sample collection, are unlikely to be justified.

For continuation of therapy, including appropriate open-label extension programmes, we feel there is an obligation for sponsors to offer access to active therapy for patients, regardless of whether trial procedures can be performed or not.

### 5.3. Safety reporting and considerations

Safety of participants in clinical trials is of paramount importance and serious adverse event [SAE] reporting is considered a critical aspect of this—with an expectation that strict reporting timelines will



**Figure 3.** Impact of SARS-CoV-2 on inflammatory bowel disease [IBD] research trial visits, procedures, data collection, and readiness for serious adverse event reporting. [A] Impact of SARS-CoV-2 on method for conducting IBD research trial clinic visits. [B] Impact of SARS-CoV-2 on conduct of IBD research endoscopy and imaging procedures. [C] Data considered 'critical trial data collection' compared with data that will be collected at each local site as part of 'critical trial data collection'. Multiple answers could be selected for [C]. [D] Readiness for serious adverse event reporting in terms of both process and personnel at sites, to enable prompt reporting for patients taking part in an IBD trial hospitalised with COVID-19. Results from survey of research active IBD sites across the UK [ $n = 25$ ].

be maintained even in the context of SARS-CoV-2.<sup>21</sup> Whereas safety reporting can vary between trials, hospitalisation with COVID-19 will fulfil requirements for SAE reporting. Reassuringly, of sites we surveyed, almost all teams have local processes and personnel in place to allow such reporting [Figure 3D].

An important further consideration is that most clinical trials would not advocate co-enrolment into another interventional clinical trial. However, in the current climate, we regard it as unethical not to allow patients already taking part in an IBD trial to also enrol into a trial for COVID-19 if hospitalised.

## 6. Future perspectives

Even before the advent of SARS-CoV-2, there was a growing realisation of the many problems for trial recruitment in IBD and the need for more efficiency in IBD trials.<sup>41</sup> This was characterised by multiple competing individual trials in IBD<sup>44</sup> with multiple control [often placebo] groups, and current regulatory requirements such as the need for two identical, but separate, induction trials in the phase III setting—with each induction cohort requiring several hundreds of patients to be recruited.<sup>42</sup> These inefficiencies will be felt more

keenly during and after the COVID-19 period, and left unmitigated will carry significant risks of delay [at best] or potentially early termination for promising therapeutic options.

### 6.1. Trial design, analysis, and reporting

There is an urgent need for regulatory agencies to re-assess registration requirements for IBD trials. The current climate has highlighted the need to reduce inefficiencies such as performing two, separate induction trials for phase III trials of new therapeutic agents. The distinction between induction and maintenance is to some extent artificial and dependent on the response for each individual patient and the mechanism of action for the treatment under investigation. It is also worth reflecting that in analogous immune-mediated conditions across rheumatology and dermatology, it is quite typical to treat patients for an extended initial period of time and then review onset of action and efficacy over longer-term follow-up.

In this respect, a potential alternative for regulators would be to advocate for single, phase III induction trials and allow further regulatory requirements to be explored in subsequent mandated, larger post-registration trials. Taking such positive steps would offer welcome relief to trial sponsors and funders and still enable generation



of sufficient data to provide useful answers after the SARS-CoV-2 period. However, a failure to address these issues in the near future by regulatory bodies may otherwise contribute to the early closure of many IBD trials due to insufficient recruitment.

Historical approaches to address the challenges of recruitment have included leveraging information from control arms of previous clinical trials of similar populations. The phase II trial of secukinumab, an anti-interleukin 17A antibody [NCT01009281], in Crohn's disease statistically combined patients in the placebo control group with others drawn from six previous trials in Crohn's disease, and generated a useful early signal for lack of efficacy, allowing appropriate and efficient discontinuation of the development programme.<sup>15</sup> More recently, the paediatric ulcerative colitis ENVISION phase III trial [NCT02065557], in response to low recruitment, used pooled control group data from historical ulcerative colitis trials. Importantly, this use of historical, placebo-controlled data was an adaptation made while the trial was ongoing and had already been open to enrolment for several years. This amendment was made following discussions and approval from the United States Food and Drug Administration [FDA], with no impact on use of the trial data for subsequent drug registration/labelling purposes.

Appropriate caution regarding the use of historical control groups reflects concerns around selection bias, inflation of type one error rates [ie, greater false-positive findings for interventions in these trials], and the non-contemporary nature of observations.<sup>43</sup> Accordingly, using richer patient-level datasets and appropriate statistical models to predict outcomes for a 'virtual control group' are a potentially attractive solution for future trials.<sup>44</sup>

Perhaps the best opportunity for improving efficiency of trials in IBD is for adoption of adaptive platform designs,<sup>45</sup> which have been used with enormous success in the oncology field.<sup>46–48</sup> A platform trial seeks to answer multiple primary research questions as opposed to the single research question being addressed by two-arm, parallel-group trials. This is typically characterised by a single, master protocol with a shared control arm, meaning fewer patients are required overall compared with multiple separate trials.<sup>49</sup> A shared control arm approach also results in greater allocation of patients to active interventions and ensures less competition between trials. There are further efficiency savings—notably avoiding the often excessive time taken to open sites for separate trials,<sup>50</sup> and reducing the number of individual regulatory discussions,<sup>51</sup> meaning that platform trials can both start and recruit at much greater speed than trials using classical designs.

The 'adaptive' element, allows for early stopping of interventions showing lack of benefit at interim analyses and for the addition of potentially promising future interventions, as they become available.<sup>52</sup> Importantly, the addition of intervention arms is through an approved protocol amendment rather than through the launch of a new, stand-alone, competing trial.<sup>53</sup> Adaptive platform trials are particularly attractive for potential sponsors and funders, given the reduced financial costs and time saved compared to traditional designs. Overall trial costs are shared across all partners contributing to the trial and answers can be achieved at a much faster rate than would have been possible through multiple, individual, two-arm trials for each research question.

It should be noted that adaptive and platform designs were already being explored and initiated before the SARS-CoV-2 period, with both design-specific and IBD-specific challenges being addressed. Design-specific challenges include: length of time and preparation before initiation of adaptive trials, optimising statistical parameters for interim analyses, data management and logistical implementation of amendments, and how best to share trial data

between each commercial company contributing to the platform. IBD-specific challenges include: consideration of washout periods for individual medications, assessing the impact of combination therapies, and selection of appropriate endpoints. Focusing efforts on addressing these challenges, with an emphasis on training, should allow greater adoption of adaptive platform trials in IBD and help deliver faster answers for both patients and clinicians.<sup>54</sup>

An important consideration for the near future is that several clinical trials open to recruitment in IBD share almost identical inclusion/exclusion criteria and trial assessments. Therefore, a key question will be whether it is practical to combine control arms from these existing trials, creating a *de facto* platform, with a shared comparison arm across interventions. We recognise that this is highly unorthodox, indeed anathema to the dogma of conventional trial design. However, in the extraordinary conditions in which we now find ourselves, thinking such previously unthinkable thoughts might represent the difference between multiple, methodologically sound but failed trial programmes or the salvage of data that might usefully inform either future trial development or future access to a therapeutic which improves clinical care. In this context a 'good' trial, even if not perfect, may be better than no trial at all.<sup>55</sup> One thing is clear—such approaches would need significant cooperation between commercial sponsors, funders, and regulatory bodies, with a need for careful discussions and collaboration with trial methodologists, statisticians, and academic partners.

As an adjunct to these approaches, there is also a need for greater collaboration and sharing of data from clinical trials.<sup>56</sup> This includes centralised repositories of trial outcome data, as well as greater access to individual patient data [IPD] from trials.<sup>57</sup> Such methods of data sharing would help facilitate more powerful meta-analyses using either aggregated or IPD data across multiple trials—to enable comparison or ranking of effective treatments, helping determine how best to position therapies, and identifying subgroups of patients where individual treatments might be most effective.<sup>58</sup>

## 7. Conclusions

This Viewpoint discusses the immediate and profound impacts of SARS-CoV-2 and COVID-19 on IBD clinical trials, illustrated with observations from major IBD trial centres across the UK.

It is clearly inappropriate to continue as usual for all clinical trials in IBD. Equally, stopping all clinical trial activity will inevitably expose some patients to risks from uncontrolled, active inflammation. Therefore each clinical trial, and activity within that trial, will need careful risk/benefit analysis. It is important for these decisions to be reviewed regularly and for sites to have plans in place to restart recruitment and rebuild momentum once the pandemic subsides.

There is a moral and legal commitment to existing participants in clinical trials to ensure safety; in the majority of instances this will involve securing ongoing access to current treatments, including open-label extensions where indicated. Pragmatic discussions between sites and sponsors should support delivery of telemedicine and virtual visits, greater levels of self-reported patient data, and protocol amendments to minimise the need for samples, procedures, and other invasive activities, with emphasis on preserving integrity of primary endpoint data.

The COVID-19 pandemic will likely have a sustained impact that may be felt very differently at different sites. But it is clear that, once the pandemic subsides, there must be a 'new normal' with multiple opportunities for change that have the capacity not only to salvage existing trial programmes but also to advance the design and delivery of future trials.

## Funding

This work was not supported by any specific funding. NMN is supported by a Medical Research Council PhD Studentship [MC\_UU\_171339].

## Conflict of Interest

NMN and MP declare no conflicts of interest relevant to this work. ALH declares advisory or lecture fees from AbbVie, Allergan, BMS, Celgene, Celltrion, MSD, Takeda, Shire, Ferring, Roche, Janssen, Pfizer, Tillotts, outside the submitted work. PMI declares lecture fees from AbbVie, Warner Chilcott, Ferring, Falk Pharma, Takeda, MSD, Janssen, Shire, Pfizer, Tillotts, Sandoz, financial fees for research from MSD, Takeda, Janssen, Pfizer, advisory fees from AbbVie, Warner Chilcott, Takeda, MSD, Vifor Pharma, Pharmacosmos, Topivert, Genentech, Hospital, Samsung Bioepis, VH2, Janssen, Sandoz, Lilly, Celgene, Prometheus, Gilead, outside the submitted work. SG declares consulting fees from Pfizer, Janssen, AbbVie, Bristol-Myers Squibb, Receptos, Celgene, Gilead, Boehringer Ingelheim, and speaker fees from AbbVie, Janssen, Takeda, Ferring, Shield, Falk Pharma, outside the submitted work. TR declares an unrestricted research grant from Abbvie, personal fees from MSD, Takeda, Abbvie, GSK, Sandoz, Celgene, Pfizer, Janssen, Gilead, BMS, Ferring, LabGenius, Mylan, UCB, non-financial support from Abbvie, Novartis, Janssen, Ferring, outside the submitted work.

## Acknowledgments

We are grateful to all the individuals who completed a survey to assess the impact of SARS-CoV-2 on IBD research activity around the UK. Respondents are listed in alphabetical order by surname; Tariq Ahmad [Royal Devon and Exeter Hospital, Exeter], Matthew Brookes [Royal Wolverhampton Hospital, Wolverhampton], Rachel Cooney [Queen Elizabeth, Birmingham], Fraser Cummings [University Hospital, Southampton], Anjan Dhar [County Durham and Darlington Hospital, Darlington], Shahida Din [Western General Hospital, Edinburgh], Dharmaraj Durai [University Hospital of Wales, Cardiff], John Gordon [Hampshire Hospitals, Winchester], Matthew Johnson [Luton and Dunstable Hospital, Luton], Alexandra Kent [King's College Hospital, London], Eirini Kolokouri and Johanne Brooks [Norfolk and Norwich University Hospital, Norwich], Christopher Lamb and Ally Speight [Newcastle upon Tyne Hospitals, Newcastle], James Lindsay [Barts Health, Royal London Hospital, London], Gordon Moran [Nottingham University Hospitals, Nottingham], Craig Mowat [Ninewells Hospital, Dundee], Kamal Patel [St George's Hospital, London], Christian Selinger [Leeds Teaching Hospital, Leeds], Sebastian Shaji [Hull and East Yorkshire Hospitals, Hull], Melissa Smith [Royal Sussex County Hospital, Brighton], Philip Smith [Liverpool University Hospitals, Liverpool], Simon Travis [John Radcliffe Hospital, Oxford], Horace Williams [St Mary's Hospital, London]. The remaining three sites surveyed include collated responses from the co-authors [Addenbrooke's Hospital, Cambridge; St Mark's Hospital, London; Guy's and St Thomas' Hospital, London].

## Author Contributions

NMN, MP, and TR conceived of the idea and were responsible for the planning, content, and structure of the article. NMN wrote the initial manuscript draft with input and oversight from TR. ALH, PMI, SG, and MP reviewed the article and contributed to critical revisions of the manuscript. All authors approved the final version of the manuscript.

## References

- Kennedy NA, Jones GR, Lamb CA, *et al.* British Society of Gastroenterology guidance for management of inflammatory bowel disease during the COVID-19 pandemic. *Gut* 2020;69:984–90.
- Rubin DT, Abreu MT, Rai V, Siegel CA. Management of patients with Crohn's disease and ulcerative colitis during the COVID-19 pandemic: results of an international meeting. *Gastroenterology* 2020; doi: [10.1053/j.gastro.2020.04.002](https://doi.org/10.1053/j.gastro.2020.04.002).
- Fiorino G, Allocca M, Furfaro F, *et al.* Inflammatory bowel disease care in the COVID-19 pandemic era: the Humanitas, Milan experience. *J Crohns Colitis* 2020. doi: [10.1093/ecco-iccf/jjaa058](https://doi.org/10.1093/ecco-iccf/jjaa058).
- Danese S, Cecconi M, Spinelli A. Management of IBD during the COVID-19 outbreak: resetting clinical priorities. *Nat Rev Gastroenterol Hepatol* 2020;17:253–5.
- Reinisch W, Danese S, Peyrin-Biroulet L, Loftus EV. Clinical trials for inflammatory bowel disease: a global guidance during COVID-19 pandemic. *J Crohns Colitis* 2020. PMID: 32520311.
- Paramsothy S, Rosenstein AK, Mehandru S, Colombel JF. The current state of the art for biological therapies and new small molecules in inflammatory bowel disease. *Mucosal Immunol* 2018;11:1558–70.
- Baker JR, Vandal AC, Yeoh J, Zeng I, Wong S, Ryan SN. Clinical trial participation improves outcome: a matched historical cohort study. *Clin Trials* 2013;10:735–43.
- Jonker L, Fisher SJ. The correlation between National Health Service trusts' clinical trial activity and both mortality rates and care quality commission ratings: a retrospective cross-sectional study. *Public Health* 2018;157:1–6.
- Ozdemir BA, Karthikesalingam A, Sinha S, *et al.* Research activity and the association with mortality. *PLoS One* 2015;10:e0118253.
- Downing A, Morris EJ, Corrigan N, *et al.* High hospital research participation and improved colorectal cancer survival outcomes: a population-based study. *Gut* 2017;66:89–96.
- Hull MA, McLaughlin JT. Successful delivery of clinical gastroenterology studies in the UK. *Gut* 2015;64:854–6.
- Danese S, Schabel E, Ainsworth MA, Peyrin-Biroulet L. Challenges and opportunities for IBD drug development: from early stage to regulatory approval. *Gut* 2020. doi: [10.1136/gutjnl-2019-320542](https://doi.org/10.1136/gutjnl-2019-320542).
- Herfarth HH, Jackson S, Schliebe BG, *et al.* Investigator-initiated IBD trials in the United States: Facts, obstacles, and answers. *Inflamm Bowel Dis* 2017;23:14–22.
- Harris MS, Wichary J, Zadnik M, Reinisch W. Competition for clinical trials in inflammatory bowel diseases. *Gastroenterology* 2019;157:1457–61.
- Hueber W, Sands BE, Lewitzky S, *et al.* Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind, placebo-controlled trial. *Gut* 2012;61:1693–700.
- Carlisle B, Kimmelman J, Ramsay T, MacKinnon N. Unsuccessful trial accrual and human subjects protections: an empirical analysis of recently closed trials. *Clin Trials* 2015;12:77–83.
- Danese S, Neurath MF, Kopoń A, *et al.* Effects of apremilast, an oral inhibitor of phosphodiesterase 4, in a randomized trial of patients with active ulcerative colitis. *Clin Gastroenterol Hepatol* 2020. doi: [10.1016/j.cgh.2019.12.032](https://doi.org/10.1016/j.cgh.2019.12.032).
- Ledford H. Chloroquine hype is derailing the search for coronavirus treatments. *Nature* 2020;580:573.
- National Institute for Health Research. *DHSC Issues Guidance on the Impact of COVID-19 on Research Funded or Supported by NIHR*. <https://www.nihr.ac.uk/news/dhsc-issues-guidance-on-the-impact-on-covid-19-on-research-funded-or-supported-by-nihr/24469> Accessed May 8, 2020.
- Health Research Authority. *Guidance About COVID-19 for Sponsors, Sites and Researchers*. <https://www.hra.nhs.uk/covid-19-research/covid-19-guidance-sponsors-sites-and-researchers/> Accessed May 13, 2020.
- Medicines and Healthcare Products Regulatory Agency. *Managing Clinical Trials During Coronavirus [COVID-19]*. <https://www.gov.uk/guidance/managing-clinical-trials-during-coronavirus-covid-19> Accessed May 13, 2020.
- Kurin M, Katz J, Kodish E, Lashner B. Informed consent in IBD trials: where we are and where we need to go. *Inflamm Bowel Dis* 2019;25:1115–9.
- Lichtenstein GR, Feagan BG, Cohen RD, *et al.* Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT™ registry. *Am J Gastroenterol* 2012;107:1409–22.

24. Wisniewski A, Kirchgerner J, Seksik P, et al. Increased incidence of systemic serious viral infections in patients with inflammatory bowel disease associates with active disease and use of thiopurines. *United Eur Gastroenterol J* 2019;0:1–11.
25. Mao R, Liang J, Shen J, et al. Implications of COVID-19 for patients with pre-existing digestive diseases. *Lancet Gastroenterol Hepatol* 2020;5:426–8.
26. Bezzio C, Saibeni S, Variola A, et al. Outcomes of COVID-19 in 79 patients with IBD in Italy: an IG-IBD study. *Gut* 2020. doi: [10.1136/gutjnl-2020-321411](https://doi.org/10.1136/gutjnl-2020-321411).
27. Brenner EJ, Ungaro RC, Geary RB, et al. Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an international registry. *Gastroenterology* 2020. doi: [10.1053/j.gastro.2020.05.032](https://doi.org/10.1053/j.gastro.2020.05.032).
28. D'Amico F, Baumann C, Rousseau H, Danese S, Peyrin-Biroulet L. Phase I, II and III trials in inflammatory bowel diseases: a practical guide for the non-specialist. *J Crohns Colitis* 2020. doi: [10.1093/ecco-jcc/fjz214](https://doi.org/10.1093/ecco-jcc/fjz214).
29. European Medicines Agency. *EU Authorities Agree New Measures to Support Availability of Medicines Used in the COVID-19 Pandemic*. 2020. [EMA/174606/2020 EMA News 2020](https://www.ema.europa.eu/EMA/174606/2020-EMA-News-2020) Accessed May 13, 2020.
30. Iacucci M, Cannatelli R, Labarile N, et al. Endoscopy in inflammatory bowel diseases during the COVID-19 pandemic and post-pandemic period. *Lancet Gastroenterol Hepatol* 2020;5:598–606.
31. British Society of Gastroenterology. *Endoscopy Activity and COVID-19: BSG and JAG Guidance*. <https://www.bsg.org.uk/covid-19-advice/endoscopy-activity-and-covid-19-bsg-and-jag-guidance/> Accessed May 13, 2020.
32. Ungaro RC, Yzet C, Bossuyt P, et al. Deep remission at 1 year prevents progression of early Crohn's disease. *Gastroenterology* 2020. doi: [10.1053/j.gastro.2020.03.039](https://doi.org/10.1053/j.gastro.2020.03.039).
33. European Medicines Agency. *Guidance on the Management of Clinical Trials During the COVID-19 [Coronavirus] Pandemic*. [https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials\\_covid19\\_en.pdf](https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf) Accessed May 13, 2020.
34. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA* 2020;323:1843–4.
35. Wu Y, Guo C, Tang L, et al. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. *Lancet Gastroenterol Hepatol* 2020;5:434–5.
36. Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. *Nature* 2020;581:465–9.
37. Bello C, Roseth A, Guardiola J, et al. Usability of a home-based test for the measurement of fecal calprotectin in asymptomatic IBD patients. *Dig Liver Dis* 2017;49:991–6.
38. Derwa Y, Williams CJM, Sood R, et al. Factors affecting clinical decision-making in inflammatory bowel disease and the role of point-of-care calprotectin. *Therap Adv Gastroenterol* 2018;11:1756283X17744739.
39. European Medicines Agency. *ICH E9 Statistical Principles for Clinical Trials*. 1998. <https://www.ema.europa.eu/en/ich-e9-statistical-principles-clinical-trials> Accessed May 13, 2020.
40. McDermott MM, Newman AB. Preserving clinical trial integrity during the coronavirus pandemic. *JAMA* 2020. doi: [10.1001/jama.2020.4689](https://doi.org/10.1001/jama.2020.4689).
41. D'Haens G, Feagan B, Colombel JF, et al.; International Organization for Inflammatory Bowel Diseases [IOIBD] and the Clinical Trial Committee Clincom of the European Crohn's and Colitis Organisation [ECCO]. Challenges to the design, execution, and analysis of randomized controlled trials for inflammatory bowel disease. *Gastroenterology* 2012;143:1461–9.
42. Sandborn WJ, Su C, Sands BE, et al.; OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2017;376:1723–36.
43. Viele K, Berry S, Neuenschwander B, et al. Use of historical control data for assessing treatment effects in clinical trials. *Pharm Stat* 2014;13:41–54.
44. Switchenko JM, Heeke AL, Pan TC, Read WL. The use of a predictive statistical model to make a virtual control arm for a clinical trial. *PLoS One* 2019;14:e0221336.
45. Angus DC, Alexander BM, Berry S, et al. Adaptive platform trials: definition, design, conduct and reporting considerations. *Nat Rev Drug Discov* 2019;18:808.
46. James ND, Sydes MR, Clarke NW, et al. STAMPEDE: systemic therapy for advancing or metastatic prostate cancer—a multi-arm multi-stage randomised controlled trial. *Clin Oncol* 2008;20:577–81.
47. James ND, Sydes MR, Clarke NW, et al.; STAMPEDE investigators. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer [STAMPEDE]: survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet* 2016;387:1163–77.
48. Parker CC, James ND, Brawley CD, et al.; Systemic Therapy for Advanced or Metastatic Prostate cancer: Evaluation of Drug Efficacy [STAMPEDE] investigators. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer [STAMPEDE]: a randomised controlled phase 3 trial. *Lancet* 2018;392:2353–66.
49. Woodcock J, LaVange LM. Master protocols to study multiple therapies, multiple diseases, or both. *N Engl J Med* 2017;377:62–70.
50. Kearney A, McKay A, Hickey H, et al. Opening research sites in multicentre clinical trials within the UK: a detailed analysis of delays. *BMJ Open* 2014;4:e005874.
51. D'Haens G. Standardisation of study protocols—pros and cons. *J Crohns Colitis* 2016;10:553–9.
52. Parmar MK, Sydes MR, Cafferty FH, et al. Testing many treatments within a single protocol over 10 years at MRC Clinical Trials Unit at UCL: Multi-arm, multi-stage platform, umbrella and basket protocols. *Clin Trials* 2017;14:451–61.
53. Saville BR, Berry SM. Efficiencies of platform clinical trials: A vision of the future. *Clin Trials* 2016;13:358–66.
54. Sydes MR, Parmar MK, Mason MD, et al. Flexible trial design in practice - stopping arms for lack-of-benefit and adding research arms mid-trial in STAMPEDE: a multi-arm multi-stage randomized controlled trial. *Trials* 2012;13:168.
55. Angus DC. Optimizing the trade-off between learning and doing in a pandemic. *JAMA* 2020. doi: [10.1001/jama.2020.4984](https://doi.org/10.1001/jama.2020.4984).
56. Rockhold F, Bromley C, Wagner EK, Buyse M. Open science: The open clinical trials data journey. *Clin Trials* 2019;16:539–46.
57. Green AK, Corty RW, Wood WA, et al. Comparative effectiveness of mitoxantrone plus prednisone versus prednisone alone in metastatic castrate-resistant prostate cancer after docetaxel failure. *Oncologist* 2015;20:516–22.
58. Tierney JF, Fisher DJ, Burdett S, Stewart LA, Parmar MKB. Comparison of aggregate and individual participant data approaches to meta-analysis of randomised trials: An observational study. *PLoS Med* 2020;17:e1003019.