Developing an adaptive platform trial to accelerate the evaluation of medical treatments for people living with Crohn's disease

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Abstract

There are a growing number of medical treatments demanding evaluation by patients and clinicians in Crohn's disease. However conventional clinical trial designs may take several decades to provide the answers being sought particularly regarding sequencing of treatments. Adaptive platform trials using a master protocol approach offer an opportunity for more efficient trials i.e. provide answers from fewer patients and in a shorter timeframe. But there are multiple challenges to overcome prior to their implementation. A workshop was convened to consider the opportunities and challenges of developing a platform trial in Crohn's disease. The workshop and reporting was contributed to by eight clinical experts, four experts in clinical trial methodology and statistics, with further input from two professional representatives from Crohn's and Colitis UK, and two patient representatives.

Key disease-specific and trial design-specific considerations were discussed and recommendations made based on these discussions. Platform trials enable the evaluation of multiple interventions simultaneously, allowing seamless recruitment of patients, with addition of promising new interventions to an ongoing trial protocol. Crucially platform trials enable halting recruitment to interventions not demonstrating sufficient benefit (or indeed evidence of harm) – allowing resources to be focused on more promising and important questions for patients. Multiple benefits and potential challenges were identified in order to bring adaptive platform trials to Crohn's disease. Successful delivery and implementation of such trials was considered achievable through commitment and partnership between patients, clinicians, trial methodologists, regulatory authorities, funding agencies and industry partners.

Introduction

Global clinical estimates indicate a rising number of people living with Crohn's disease.[1] With major advances in the management of Crohn's disease, there are now multiple licensed therapies available and further treatments on the horizon.[2] However despite this progress, there remains a large area of unmet need with many patients not achieving optimal disease control with current options.[3] In addition, despite an increased understanding of the biology behind inflammation,[4] the design of clinical trials in Crohn's disease have not advanced at the same rate.[5] Historically, with few therapeutic options, it was appropriate to perform two-arm, randomised controlled trials (RCTs). Now with numerous therapeutic options, it is inefficient to conduct multiple separate RCTs for the purposes of comparative effectiveness, which may take several decades to provide the answers being sought by patients and clinicians today. As a result, there has been a drive for more "efficient RCTs" in IBD.[6] Adaptive platform trials which use a multi-arm and multi-stage (MAMS) approach, offer an attractive solution to some of these problems,[7] and have been used with success across other disease areas, notably in oncology and infectious disease.[8] There is increasing interest in applying this concept to Crohn's disease.[9] In this article we evaluate the benefits and challenges of developing an adaptive platform trial to accelerate the evaluation of medical treatments in Crohn's disease.

Methods

A workshop was convened in London, UK on 25 September 2024 at the Medical Research Council Clinical Trials Unit at University College London, to consider the opportunities and challenges of developing a platform trial in Crohn's disease. The workshop and reporting was contributed to by eight experts in Crohn's disease including one paediatrician and one nurse specialist, four experts in clinical trial methodology and statistics, with further input from two professional representatives from Crohn's and Colitis UK, and two patient representatives.

Current landscape of trials

Current clinical trials were noted to be lengthy, costly and typically conducted as two-armed trials, with trials competing against each other for recruitment of patients[10], compounding the global problem of low and declining recruitment numbers.[11] There was concern about the ongoing use of placebo control arms, which has been

associated with harms to patients.[12,13] Although there has been an increase in the number of active comparator and head-to-head trials, it was noted that these still remain sparse in the field.[14]

Adaptive platform trials

Platform trials have the potential to answer multiple primary research questions as opposed to the single research question being addressed by two-arm, parallel-group trials.[7] Crucially, they are adaptive, which means that trial design elements can be modified during the course of the trial, typically at interim analyses and in response to accruing information. Notable modifications which allow increased efficiency include: multiple interventions being investigated in parallel, use of a shared control arm, with "early dropping" of interventions demonstrating "lack of benefit", addition of intervention arms when new treatments become available, and updating of the control arm based on emerging data on current best practice.[15] As well as obtaining faster answers, there are notable operational efficiencies including: streamlined research ethics and regulatory submissions, faster recruitment of patients overall and seamless site setup.[16]

Ensuring diverse and inclusive population

Given the ongoing areas of unmet clinical need for patients with moderate and severe Crohn's disease, this workshop sought to focus on this population. We noted that the largest benefit of medical treatments is achieved when initiated as early as possible in the disease course,[17] therefore it was proposed that patients due to start an "advanced" biological or small molecule therapy would be the most appropriate to recruit to a potential platform trial. However, we recognised the importance of also being able to offer clinical trial involvement for patients who had previously had loss of response/non-response to single or multiple classes of advanced therapies. Importantly we recognised that a platform trial can incorporate additional elements to allow answers to be provided for patients with less common phenotypes of disease. This was felt to be important for phenotypes which had been historically excluded from clinical trials including (but not limited to): peri-anal Crohn's disease, young or older patients, patients with strictures/fistulate/ostomies/pouches, and extraintestinal manifestations.

Intervention arms and control arm

Agreement was reached that the most helpful positioning of a platform trial would be in the post-registrational setting, allowing for a pragmatic design and greater flexibility with regulatory guidance.[18] There was recognition that the current highest levels of evidence for both efficacy and safety for first-line use of medication would be for anti-TNF therapy, and that this would be an appropriate standard of care treatment arm in bio-naïve patients. Importantly, in terms of ensuring inclusivity, it was felt important that patients who did not respond or had loss of response to one intervention arm, could re-enter and be re-randomised within the platform, so long as they were not randomised to interventions they had received before. We agreed that recruitment of bio-exposed populations should be stratified by the number of drug exposures (2 domains, 1 or more than 1 prior advanced treatment exposures) with the standard care treatment in each domain changing based on prior drug exposure.

We agreed that the most appropriate intervention arms to investigate would be a range of different "rational" combinations (**Figure 1**). This could include combinations of medical therapies, however a benefit of the platform approach would be that future combinations need not just be limited to medical interventions and could also investigate combinations with diet, surgery and more. The selection of initial medical treatments would be guided by already-undertaken evidence synthesis and network-meta analyses.[19] The literature for current adaptive platform trials was reviewed and it was agreed that to launch the initial platform it would be appropriate to start with a lower number of initial arms. This would allow the flexibility for adding-in intervention arms early, particularly with more licensed therapeutics on the horizon.

Outcome measures to use

We felt it important that any outcomes measured should be in line with those consistently reported to be of most importance to patients, and that the pragmatic nature of the trial allowed greater freedom from regulatory advice/guidance. Our group has already undertaken a multinational survey to clarify what are the critical and important outcomes in Crohn's disease and the thresholds that define 'trivial', 'small', 'medium' and 'large' differences between interventions.[20] Supported by findings from STRIDE II,[21] we agreed that the primary outcome measure should encompass corticosteroid-free sustained remission and absence of inflammatory disease activity

on endoscopy or imaging depending on disease location, with a one-year timepoint felt to be appropriate for a primary comparison of the intervention arms. Moreover, the strength and importance of long-term outcomes and cost-effectiveness was agreed and that the integration of electronic health records with involvement of data science experts and health economists deemed essential to widen stakeholder involvement.[22]

Patient centricity with patient and public involvement

The central and key role of patient and public involvement was discussed in detail.[23] In line with making clinical trials more patient-centric and more patient-friendly, it was agreed that virtual data collection should be encouraged and indeed enabled, as a future vision towards better and more futuristic trials in Crohn's disease.[24] There was strong agreement that patients and patient groups (notably Crohn's and Colitis UK) should be involved at all stages of design, conduct, analysis and reporting of results, as well as ensuring inclusivity and diversity of patient and public involvement in guiding the platform trial itself.

Sponsorship and leadership of a platform

It was clear that there are many additional practical issues to design, initiate and undertake platform trials.[25] With increased complexity in the operational conduct of the trial,[26] data management,[27] as well as the large number of individuals needed to run and oversee a platform trial.[28] Although it was felt crucial to have commercial/industry support for any platform, there was widespread agreement that successful delivery of a platform trial would likely need academic leadership and sponsorship from a non-commercial organisation/entity, particularly of clinical trials units with expertise in delivery of previous platform trials.

Implications for funders

An important discussion related to the fact that funding of platform trials, which require significant pre-trial methodological planning, and last for many years, does not lend itself well to many current funding streams or applications. There was widespread agreement that more innovative approaches to funding will need to be considered by funders to support adaptive platform trials and that there would likely be a key role for international patient support groups and organisations, who are keen to see more

rapid clinical advances in the field of Crohn's disease. The team felt that accelerator grants to support development of the trial platform would be critical.

Conclusions

There is a need for "more efficient trials" in Crohn's disease, especially for comparative effectiveness and the opportunity for clinical trials to be more in line with patient expectations. In order to bring adaptive platform trials to Crohn's disease, there are several challenges to overcome. However it is clear from other disease areas, that once initiated, practical issues can be overcome. Focusing efforts on addressing these challenges, should enable adoption of platform trials in Crohn's disease and help deliver faster answers to clinically important questions for patients and clinicians.

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Figure Legends

Figure 1 – Platform trial design for moderate and severe Crohn's disease.

Figure 1 – Platform trial design for moderate-severe Crohn's disease (CD).