Nature Reviews Gastroenterology & Hepatology 10.1038/s41575-025-01052-0

Developing an adaptive platform trial for evaluation of medical treatments for Crohn's disease

Nurulamin M. Noor[1,2,3], Shellie J. Radford[4], Babak Choodari-Oskooei[3], Morris Gordon[5], Ailsa L. Hart[6], Trish Hepburn[7], Ed Juszczak[7], James O. Lindsay[8], Nicholas A. Kennedy[9], Mahesh K.B. Parmar[3], Vipul Jairath[10] & Gordon W. Moran[4†]

[1]Department of Gastroenterology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK.

[2]Department of Medicine, University of Cambridge School of Clinical Medicine, Cambridge, UK.

[3] MRC CTU at UCL, Institute of Clinical Trials and Methodology, UCL, London, UK.

[4]National Institute of Health Research Nottingham Biomedical Research Centre, University of Nottingham and Nottingham University Hospitals, Nottingham, UK.

[5]University of Central Lancashire, Preston, UK.

[6]St Marks Hospital, Harrow, UK.

[7]Nottingham Clinical Trials Unit, School of Medicine, University of Nottingham, Nottingham, UK.

[8]Department of Gastroenterology, Royal London Hospital, Barts Health NHS Trust, London, UK.

[9]Department of Gastroenterology, Royal Devon University Healthcare NHS Foundation Trust, Exeter, UK.

[10]Division of Gastroenterology, Department of Medicine, Western University, London, Ontario, Canada.

[†]email: Gordon.Moran@nottingham.ac.uk

There is emerging interest in adaptive platform trials for inflammatory bowel disease. In this Comment, we present the results of a workshop that was convened to consider the opportunities and challenges of developing a platform trial in Crohn's disease.

Despite major advances in the management of Crohn's disease, there remains a large area of unmet needs, with many patients not achieving optimal disease control with current treatment options. In addition, despite an increased understanding of the biology underlying inflammation, the design of clinical trials in Crohn's disease has not advanced at the same rate. Historically, when there were few therapeutic options, it was appropriate to perform two-arm, randomized controlled trials (RCTs). Now, with numerous therapeutic options available, it is inefficient to conduct multiple separate RCTs for the purposes of comparative effectiveness, which could 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. Adaptive platform trials that use a multi-arm 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] We convened a workshop (Supplementary Box 1) to evaluate the benefits and challenges of developing an adaptive platform trial to accelerate the evaluation of medical treatments in Crohn's disease, and this Comment presents the results.

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, these still remain sparse in the field.

Platform trials have the potential to answer multiple primary research questions, as opposed to the single research question 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 design characteristics and modifications that enable 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]

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 who are 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 or non-response to single or multiple classes of advanced therapies. Importantly, we recognised that a platform trial can incorporate additional elements to

enable answers to be provided for patients with less common phenotypes of disease. This was felt to be important for phenotypes that have 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 or pouches, and extraintestinal manifestations.

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. 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 patients who are biologic-naïve. Importantly, in terms of ensuring inclusivity, it was felt that patients who did not respond or had loss of response to one intervention arm could re-enter and be re-randomized within the platform, so long as they were not randomized to interventions they had received before. We agreed that recruitment of bio-exposed populations should be stratified by the number of drug exposures (two domains, one or more than one 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 enable flexibility for adding intervention arms early, particularly with more licensed therapeutics on the horizon.

We felt it to be 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 and guidance. 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 has already been undertaken.[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 1-year timepoint thought 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, as was the integration of electronic health records with involvement of data science experts and health economists, which was deemed essential to widen stakeholder involvement.

The central and key role of patient and public involvement was discussed in detail. 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 step towards better and more forward-looking trials in Crohn's disease. 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. The workshop also discussed sponsorship, leadership and implications for funders (Supplementary Box 2).

To bring adaptive platform trials to Crohn's disease, there are several challenges to 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.

References

1. Kaplan, G. G. & Windsor, J. W. The four epidemiological stages in the global evolution of inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol* **18**, 56–66 (2021).

2. Noor, N. M., Bourke, A. & Subramanian, S. Review article: Novel therapies in inflammatory bowel disease – An update for clinicians. *Aliment Pharmacol Ther* **60**, 1244–1260 (2024).

3. Parigi, T. L. *et al.* Prevalence, characteristics, management, and outcomes of difficult-to-treat inflammatory bowel disease. *J Crohns Colitis* (2024) doi:10.1093/ecco-jcc/jjae145.

4. Stankey, C. T. *et al.* A disease-associated gene desert directs macrophage inflammation through ETS2. *Nature* **630**, 447–456 (2024).

5. Ma, C. *et al.* Interpreting modern randomized controlled trials of medical therapy in inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol* **21**, 792–808 (2024).

6. Dubinsky, M. C. *et al.* Challenges and Opportunities in IBD Clinical Trial Design. *Gastroenterology* **161**, 400–404 (2021).

7. Woodcock, J. & LaVange, L. M. Master protocols to study multiple therapies, multiple diseases, or both. *New England Journal of Medicine* **377**, 62–70 (2017).

8. Noor, N. M. *et al.* Uptake of the multi-arm multi-stage (MAMS) adaptive platform approach: a trial-registry review of late-phase randomised clinical trials. *BMJ Open* **12**, e055615 (2022).

9. Honap, S. *et al.* Basket, Umbrella, and Platform Trials: The Potential for Master Protocol - Based Trials in Inflammatory Bowel Disease. *Gastroenterology* (2024) doi:10.1053/j.gastro.2024.04.020.

10. Harris, M. S., Wichary, J., Zadnik, M. & Reinisch, W. Competition for Clinical Trials in Inflammatory Bowel Diseases. *Gastroenterology* **157**, 1457–1461 (2019).

11. Uzzan, M. *et al.* Declining enrolment and other challenges in IBD clinical trials: Causes and potential solutions. *J Crohns Colitis* **17**, 1066–1078 (2023).

12. Din, S. *et al.* Harms with placebo in trials of biological therapies and small molecules as induction therapy in inflammatory bowel disease: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* **9**, 1020–1029 (2024).

13. Gros, B. *et al.* Harms with placebo in trials of biological therapies and small molecules as maintenance therapy in inflammatory bowel disease: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* **9**, 1030–1040 (2024).

14. Pouillon, L., Travis, S., Bossuyt, P., Danese, S. & Peyrin-Biroulet, L. Head-to-head trials in inflammatory bowel disease: past, present and future. *Nat Rev Gastroenterol Hepatol* **17**, 365–376 (2020).

15. Sydes, M. R. *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* **13**, 168 (2012).

16. Parmar, M. K. B. *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. *Clinical Trials* **14**, 451–461 (2017).

17. Noor, N. M. *et al.* A biomarker-stratified comparison of top-down versus accelerated step-up treatment strategies for patients with newly diagnosed Crohn's disease (PROFILE): a multicentre, open-label randomised controlled trial. *Lancet Gastroenterol Hepatol* **9**, 415–427 (2024).

18. Noor, N. M., Sebastian, S., Parkes, M. & Raine, T. The need for affordable, pragmatic, investigator-led clinical trials of treatment strategies in inflammatory bowel disease. *Lancet Gastroenterol Hepatol* (2024) doi:10.1016/S2468-1253(24)00225-5.

19. Darie, A.-M. *et al.* BSG 2024 IBD guidelines protocol (standard operating procedures). *BMJ Open Gastroenterol* **10**, e001067 (2023).

20. Shaban, N., Sinopoulou, V., Vuyyuru, S., Moran, G. & Gordon, M. DOP02 Developing explicit thresholds for outcomes to inform (GRADE) Evidence to Decision frameworks for Inflammatory Bowel Disease guidelines. *J Crohns Colitis* **18**, i73–i74 (2024).

21. Turner, D. *et al.* STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. *Gastroenterology* **160**, 1570–1583 (2021).

22. Lensen, S. *et al.* Access to routinely collected health data for clinical trials - review of successful data requests to UK registries. *Trials* **21**, 398 (2020).

23. Honap, S., Buisson, A., Danese, S., Beaugerie, L. & Peyrin-Biroulet, L. Patient and Public Involvement in Research: Lessons for Inflammatory Bowel Disease. *Journal of Crohn's and Colitis* vol. 17 Preprint at https://doi.org/10.1093/ecco-jcc/jjad090 (2023).

24. Noor, N. M., Parkes, M. & Raine, T. Moving towards more patient-centred clinical trials in IBD. *Nat Rev Gastroenterol Hepatol* **18**, 673–674 (2021).

25. Noor, N. M. & Siegel, C. A. Leveraging Virtual Technology to Conduct Clinical Trials in Inflammatory Bowel Disease. *Gastroenterol Hepatol (N Y)* **19**, (2023).

26. Sydes, M. R. *et al.* Issues in applying multi-arm multi-stage methodology to a clinical trial in prostate cancer: The MRC STAMPEDE trial. *Trials* **10**, 39 (2009).

27. Schiavone, F. *et al.* This is a platform alteration: A trial management perspective on the operational aspects of adaptive and platform and umbrella protocols. *Trials* **20**, 264 (2019).

28. Hague, D. *et al.* Changing platforms without stopping the train: Experiences of data management and data management systems when adapting platform protocols by adding and closing comparisons. *Trials* **20**, 294 (2019).

29. Morrell, L. *et al.* Mind the gap? the platform trial as a working environment. *Trials* **20**, 297 (2019).

Acknowledgements

The authors would like to thank individuals at Crohn's and Colitis UK (Katie Nightingale and Rachel Ainley) and patient research champions from Crohn's and Colitis UK (Si Andrew and Tricia Kelly) for their review and valued contributions. We would also like to acknowledge advice from additional individuals who were not able to join for this workshop (Jakob Begun, Australia; Peter Irving, UK; Shaji Sebastian, UK). There is no specific funding associated with the development of this manuscript. N.M.N. is supported by the NIHR Cambridge Biomedical Research Centre (NIHR203312). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. B.C.O. and M.P. are supported by the UK Medical Research Council (MRC) (MC_UU_00004_09).

Competing interests

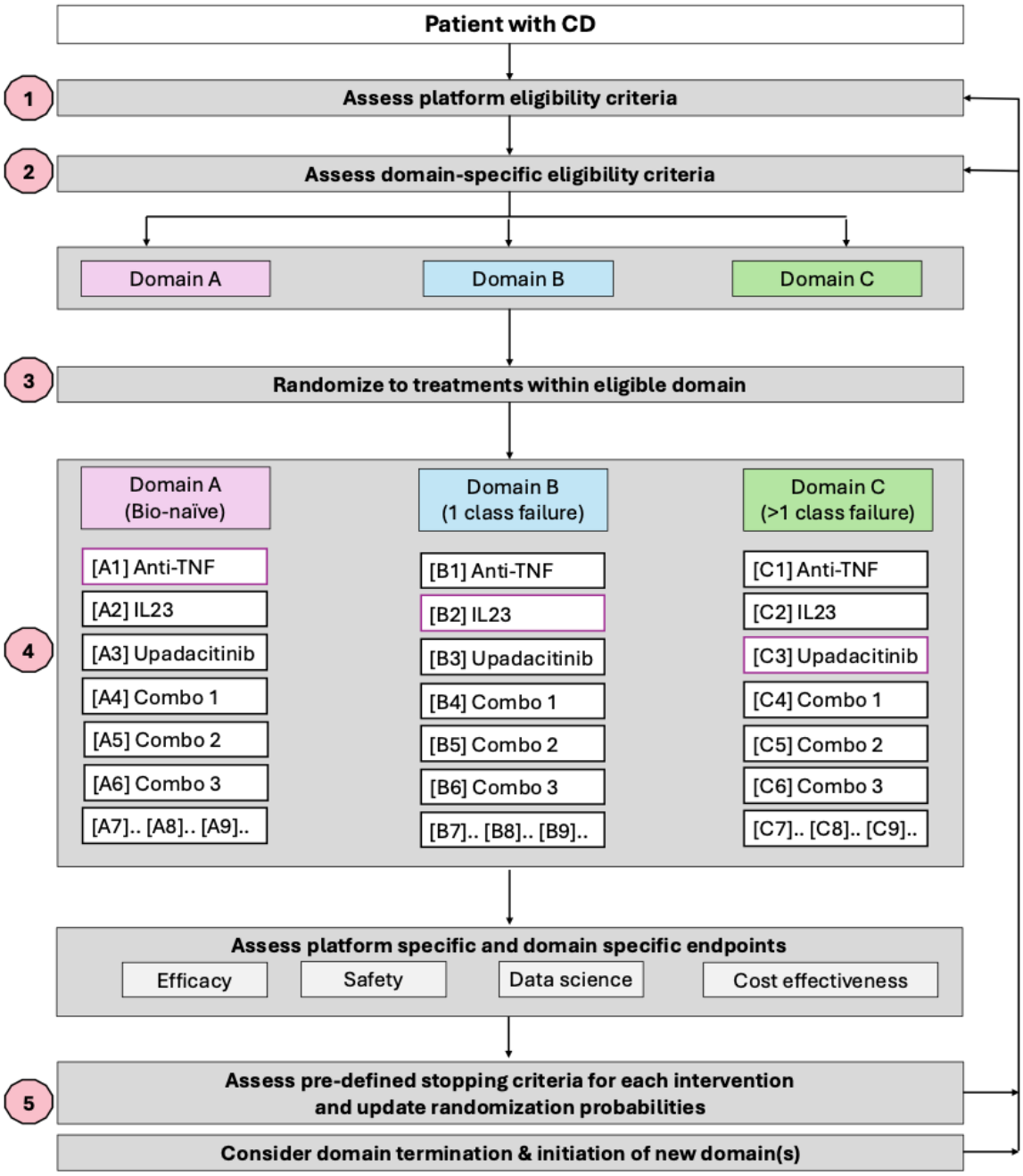
N.M.N. has received educational grants and/or speaker fees from AbbVie, BMS, Celltrion, Dr Falk Pharma, Ferring, Galapagos, Janssen, Lilly, Medfyle, Pfizer, Pharmacosmos, Takeda and Tillotts Pharma AG; all outside of the submitted work. A.L.H. has received consultancy fees from AbbVie, Bristol Myers Squibb, Celltrion, Galapagos, Johnson & Johnson, Takeda, Pfizer, and Lilly; has received honoraria from AbbVie, Bristol Myers Squibb, Celltrion, Galapogos, Johnson & Johnson, Takeda, Pfizer, Lilly; and has received support for attending meetings or travel from AbbVie, Bristol Myers Squibb, Celltrion, Galapagos, Johnson & Johnson, Takeda, Pfizer, and Lilly; all outside of the submitted work. J.O.L. reports personal fees from AbbVie, Atlantic Healthcare, Bristol Meyer Squibb, Celgene, Celltrion, Engytix, Eli Lilly, Ferring, Galapagos, Gilead, GSK, Janssen, MSD, Norgine, Pfizer, Shire, and Takeda outside the submitted work; and grants from AbbVie, Ferring, Gilead, Takeda, and Shire outside the submitted work. N.A.K. reports personal fees from Amgen, Bristol

Myers Squibb, Celltrion, Falk, Galapagos, Janssen, Pfizer, Pharmacosmos, Takeda, and Tillotts Pharma outside the submitted work; and reports data monitoring board membership for the BEACON study outside the submitted work. V.J. reports personal fees from AbbVie, Alimentiv (formerly Robarts Clinical Trials), Arena Pharmaceuticals, Asahi Kasei Pharma, Asieris, AstraZeneca, Avoro Capital, BMS, Celltrion, Endpoint Health, Enthera, Ferring, Flagship Pioneering, Fresenius Kabi, Galapagos, Gilde Healthcare, GSK, Genentech, Gilead, Innomar, JAMP, Janssen, Lilly, Merck, Metacrine, Mylan, Pandion, Pendopharm, Pfizer, Protagonist, Prometheus, Reistone Biopharma, Roche, Roivant, Sandoz, SCOPE, Second Genome, Sorriso Pharmaceuticals, Takeda, Teva, Topivert, Ventyx, and Vividion outside the submitted work; and fees from advisory board membership of AbbVie, Alimentiv (formerly Robarts Clinical Trials), Arena Pharmaceuticals, Asahi Kasei Pharma, Asieris, AstraZeneca, BMS, Celltrion, Ferring, Flagship Pioneering, Fresenius Kabi, Galapagos, Gilde Healthcare, GSK, Genentech, Gilead, Innomar, JAMP, Janssen, Lilly, Merck, Metacran, Mylan, Pandion, Pendopharm, Pfizer, Protagonist, Prometheus, Reistone Biopharma, Roche, Sandoz, SCOPE, Second Genome, Sorriso Pharmaceuticals, Takeda, Teva, Topivert, Ventyx, and Vividion; all outside the submitted work. G.W.M. declares consultancy fees/grant funding from AbbVie, AstraZeneca and Janssen; all outside the submitted work. All other authors declare no conflicts of interest.

Supplementary information

Supplementary information is available for this paper at Nature Reviews Gastroenterology & Hepatology 10.1038/s41575-025-01052-0

Figure 1. Proposed platform trial design for moderate and severe Crohn's disease.



Step 1: People with IBD will be assessed for platform eligibility criteria.
Step 2: screening for domain specific eligibility criteria.
Step 3: Patients who will meet eligibility criteria for at least one domain will be randomized to an intervention from each domain, which could include a variety of different options depending on the available interventions.
Step 4: Patients would then be initiated on therapy and complete study assessments which allow analysis of efficacy, safety and cost-effectiveness outcomes.
Step 5: Predefined stopping criteria for each intervention will be assessed throughout their participation in the study.