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Innovations to improve the efficiency of phase II IBD clinical trials

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Inflammatory bowel disease (IBD) clinical trials face a recruitment crisis. This is attributable to multiple individual trials competing for the same pool of participants, growing sample size demands and the increased availability of licensed alternative options for many potential participants. We need phase II trials that are more efficient both in design and in outcomes measured in order to deliver earlier and more precise answers, rather than simply offering a crude preview of what a subsequent phase III trial might look like.

The COVID-19 pandemic amplified many of the recruitment challenges of inflammatory bowel disease (IBD) clinical trials, but it also highlighted solutions for more efficient and patient-centric trials, not only for patients with COVID-19 (ref. 1) but also for patients with IBD[2]. These innovations in trial design, coupled with a change in approach to endpoint determination, have the potential to deliver more efficient phase II IBD clinical trials.

Trial designs to improve efficiency

The adoption of master protocol trials for IBD has increasingly been advocated[3]. These trials typically involve a single over-arching trial protocol, which can be used to address multiple primary research questions, often with pre-specified adaptations being permitted during the trial[4]. Basket trials are one subtype of master protocol trials; these trials evaluate the efficacy and safety of one intervention across a range of different diseases or subtypes. This approach permits the pooling and borrowing of information across different pathologies, meaning that more power can be gained than would otherwise be the case from single-disease trials. Such approaches are relevant for greater appreciation of the distinct clinical and molecular phenotypes of IBD, but they are also applicable across multiple inflammatory diseases, such as in the POLARISE phase II trial (ISRCTN80103507), which assesses multiple doses of mesenchymal stem cells in the treatment of patients with a range of inflammatory diseases, including Crohn's disease.

In addition to testing a single intervention across different patient groups, efficient trials can test multiple interventions across a single group. Umbrella trials enable parallel evaluation of multiple treatments. The VIBRATO phase II trial (NCT02958865) assessed two oral Janus kinase (JAK) inhibitors, ritlecitinib and brepocitinib, for patients with ulcerative colitis. But perhaps the most efficient design comes with the implementation of multi-arm multi-stage platform trials, which enable the evaluation of multiple interventions in parallel compared with a single, shared control arm[5]. These trials also enable intervention arms to be added or removed at interim analyses, before progression to a subsequent stage of the trial. Crucially, these adaptations to add entirely new intervention arms, or to stop recruitment to ongoing intervention arms, are made via protocol amendments rather than needing to set up, register and conduct entirely separate clinical trials. Given the efficiencies of trial design involved, all these approaches are particularly appealing for assets at the phase II stage, permitting initial testing in a population with a disease in a manner that controls both financial expenditure and patient risk.

Novel outcome measures to improve efficiency

Although phase III trial outcome measures must align with regulatory requirements for registrational trials, there is greater leeway for

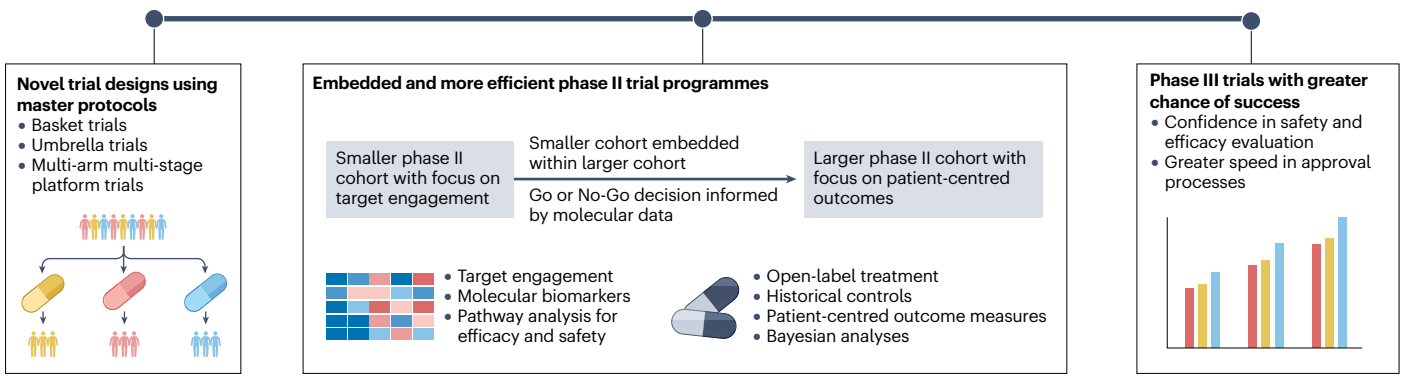

Fig. 1 | Innovations to increase efficiency of phase II IBD clinical trials. Innovative trial designs and molecular outcome measures offer the opportunity for a paradigm shift in inflammatory bowel disease (IBD) trial design.

selection of outcome measures in phase II trials. Despite this, many phase II IBD trials use the same endpoints as or similar endpoints to phase III trials, to obtain possible signals for later efficacy[6]. This allows trial sponsors to use a relevant endpoint from their phase II trial for estimating effect size and determining sample sizes for phase III trials. It also facilities engagement with regulators who can more easily understand the justification for a proposed phase III programme. However, such approaches have resulted in the majority of IBD clinical trials in fact overestimating efficacy rates and being subsequently underpowered[7]. These phase II trials risk becoming small, underpowered versions of their phase III counterparts but still require considerable investment to enrol sufficient participants to obtain meaningful results[3]. Furthermore, there is a risk that interventions tested in the current manner can seem promising early on, but then fail to demonstrate required benefits in the later phase III setting[8].

One solution is to leverage advances in ex vivo analyses of biological samples, such as the use of single-cell RNA sequencing performed on biopsy samples obtained from early trial recruits. This could generate evidence of target engagement and test biological efficacy and safety predictions from preclinical work, using relatively small sample sizes. These scientific endpoints could be analysed at early stages to support decision-making regarding continuation and expansion of the phase II programme.

Focus on target engagement to improve efficiency

It is more efficient if these solutions are not just obtained in a sequential manner as a preliminary phase Ib programme but embedded within a phase II programme. For a drug with a well-established mechanism and with sufficient data for dose selection in later-phase trials, it might be appropriate to use open-label initial cohorts to demonstrate molecular engagement, without placebo controls. Such unblinded patients would not be able to contribute clinical outcome data to a larger cohort, but more objective measures such as blinded reading of trial endoscopies or changes in faecal calprotectin could still be incorporated into the final analysis cohort.

Inevitably, this would require regulatory alignment as fewer data would be available regarding conventional clinical endpoints to generate predictions of phase III outcomes, such as for sample size estimation. However, this would be offset by a greater confidence in the mechanistic engagement of the drug. In particular, the use of molecular signatures of disease response from previous trial datasets could be leveraged to inform predictions of clinical efficacy based on detection (or otherwise) of similar molecular changes within key pathogenic cell populations in the mucosa of recipients of the novel therapeutic. Historical placebo or active comparator controls could also be used, ideally with patient-level data, using Bayesian analyses to further improve efficiency of trials. Ultimately, if used for purposes beyond decision-making within the development team, this would also require regulatory agencies to consider evidence supporting a proposed phase III programme including molecular evidence of response and historical control data.

A notable example of such innovation is the FUTURE phase IIa trial of olamkicept (EudraCT number 2016-000205-36)[9]. In this trial, a group of only 16 patients with ulcerative colitis or Crohn's disease was enrolled to an open-label study that demonstrated informative differences in a primary outcome measure assessing changes in mucosal gene signatures related to the drug's mechanism of action. Likewise, the TUSCANY trial (NCT02840721) was an open-label study of 50 patients with ulcerative colitis that leveraged patient-level data from historical controls as well as blinded reading of a primary endoscopic outcome measure and propensity score matching to assess the effect of a novel TL1A antibody[10]. In both these instances, the novel phase IIa trials supported investment decisions, but further phase IIb trials were planned before any decisions regarding phase III development.

Conclusions

The combination of innovative trial designs and molecular outcome measures offer the opportunity for a paradigm shift in IBD trial design (Fig. 1). With appropriate collaborative efforts from industry, academia, clinicians, patients and regulators, this could accelerate phase II trial delivery and build confidence in later-phase trials.

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Competing interests

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