Seek a System that Makes the Complex, Simple

Successfully designing an IRT for adaptive and platform trials eases the burden on researchers and can speed up trial processes, and alleviate the risks associated with randomisation

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As a way to increase clinical trial productivity, sponsors are increasingly turning to adaptive trial designs to gather more information, involve fewer patients, and improve the ethical treatment of patients – especially in oncology and rare diseases (1). So too, sponsors in these therapy areas are finding that platform trials that use master protocols can increase efficiency and accelerate development timelines.

Still, these modern trial designs are not yet common because they're complex to manage and present more risk than the traditional series of trials that investigate one drug using a typical blocked randomisation design. The complexities extend to programming and configuring the interactive response technology (IRT) system that supports patient randomisation, drug assignment, and supply management.

Although the industry generally places a premium on accelerating IRT start-up timelines, in the case of these complex trials, sponsors are better served to focus on the experience of the vendor and the quality/thoroughness of the work. The adage, 'more haste, less speed' applies here.

Adaptive Trial Designs

The FDA defines adaptive trials as those that 'allow the trial to adjust to information that was not available when the trial began' (2). This adaptability presents challenges for the accompanying IRT system, as it is impossible to know at the outset of the trial what changes may ultimately occur. For example, in a dose-finding study, one may assume that some treatment arms, or dose levels, may close (for futility) while others may open. However, until the data from an interim analysis are available, one cannot know exactly which arms will be affected, or which new doses will be investigated (see **Figure 1,** page 30).

Randomisation/Drug Assignment

When an arm is closed, the IRT system must reflect the decision, immediately, to avoid recruiting more patients in the futile arm. The randomisation algorithm must be intelligent enough to know which treatment arms are open at any point in time.

From a system perspective, adding a treatment arm is more complicated than closing one, and again, it must be done quickly. Because this involves rewriting the randomisation list, or finding ways to expand it so that the randomisation algorithm takes into account the new treatment arm, the change will require reconfiguring (and possibly reprogramming) the system. When a clear, closed set of adaptations are defined in the protocol, a randomisation list adapted to each scenario can be prepared in advance. Unfortunately, when the protocol allows for an open set of adaptations, it is impossible to prepare for future changes. Many, but by no means all, adaptive studies may well include a closed set of options. Bayesian response adaptive studies and also platform trials (discussed below) illustrate the need for an IRT to cater to any eventuality.

Supply Management

When an arm is closed, the medication supply algorithm will have to be updated to reflect the doses that will no longer be needed. For the benefit of blinded staff, the new supply scheme may need to maintain the illusion that nothing has changed. If the design is suitably structured, it may be that kits earmarked for one arm can be used for another. For instance, kits originally intended for an arm receiving a 25mg dose may be doubled up for use in a newly opened arm receiving a 50mg dose. Thus, in this situation, the supply algorithm within the IRT must be able to substitute one kit type with another, or a combination of kit types.

Recommendations for Sponsors

To ensure that sponsors realise the full benefits of an adaptive trial design, they should:

- Select an IRT vendor with demonstrable experience in supporting adaptive trials and in building flexible systems. There are unique elements to adaptive trials, and experience with other trial types isn't necessarily transferable.
- Look for significant, in-house statistical expertise in the IRT provider. This is necessary to ensure that randomisations will remain

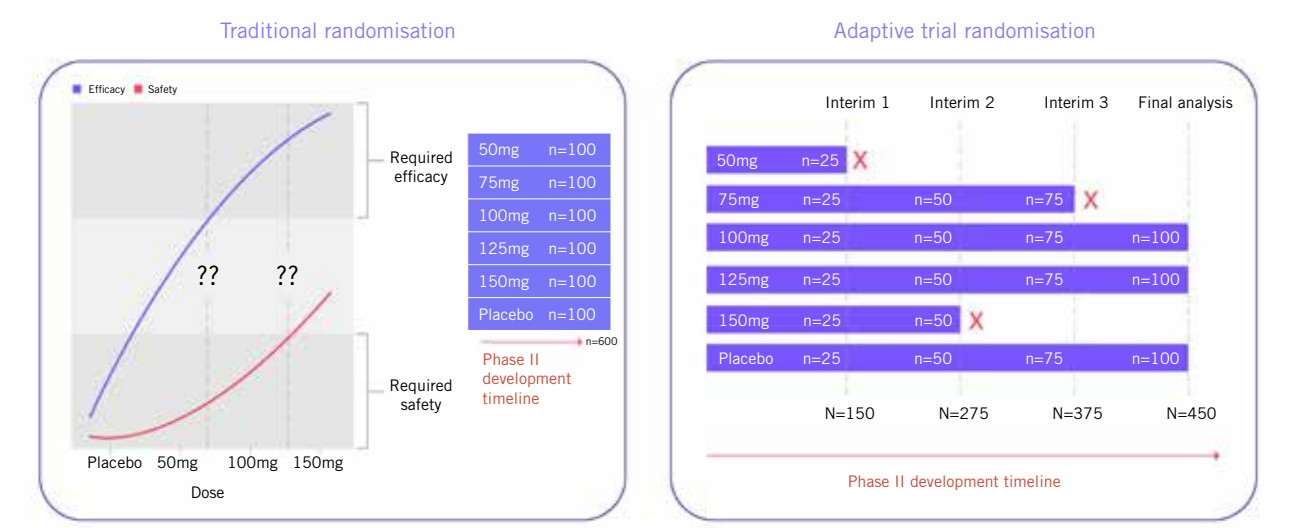

Figure 1: Differences between traditional and adaptive designs in a typical Phase IIb dose selection trial and the positive impact on patient population

balanced across treatment arms, even as they change. Without the right statistical input, the validity of a trial could be jeopardised.

- Keep the vendor appraised of the status of their analyses and assessments. Ideally, the sponsor should consider the IRT vendor as an extension of the clinical trial team and maintain strong communications with the IRT partner.

Platform Trials

Platform trials have 'an overarching protocol or trial mechanism comprised several parallel sub-trials differing by molecular features'. They can be basket trials where a treatment is tested in different indications, or umbrella trials where different treatments are tested in one indication (3).

Platform trials can study beneficial treatments with fewer patients, fewer patient failures, in less time, and greater probability of success than a traditional two-arm strategy (4). However, just as with adaptive trial designs, a platform trial will make special demands on the IRT system.

First, the IRT must have the flexibility to 'anticipate' that sub-protocols will be included in the future, while also employing an efficient change management process for any unforeseen adaptations required for a future protocol (see **Figure 2**). However, the extent to which any IRT can anticipate what is to come is limited to what is known about the potential future pipeline, or indeed, to the overarching sub-protocol restrictions stated within the master protocol, if any.

Of course, short-term predictions are most accurate, although one of the benefits of platform trials is the potential to facilitate further lines of investigation many years after the first sub-protocol has closed. Supporting a study long after the original master protocol was written and following years of implementing additional sub-protocols becomes ever more challenging.

New sub-protocols that are added to the master protocol could include studies of completely different treatments, different patient populations, or visit schedules. Therefore, accommodating a new sub-protocol within an IRT is essentially like building a system for a new study.

Randomisation

The study design will establish targets for the number of patients in each sub-protocol. Once that target is reached across investigator sites, the IRT will need to automatically cap enrolment in that sub-protocol and carry on enrolling new patients in another sub-protocol. The system must 'know' which sub-protocols have met their randomisation target, and which have not; moreover, randomisations between the open treatments at a site requires accurate tracking of each site's sub-protocol approval status. Otherwise, there is a risk of protocol deviations.

To accommodate the eventual move to enrol patients in newly opened sub-protocols, the system's randomisation list should have expansion capacity, rather like having extra holes in a belt. For example, the trial may be started with blocks, or lists, of a random combination of 10 treatment groups, assigned through a validated randomisation algorithm. In the early days of the platform trial, perhaps only three treatment groups will be used, but as sub-protocols are added, the assignments will draw from the expanded list. A sufficiently sophisticated algorithm can also handle randomisations managed not in blocks, but by meeting certain probability criteria. For instance, the sponsor may require that a ratio be applied to a patient's chance of being randomised into a given protocol so that a sponsor can prioritise one sub-protocol over others.

For regulatory purposes, the sponsor must be able to justify why a patient was randomised into a specific treatment arm or protocol. The system needs to ensure that randomisation entries were skipped for the right reason, e.g., because a treatment was closed at a site or because

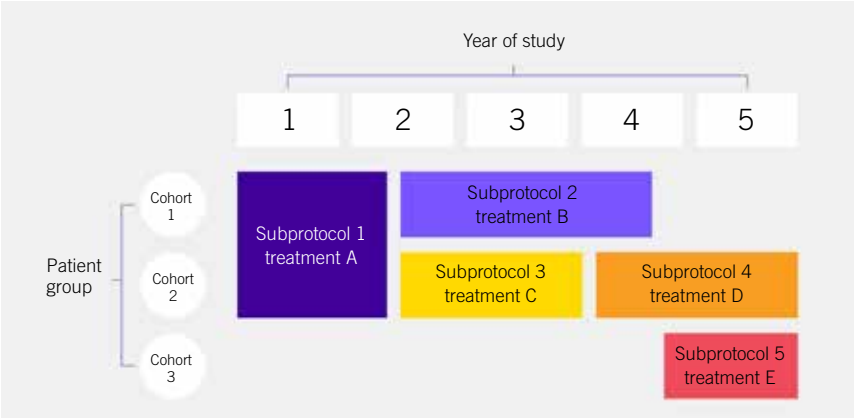

Figure 2: Example of platform trial design, with sub-protocols opening and closing at different time points

it was not yet approved at a site, and not because the medication was not on hand. Therefore, the IRT system must be able to provide a snapshot of what sub-protocols were open at any point in time.

Supply Management

Managing the supply chain in a platform trial becomes very challenging, as one treatment and comparator may be used for one set of sub-protocols, while another is used for a different set of sub-protocols (this can be further complicated when certain formulations are not permitted in certain countries). The IRT must be able to base the needs of shipments to a site on the needs across the sub-protocols open at that site.

Recommendations for Sponsors

In addition to the experience, statistical expertise, and communication skills recommended for adaptive trials, we suggest that sponsors select an IRT vendor with these factors in mind:

- Expect your IRT partner to ask a multitude of questions during requirements gathering. The most experienced IRT vendors will push the sponsor to think beyond the scenarios/contingencies that have already been considered. The goal will be to foresee – to the extent possible – how the platform trial may evolve several years into the future.
- The extended duration of platform trials presents the potential for changes in the trial team composition – both at the sponsor and the IRT vendor. It is important to have an IRT vendor who manages project transitions well and who can help new sponsor team members get up to speed quickly.
- Over the course of a lengthy platform trial, clinical staff will need regular training and good documentation on tasks. Team members should expect supporting tools to be included in the training and for extra documentation to be available. Traceability of documentation and decision making combined with the quality of the documentation in place at the IRT vendor are key to ensuring good trial conduct.
- Site compliance with protocol requirements and system use is critical due to the complexity of updates and the risk that a site – rather than the system – may select a kit for dispensing. These protocols can become very challenging for sites who work on several sub-protocols, so the IRT should be simple to use to hide the protocol complexity as much as possible. Site training is also key to ensuring the team understands the nuances between sub-protocols and the importance of using the IRT for all dispensing, which will allow for good control of the supply chain to sites.

The IRT – and the partner who provides it – are indispensable in both adaptive and platform trials to control the risks linked to randomisation and clinical supplies, so the choice of service should be made carefully with a full understanding of what will be required for success. The system should be highly configurable and the vendor team able to foresee the type of adaptations that will likely arise. Sponsors should be able to leverage the experience of their IRT partner to run these types of trials smoothly.

References

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