Three Keys To Mitigating Risk In Adaptive Trials

By Sy Pretorius, Chief Scientific Officer, PAREXEL International

About 50 percent of all Phase III trials fail. That is an expensive problem for the pharmaceutical industry, as a 2014 study by the U.S. Department of Health and Human Services estimated the average cost of a Phase III trial to be $20 million. This high rate of failure can be attributed in part to the traditionally rigid, inflexible designs of late stage clinical trials that prevent misguided preliminary assumptions from being fixed. In contrast, adaptive trial designs (ATDs) allow developers to revisit initial assumptions and change course during a trial. This can generate more and higher-quality information about a drug’s safety and efficacy (or lack thereof) in the target patient population. The result? Faster, smarter terminations, and the conservation of precious R&D resources.

However, due to the complexity of the process, many companies do not design and conduct adaptive trials.

**Revolution, Not Evolution**

ATDs represent more of a revolution than an evolution in clinical trials. Changing a sample size based on treatment effects, or dropping a dose arm that is ineffective (or has undesirable side effects), can accelerate timelines and reduce costs while simultaneously improving program success rates.

Still, ATDs raise concerns about bias, especially when data are unblinded during a trial. Some developers fear that regulators may not accept data from adaptive trials, and examples of successful late-stage ATDs to serve as precedents are lacking.

Adaptive trials require a cross-functional operational approach and technology that enables real-time decision making. Discussions about whether, and when, to make changes can get complicated.

To conduct successful adaptive trials, companies need to:

1. Choose the right compounds and conditions
2. Ensure statistical validity
3. Build a supportive operational infrastructure

**Choose The Right Compounds And Conditions**

A substantial portion of drugs in development are likely suitable for adaptive trial designs, but many companies lack the experience and expertise to pursue them. A suitable compound/condition has at least some of the following attributes (list is not exhaustive):

- **A rapid clinical effect readout:** Adaptive designs are most valuable when the effect of the treatment (or absence thereof) is known relatively quickly, directly, or via validated biomarkers.

- **A relationship:** It is not possible to design adaptive studies if the relationship between the dose administered and the expected effect is not well-characterized.

- **A life-threatening or debilitating disease or condition:** Keeping patients with life-threatening conditions in a trial cohort for many years, when it is clear that the dose being tested is ineffective, is unethical. These conditions are well-suited for ATDs.

- **A drug at the right stage of development:** Early-stage trials may accommodate adaptive designs more easily than later stage trials, but ATDs can be utilized at any stage.

**Ensure Statistical Validity**

There are good reasons why traditional trial designs do not allow interim looks at efficacy or safety data. Unblinding data can introduce bias and skew results. As a result, regulatory agencies at first did not embrace ATDs. However, in recent years, both the FDA and EMA have begun to encourage their use to produce more efficient studies and speed approvals.

The first hurdle any adaptive design must overcome is to ensure the statistical integrity and validity of the trial data while adapting flexibly in real time as the data are interpreted. To avoid generating data that leads to a Type I errors (false positives) for instance, the adaptive trial design must: 1) provide correct statistical inference and 2) provide pre-specified adaptation rules.

**Build A Supportive Operational Infrastructure**

The advantages of an adaptive trial come at a cost: the infrastructure required to execute an adaptive trial is more complex than that for traditional trials. So, in addition to very specialized statistical expertise, adaptive trials require an experienced cross-functional and integrated operational approach. Luckily, there have been several recent advances in operational execution. Operational excellence requires:

- Avoiding delays and disruptions, including those related to patient recruitment, or drug supplies; supply chain logistics must be able to handle study changes nimbly and flexibly.

- Communicating frequently and effectively with independent data monitoring committees (IDMCs) so they can digest data and make quick decisions about adaptations. This involves:
  - Real-time delivery of data with minimal disruptions: New patient enrollment while an IDMC deliberates on whether to or not.
  - Procedures that ensure high levels of security and clearance: Access to data needs to be managed tightly and documented. The FDA wants to be sure that only those individuals that were intended to be unblinded were unblinded, and no others.

- Building a technology infrastructure that enables real-time decision making and implementation. Decision support software needs to provide: 1) proof that only authorized individuals see unblinded data; 2) real-time response data to support decisions and 3) the ability to link decision-making to drug supply and randomization of patients.

Developers who use ATDs for well-suited compounds, and who achieve statistical, operational, and technological excellence, can substantially improve the efficiency, yield and return on investment for their drug development efforts.

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