

Seamless Designs in Adaptive Research

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With growing appreciation of drug development as a continuous process, the notion of defining best doses and then rolling straight into pivotal studies utilizing the identified best doses becomes compelling. The strongest reasons for doing so are: (1) minimizing the delay, often 12 months or more, between dose-finding studies and initiation of pivotal studies; (2) the efficiencies gained from going through the trial startup process a single time rather than twice; (3) gaining a head start in recruiting investigators and test subjects for the pivotal study; (4) the potential to adapt the population of the confirmatory phase based on data on responsive subgroups from the learning phase; and (5) the ability to combine data from the learning phase and the confirmatory phase in a final analysis of trial data. However, it is important to recognize as well that the break between phases can be an important time to analyze data and perfect the final design of a separate pivotal study. Study managers should weigh the possible need for an interval to allow greater analysis and more refined planning against the potentially huge savings in time and expense if phases can be combined. Additionally, managers should weigh the need to take advantage of an interim period for discussions with regulatory authorities to assure their acceptance of the plan as a basis for approval in the event of a successfully executed study.

A large study that is progressively refined from the phase II dose-finding stage and then continues into the phase III confirmatory study is among the most complex adaptive strategies but also the most rewarding. Executing this strategy is demanding because it requires a great deal of advance planning to anticipate and deal with different possible outcomes. In addition, the final statistical analysis may be extraordinarily complex.

The use of adaptive methods to combine phase II and phase III studies begins with establishing a number of dosing arms and pruning those down to a manageable two to three (including a comparator) for a confirmatory stage. Once the final doses have been identified, the study is then quickly expanded and, assuming a second pivotal study is warranted, it is implemented immediately. Simulations can be extremely useful in modeling possible outcomes and their ramifications. Adopting the strategy of rolling a phase II study into phase III requires confidence that all the methodologies and infrastructure essential for the adaptive approach are in place and functioning well. These include quick and accurate data capture, rapid data validation, the prompt generation of meaningful information, readiness for continuous decision making, and the capacity to manage logistics of the study, such as supply chain management, with great efficiency based on timely data. The benefits of rolling a phase II study into phase III are commensurate with the effort: This approach can easily reduce development time by a year or more and save many millions of development dollars.

Eliminating the gap between phases is only one of the benefits of rolling directly from a phase II study into phase III, conducting, in effect, one continuous study instead of two separate ones. Eliminating the gap has the added advantage of incorporating in the phase III study the knowledge gained from relevant arms in the early dose-finding portions. There are also benefits for patient recruitment and data collection. Patients already screened in the dose-finding phase can be enrolled in the pivotal portion of the study, and existing patient data collected in the dose-finding phase can contribute to greater efficiency in the

pivotal phase. However, it is important to be mindful that the protocol must not change from that specified at the initiation of the study, placing a premium on the challenging task of anticipating all outcomes when planning the study. Despite the challenges, the risks associated with combining phases II and III are low. The worst-case scenario for such an adaptive study, with no successful adaptations carried out, is the equivalent of conducting the same study conventionally, without the use of adaptive methods.

Combining data from the two phases requires procedures to control the type 1 error rate for the comparison of the test drug with the control. In addition, the final statistical analysis for the combined data from the learning and confirmatory phases will be more complex than usual.¹ It is also important to think through the plan for the seamless trial to ensure that the issues that might be analyzed between two separate studies are adequately analyzed in advance.

One of the greatest advantages of combining phases is that the entire startup process is handled once instead of twice. A single protocol can be developed, reviewed and approved in a single process for both phases. Recruitment of investigators and patients is simplified because some of the investigators for the pivotal phase will already be familiar with the study. However, combined studies also require that many other investigators be set and ready to go when the final dosing decision is made. This raises a host of other issues, such as making appropriate provisions for addressing an investigational review board (IRB) and making consent forms and study materials available in a timely manner. Considerably greater attention than usual is required to ensure that all requisite components mesh.

Reference

1. Chow, S.-C., and Chang, M. (2007), *Adaptive Design Methods in Clinical Trials*, Chapman & Hall/CRC, Boca Raton, FL, pp. 47–67, 55–59, 58–60, 171.

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