CLINICAL INVESTIGATION

Adaptive clinical trials and their potential to improve drug-development efficiency

"...the greatest benefit from the use of adaptive designs in Phases I and II is that the enhanced information provided will greatly improve the chances of selecting a dose that will ultimately lead to success in Phase III."

Keywords: 3+3 design • adaptive seamless • bayesian curve-free • continual reassessment method • multiarm multistage • response adaptive

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"*The wise adapt themselves to circumstances, as water moulds itself to the pitcher*"
– Chinese proverb.

Ever escalating costs of pharmaceutical research and development [1] have prompted a drive for greater efficiency in clinical trial design. This has included use of surrogate outcomes [2], biomarker/genetic-based designs [3] and promotion of a range of adaptive designs [4]. While the broader class of adaptive designs includes adaptive randomization (using either minimization or stratification), here we focus on response adaptive designs, where the design is modified during the course of the trial based on the responses (either on a safety indicator or an efficacy outcome or both) of participants who have already been enrolled in the trial.

Here, we undertake a brief tour of three key areas in which adaptive designs provide an effective contribution to drug development and then consider some implications of applying adaptive designs in practice.

Safety first (Phase I)

Early phase cancer trials, in which for ethical reasons the first use in humans of new cytotoxic treatments takes place in patients with late-stage disease in whom standard treatment regimens have been unsuccessful, have historically been a fruitful development ground for clinical trial designs aiming to establish the maximum tolerated dose. The basic principle of such designs is first, to treat a small number of patients on a low dose; then, to observe the number of these patients who experience a dose-limiting toxicity; and next, on the basis of this, to determine the dose to be given to the next cohort of patients to be studied. The whole process is then repeated until a relevant statistic indicates that the maximum tolerated dose has been identified.

The longest-established designs are algorithmic and include the so-called '3+3' design [5]. Since 1990, thanks to advances in methodology and computing power, designs based on statistical modeling of the dose–toxicity relationship have emerged. These either assume a particular form for the dose–toxicity curve (e.g., the continual reassessment method) [6] or model the toxicity risk directly (e.g., Bayesian curve-free designs) [7] using only the assumption that risk of a dose-limiting toxicity does not decrease as the dose increases. Despite clear statistical evidence that model-based designs provide a superior basis on which to select the dose for further study in Phase II [8], uptake has been relatively slow. A recent review found that 97% of published Phase I cancer trials still used an algorithm-based design [9]. The superiority of model-based designs is due in part to the decision on dose escalation using all of the toxicity data gathered in the trial to date, rather than only the results from one or two small cohorts as is the case for algorithm-based designs.

Learning as we go (Phase II)

Having established the range of doses with an acceptable safety profile in the target patient population, the next step is to select

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the best dose (with respect to efficacy) to take forward to the confirmatory Phase III trial. Adaptive designs are of particular use here, either to guide decisions on whether to drop treatment arms from the trial or to vary the randomization probabilities assigned to each dose group.

A range of approaches is used to guide the adaptations. In situations where the primary outcome of the clinical trial is readily available soon after treatment (e.g., [10]), this may be used to inform the adaptations. Adaptation may also be performed using intermediate outcome data if the main outcome measure is also recorded on other occasions prior to the primary time point of interest. In an acute stroke trial [11], the dose–response curve was modeled using a flexible parametric model with an embedded longitudinal model to estimate the primary outcomes of patients who had only had outcome measured at an earlier time point. If the primary clinical outcome is only available long after treatment, adaptations may instead be guided using the value of a biomarker to enable timely adaptation of the study design. One such example, in a trial of IL-2 treatment in Type I diabetes [12], is % change in CD4 Treg cells within the CD3 CD4 T-cell gate during the first seven days of follow-up – a biomarker which is relevant to the mechanism of action of treatment and which would need to be influenced by an IL-2 dose for this to have any impact on clinical outcomes of interest.

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Regardless of the approach taken, the value of the adaptive design here is in minimizing the study of patients on 'wasted' doses which would provide little information on the characteristics of the (unknown) underlying dose–response curve. This efficient learning means that the adaptive trial provides more information per enrolled patient than a standard trial design.

Confirming what has been learned (Phase III)

Adaptive designs also bring a number of advantages to Phase III trials. One type of adaptation incorporates formal interim analyses to apply early stopping rules for efficacy, safety or futility. In another, adaptive seamless Phase II/III trials allow one to study several doses or treatments in Phase II and then immediately switch to Phase III, carrying forward the treatment(s) that appeared most promising in Phase II. The decision on which treatments to move forward to Phase III is often based on an intermediate outcome to allow more rapid selection of promising treatments, avoiding the need to wait a longer period of time for the primary outcome of interest to be recorded. For example, in secondary progressive multiple sclerosis, an intermediate MRI T2 lesion volume outcome at 12 months might be used to guide selection of Phase III treatment for the primary outcome (measured at 3 years) of improvement in Expanded Disability Status Scale [13].

This approach extends to multi-arm, multi-stage designs [14] which have a treatment selection stage and then one or more subsequent interim analyses to allow early stopping for efficacy or futility as appropriate. In addition, the STAMPEDE trial [15] in locally advanced or metastatic prostate cancer has demonstrated that as well as dropping treatment arms from the trial according to predefined stopping rules, with careful planning further investigative treatments may also be added to the design as the trial progresses. This brings statistical efficiency (through the use of a common placebo group) and practical benefits (by making use of existing trial infrastructure).

Practical considerations

Given all of the potential benefits described above, are there any practical issues to consider when implementing an adaptive design? The first thing to bear in mind is that, unlike a conventional parallel group trial, it is impossible to know in advance exactly how an adaptive design will perform in practice. Usually, considerable preparatory work is therefore required to assess, using simulation studies, the properties (e.g., statistical power and Type I error) of a proposed adaptive design. Another aspect to take into account is that, because an adaptive design generally involves formal unblinded interim analyses during the course of the trial, particular attention must be paid to protecting the integrity of the trial. This means planning the flow of information carefully to avoid interim data leading to subsequent operational bias in researchers measuring patient outcomes [16]. Tailored guidance is available for organizing data monitoring committees for adaptive trials [17]. Finally, systems must be in place to streamline communication and data transfer to ensure that adaptations take place in a timely manner.

Conclusion

Although they present some practical challenges, adaptive designs have the potential to increase the efficiency of drug development. They will sometimes enable quicker decisions to be made on whether to discontinue the development of a drug. Throughout the development process, adaptive designs will tend

to derive a greater quantity of information from a given size of clinical trial to support more effective decision making at each stage. Due to the substantial investment required to undertake a Phase III confirmatory trial, the greatest benefit from the use of adaptive designs in Phases I and II is that the enhanced information provided will greatly improve the chances of selecting a dose that will ultimately lead to success in Phase III.

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