An operational perspective of adaptive clinical trials

Peter Thomas

Novartis Horsham Research Centre, Horsham, UK

Corresponding Author:
Peter Thomas, Novartis Horsham Research Centre,
Wimblehurst Road, Horsham, RH12 5AB, UK
E-mail: peter-1.thomas@novartis.com

Summary

Adaptive and adaptive seamless design clinical trials offer several attractive features:

• Better informed decision making leading to quicker development of more effective drugs with fewer patients exposed during the development.

• Adjustment to ongoing trials to ensure adequate power; thus increasing the proportion of 'successful' trials and the benefit from patient treatment data.

• Reduced exposure of patients to suboptimal treatments.

• Reduction of the so-called 'white space' or the time between trials or phases of development – leading to an overall reduction in development time implying quicker availability of effective new medications for patients.

To implement these designs careful consideration must be given to the early planning requirements, e.g. initial protocol development, setting up of decision rules, logistics, establishing Data Monitoring Committees. Health Authorities generally support trials using adaptive methodologies when appropriately designed and conducted. However, more time will be needed for Health Authority interactions and more extensive communication and interaction with authorities are required for those approaches, especially in the case of confirmatory studies. Dialogue and agreement with Ethics Committees is needed to ensure appropriate communication to patients. The statistical methodology supporting these trials is well established but simulation techniques often need to be used to optimize the design and analysis options. Strict control of data processes and access to information during the trial is critical.

KEY WORDS: *adaptive, seamless, trials, operational.*

Introduction

Over recent years the pharmaceutical industry and regulatory agencies have been discussing how to increase the efficiency of the drug development process. One possible method to make clinical trials more effective is the use of adaptive trial designs (1). The FDA through its Critical Path Initiative, has reached out to pharmaceutical companies to express openness to these trial designs and in March 2006 the CHMP issued a draft 'Reflection Paper' on flexible designs, endorsing the use of adaptive designs provided they are well controlled and improve decision making (2).

Adaptive trial designs may present advantages over traditional approaches, e.g., improved decision making; adjustment of ongoing trials which might be heading towards failure; more comprehensive exploration of dose-response relationships; reduced exposure of patients to ineffective treatments; earlier stopping of futile trials; reduction of the so-called 'white space' (the time between trials or phases of development).

Several types of adaptive trials can be recommended and these trial designs are described along with their advantages, disadvantages and the issues that must be considering when implementing adaptive trial designs. This paper does not describe detailed statistical methodology.

Definitions

Adaptive Designs (AD) - allow for initial uncertainties in trial design to be confirmed/adapted during

the trial. The integrity of the trial is maintained and the evidence for the same hypothesis before and after the adaptation is combined.

Seamless Designs (SD) join two distinct subsequent trials in a drug program into a single trial without combining the information. The trials should not differ operationally (essentially the same Case Report Form, centers, indication, …) and be defined in a single protocol. The main benefit of a seamless design is to reduce the white space between trials.

Adaptive Seamless Designs (ASD) take advantage of both: information gathered in the first stage (learn) of the trial is used to adapt the design for the next stage (confirm), which seamlessly follows; the information from the learning stage will contribute evidence to the overall conclusions

Adaptive designs

In many trials, much of the required information will not be available at the desired level of precision when the trial is undertaken. Indeed, it may frequently be the case that final data from a clinical trial provides the first opportunity to confirm or correct some of the assumptions of the trial design. After completion of the trial it may become evident that there was some potential for the trial to have been designed, undertaken, or analyzed in a different manner which might have been more efficient, or which would have increased its likelihood of success. The aim of AD trials is to use data from an ongoing trial to adjust certain aspects of the trial in a predefined manner so that the integrity, quality and validity are not compromised. A clear benefit from adaptive designs is more effective use of clinical data. There are many possible types of adaptation. Some examples of AD trials are mentioned below.

Interim analysis for futility or superiority

A well established type of adaptation is stopping a trial early based on interim data which indicates that the drug has statistically established efficacy or superiority over its comparator, or that continuing the trial is likely to be futile (3). When these interim decisions are made in a pre-specified manner on data from groups (or cohorts) of patients in the trial they are termed group-sequential trials. Group-sequential trials have been conducted for more than twenty years, mainly for large phase III trials involving survival or mortality endpoints, and they are generally accepted by Health Authorities. One of the advantages in this context is the reduction of patient exposure to suboptimal treatments or prolonged trial durations.

Adaptive dose finding

Poor understanding of the dose-response relationship for both efficacy and safety is a pervasive problem that is recognized by Health Authorities as well as Industry as one of the root causes of late stage attrition and post-marketing problems with approved drugs.

Conventional dose-finding designs explore only a few doses of a drug in a fixed parallel group study, due to the relatively large sample sizes required to estimate pairwise differences (Figure 1). The doses selected for investigation may not be highly informative, unless they are correctly selected at optimal points along the true (unknown) dose-response curve.

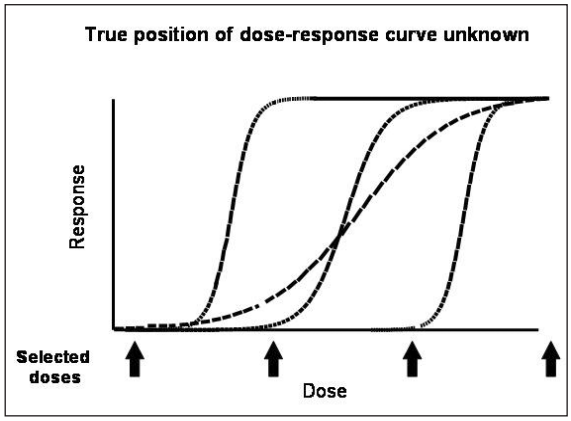

Figure 1. For most drugs the true dose-response relationship is unknown – therefore, in this traditional dose-finding example, selecting a few doses may or may not adequately describe the dose-response relationship and many patients will be allocated to 'non-informative' doses.

In contrast, adaptive trial designs provide opportunities to characterise the dose response more fully and

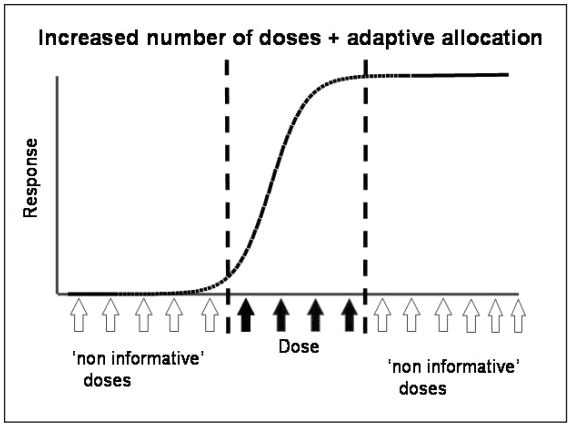

Figure 2. In this example, the strategy is to initially include few patients on many doses (open arrows) to determine the dose-response, then to allocate more patients to the dose-range of interest (closed arrows) – this reduces allocation of patients to 'non-informative' doses.

efficiently (Figure 2). Adaptive approaches facilitate iterative learning and confirming within the trial, allowing optimization of dose assignments of future patients (4). Adaptive dose-ranging designs offer significant advantages over the traditional approach by allowing flexible changes in the dose allocation ratios, including dropping or adding doses, as information is accrued in the trial (5). Coupled with the use of modelling and/or simulation techniques (to determine the dosing strategy, including number of doses, scenario planning, sample size required for decision making, and the optimal timing of any decisions), the greater flexibility of these designs leads to more efficient and reliable estimation of the dose-response relationship and, as a consequence, better estimation of target doses. An additional benefit of these designs is that they can seamlessly combine "Proof of Concept" (Phase I or IIa) and Phase IIb into a single trial.

Patient care, within an adaptive design trial, can be improved by implementing appropriate early stopping rules and adaptive treatment allocation schemes, thereby limiting patient exposure to unsafe or ineffective doses and increasing exposure to more effective doses.

Gains in efficiency with an adaptive design make it more feasible to explore the dose response earlier in the course of clinical drug development, and thus enable better data-driven decisions. Ineffective therapies could be discontinued earlier with more confidence, and late stage attrition may be reduced by improving the selection of the right dose or doses to be taken forward in confirmatory trials.

Sample size re-estimation/confirmation

Sample size re-estimation can ensure that the goals of the trial are met rather than waiting until the end of the trial only to find out that the study was underpowered and that a new trial is needed. The number of patients to be enrolled into a clinical trial is generally determined from assumptions based on the knowledge available at the time of trial design. Ultimately, it is only within the context of the trial itself that the correctness of those assumptions will be confirmed or refuted. To ensure that trials are neither too large, thus exposing more patients than needed and wasting resources, nor too small to adequately meet their objectives, the sample size may be revised as long as it is done in a way that does not compromise the integrity of the trial or interpretability of its results. If this is performed on blinded data, generally no statistical 'penalty' is required.

Parameters on which sample size re-estimation might be considered include:

- so-called "nuisance" parameters, most commonly an estimate of variability for continuous data (Figure 3), or an underlying event rate for binary data;
- the treatment effect to be detected (the desired delta), not recommended or covered here.

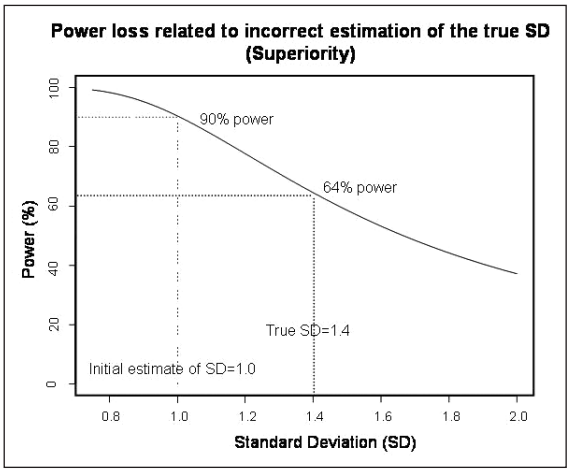

Figure 3. Loss of power as the standard deviation increases from the pre-trial initial estimate.

Statistical methods have been developed to allow sample size re-estimation on blinded data without compromising the trial validity or its integrity (6). Blinded sample size reviews to correct assumptions made about the variability in the original sample size calculations, if performed with care, are acceptable to regulatory authorities (6).

The need for sample size re-estimation should be carefully evaluated during trial planning, and the extent to which it is planned to re-evaluate sample size should be described in the protocol. Simulations are frequently used to guide discussion on the decision rules and the most appropriate timing for the interim analysis. Sample size re-estimation should never be a substitute for adequate up-front planning. Rather, it is an acknowledgement of potential limitations in the information available at the time of trial design, and of the random deviation of the observed values from the underlying true values.

The timing of the re-estimation is an important consideration for sample size review. If both increases and decreases in sample size are contemplated, the timing of the re-estimation must allow for adequate data to have accumulated and sufficient time to implement the change. Thus, the rate of enrolment and the time to endpoint occurrence are critical. Trials with very quick enrolment and a long time period before patients reach the primary efficacy endpoint are less likely to benefit from a sample size re-estimation, because enrolment may be completed before sufficient patients have reached the endpoint. Conversely, in large trials or trials with relatively long enrolment periods there is sufficient time to conduct the sample size review and to benefit from any changes in sample size.

Early consideration should be given to the range of re-estimated sample sizes to ensure the provision of clinical drug supplies and the availability of additional patients. There will usually only be one blinded interim look at the data for the sample size review.

Patient population selection

Where there is uncertainty about the patient population, it is possible to recruit from a broad population having first defined a sub-population of interest. If the selection is verified at the interim analysis, additional patients would be enrolled from the sub-population. This reduces the number of patients exposed to a treatment that is suboptimal for them. The final analysis will be performed by combining the data in the sub-population entered before and after interim analysis. The statistical analysis must be chosen to adjust for this selection, and be pre-specified.

Test statistic

It is possible to modify the fine details of the statistical test strategy for the final analysis to maximize the power of the analysis. For example, it may be possible to use interim data to define an appropriate model or model parameters to be used in the final analysis. The specifics of an endpoint, such as the timing of the final endpoint, could also be determined at the interim stage. As the regulatory hurdles would be very high, it is not recommended to change or determine the primary endpoints for a confirmatory trial using data internal to the trial.

Adaptive Seamless Design (ASD) trials

An Adaptive Seamless Design (ASD) replaces in one trial what conventionally would have required two single trials (Figure 4). ASD trials can be thought of as a trial in two stages: an ‘exploratory’ stage followed by a ‘confirmatory’ stage (7). Specifically, the initial exploratory or learning stage of an ASD trial is designed to lead to a decision on which the confirmatory stage will be based. The statistical analysis for the selected cohorts at the end of the confirmatory stage uses all data from the relevant cohorts from both stages of the trial, with appropriate statistical methodology to avoid inflation of the type I error rate or selection bias. Information gathered in the first stage of the trial is used to adapt the design for the next stage, which seamlessly follows.

Substantial benefits can be derived from ASD trials over the conventional separate-phase plan, including:

- The need for fewer patients compared to conventionally designed studies to achieve the same quality of evidence (greater power for the same number of patients).

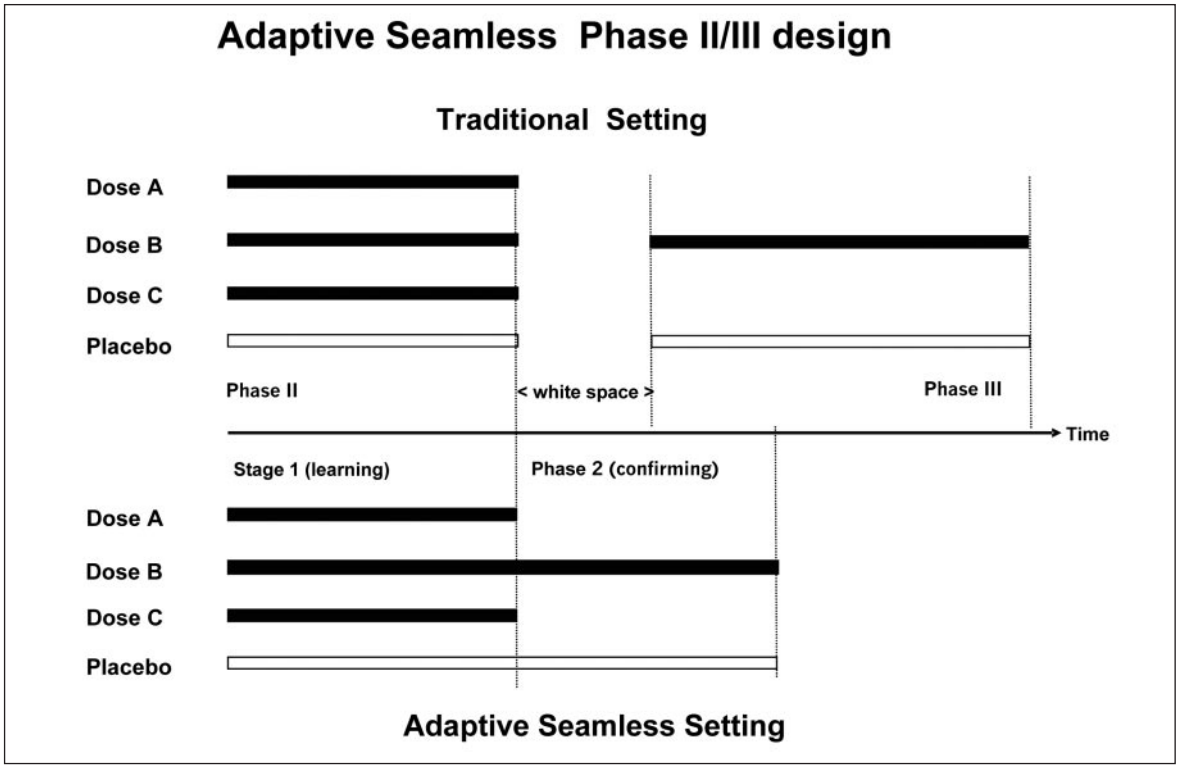

Figure 4. In the conventional setting the two trials are distinct, the results from the first trial determine the design of the second trial, there is often 6 months or more between the trials (this is termed 'white space'). In the Adaptive Seamless setting the two trials are joined seamlessly and the results from the first stage are used to adapt the design of the second stage.

- The earlier availability of effective drugs for the patients through the reduction in the overall clinical development program time.
- The opportunity to obtain longer-term data by the end of the confirmatory stage from continued observation of learning (exploratory) stage patients, i.e. making better use of patient treatment data.
- The saving in study start-up efforts.
- A more economical use of resources overall (patients, time, manpower, money, etc.).

Need for second pivotal trial

It is clear from recent Health Authority interactions and the 'Reflection Paper' from the CHMP that confirmation of findings in independent trials is necessary for registration (2). Therefore, in most cases, a single Phase II/III ASD trial alone will not be sufficient for registration. The second pivotal study should be planned to begin as soon as possible following the decision point in the ASD trial.

Influence of endpoints and enrolment

When considering the feasibility of an ASD (or an AD) the time for a patient to reach the endpoint for the interim analysis and the enrolment rate need to be taken into account.

At the time of interim analysis in an adaptive trial there will inevitably be patients who have been randomised but have not reached the endpoint by the time of interim database lock. If the time to the endpoint is short there will be relatively few such patients. However, if the time to the endpoint is long, then a large number of such patients might already be randomised. In this case, it may be necessary to temporarily pause enrolment during the interim analysis, which adds logistical complexity and erodes some of the time savings of the ASD.

Patients who have not reached the endpoint before interim database lock and who are in a study arm that is terminated will not be used in the final efficacy analysis, although their data may be useful for safety and understanding of the dose-response relationship.

Interim analyses and integrity

With the exception of blinded sample size review, un-blinding of trial data is necessary for an interim analysis. Personnel directly associated with the trial must remain blinded to protect the trial integrity; un-blinding must be restricted to as few people as possible. The protocol should describe who will have access to un-blinded data / results and the measures that will be put in place to ensure that the integrity of the trial is protected. Everyone who will have knowledge of un-blinded or semi-blinded information must undertake to keep this strictly confidential and, where appropriate, be bound by a confidentiality agreement. Such processes have been used for several years in the context of group sequential trials.

Data Monitoring Committees (DMC)

Adaptive Seamless Phase II / III trials raise particular challenges with regard to issues relating to data review performed at the end of the learning stage. Unlike conventional interim monitoring, where the decision is whether or not to stop early (for safety or efficacy), in ASD trials decisions are made which may alter key parameters in the trial. As interim decisions may make changes to the design of an ongoing study, it is particularly important that trial investigators and trial team members are kept isolated from any results that may introduce bias (8). A properly constituted independent Data Monitoring Committee (DMC) (9) should be established to review the results of the interim analysis and make decisions about the adaptation.

A DMC should have at least 3 members, one of whom should be a statistician. The chairperson, normally a clinician, must be an expert in the therapeutic area with previous experience on a DMC and preferably experience with adaptive trials. The DMC should meet prior to the start of the trial, to be briefed by the clinical team, discuss and agree the DMC charter. The DMC charter specifies the data to be reviewed, statistical analysis and results to be provided by the independent statistician, the decision rules, and the procedures to be followed at the interim analysis.

The decision process for an adaptive trial should be defined prior to the start of the study and should include all, or most of the possible outcomes. There may be some instances where an algorithmic approach to decision making is not possible, for example if the data is complex and does not follow the expected pattern. In such cases the DMC may want to consult with the sponsor before making a recommendation. The decision process may require additional expertise or perspective not usually represented on DMCs, and may potentially require sponsor input into the decision process, or at least their ratification of the DMC recommendation. The circumstances and the degree of involvement of the sponsor in the decision must be specified in the charter.

The DMC will meet in closed session, the chairperson will minute the discussions and the rationale for the decision and the DMC minutes will remain confidential until the final database lock. Only the adaptation decision will be communicated to a representative of the sponsor company, who will disseminate the decision to the clinical team in accordance with the agreed communication plan. In the case of a confirmatory trial this communication plan should also satisfy the Health Authorities.

Un-blinded review of data

If appropriate measures are not taken an un-blinded interim review may introduce bias. However, the integrity of the trial can be preserved by managing the potential sources of bias.

- **Adjusting the significance levels to compensate for repeated hypothesis testing**
  A wide range of statistical techniques are available for adaptive trial designs, it is beyond the scope of this paper to describe these in detail; the data analysis section of the trial protocol will describe the statistical methods to be used and the method for the adjustment of the level of significance.
- **Limiting access to the data**
  Personnel associated with the trial must not have access to un-blinded data, knowledge of the treatment codes, or information that would enable them to deduce treatment assignments. There are two principal ways to limit access:
  1] by using a group independent of the sponsor to

break the blind and perform the interim analysis. This could be a University Department or a Contract Research Organization;

2] by having a sponsor group that is fully isolated from the investigators and the clinical trial team.

Clearly option 2] must have safeguards that satisfy Health Authorities and Ethics Committees that confidentiality is respected. In any event access must be limited to as few people as possible.

- **Limiting access to the results of an analysis**
  Personnel associated with the trial must not have access to results of an interim analysis as this may introduce bias – either intentionally or unintentionally. An appropriately constituted decision board should review the results. It will be necessary to have an independent Data Monitoring Committee (DMC) with all the expertise required to make decisions based on the protocol decision rules and the results of an interim analysis. It is envisioned that the DMC could be within the sponsor organisation or an outside body with or without sponsor representation (7). A DMC should be set up as appropriate to the trial and Health Authorities should be appraised of the DMC charter and membership.
  In some situations where a Drug Safety Monitoring Board (DSMB) is planned, it could also act as the DMC; however, the DSMB must contain the appropriate (additional) expertise to do so. In addition, knowledge of the interim results must not compromise the ongoing safety monitoring.
- **Controlling communication of decisions**
  Communication of the outcome of an interim analysis is best made by the DMC to the Sponsor, who in turn inform Health Authorities, Ethics Committees and Clinical Trial Teams as appropriate. The decision should be communicated on an absolute need to know basis and based on a pre-defined communication plan.

In normal circumstances decision rules governing interim decisions related to early rejection of null-hypotheses must be included in the protocol. However, where bias could be introduced by simply having knowledge of the decision rules used for adaptations, it will be necessary to create a separate Decision Rule Document. This document would be made available to Health Authorities, Ethics Committees and DMCs, but not trial teams, investigators or other personnel associated with the trial.

Study management

To achieve the benefits of Adaptive Designs data from the first stage must be gathered as quickly and efficiently as possible in order to reach the adaptation decision with minimal delay. It is important to have information about patient enrolment and patient progress. Therefore, the study investigational sites must provide accurate data in a timely manner to a tracking system; for example where Interactive Voice Response Systems are used for managing drug supplies they can be utilised to track individual patients' progress in the trial. Accurate patient enrolment and progress information is necessary to determine when the necessary number of patients is recruited for the interim analysis and the when the point is reached at which the interim analysis can be performed.

To ease the timely capture and cleaning of data a subset of data appropriate to the decision required may be specified in the analysis plan which is usually made up of the primary efficacy variable and important safety data.

Some adaptations result in one or more treatment arms being dropped after the interim analysis. This means that, where it is unethical to continue, individual patients may have to be withdrawn from the trial, normally at their next scheduled visit. In trials where this is a possibility patients will have this explained to them at the time of consenting to participate in the trial; however, investigators must use their judgement in handling such discontinuations with their patients.

In some trials it may also be necessary to pause recruitment to the trial once the target number for the interim analysis has been reached. This decision depends on the availability of patients and the consequence of continuing to randomise patients to arms that will subsequently be dropped. Patients who are randomised after the cut off for the interim analysis to an arm that is subsequently dropped will not contribute to the interim analysis, however, their data will contribute to the safety profile of the compound.

Ethics

Adaptive designs present a new dimension for ethical review; generally the designs that will be used have

some ethical benefits over conventional designs. For example in adaptive or seamless adaptive trials where there is dose selection, ineffective doses or doses with unacceptable safety profiles are discontinued earlier than might be the case in a conventional trial, thus reducing patient exposure to experimental drugs or doses which are ineffective, unsafe or suboptimal.

Ethics Committees/Institutional Review Boards must be provided with extensive information about the adaptive nature of the protocol and benefits of the adaptive trial design.

Ethics Committees should pay particular attention to the safety profile of all the treatments to be used in a trial without regard to any adaptation resulting in one or more arms being dropped. If arms are to be added, the Ethics Committee should be satisfied that the added treatment / dose also has an acceptable safety profile. Ethics Committees should also carefully review grounds and processes for making decisions based on the interim results and that the integrity of the trial is protected during the interim analysis.

The possible outcomes of an interim analysis and the role of the Data Monitoring Committee must be clear to the ethical review board. They should also be in agreement with which adaptation decisions, if any, will be communicated to them. For example, if an arm is dropped in a dose ranging trial and the decision will not expose patients to any new risks, it may be sufficient to inform the committee that an arm was dropped without revealing the treatment details; the Data Monitoring Committee will have made the decision according to the protocol and the predefined decision rules that the Ethics Committee have already considered and approved.

In the case of an AD or ASD trial, no protocol amendment will be required after the interim analysis has taken place and the amendment has been made, as all of the possible, limited, outcomes have been pre-specified in the protocol.

One benefit of the adaptive approach is to potentially reduce the number of patients on "non-informative" treatment arms. Patient safety will not be compromised and may be enhanced because unnecessary exposure to ineffective doses or those with significant side effects should be minimized. At the same time it is necessary to ensure an adequate safety database of patients at or above the recommended dose.

Informed consent

For some adaptive trials it may be possible to have a single Informed Consent Form which describes both stages of the trial and the possible adaptation. However, in many adaptive designs the benefit-risk is altered as a consequence of the adaptation; therefore two or more Informed Consent Forms may be necessary. For example, consider a dose selection seamless adaptive trial where in stage I there are four doses of a treatment and placebo, which are reduced to one dosage and placebo in stage II. Patients entering stage I will have a one in five chance of getting a placebo whereas for those entering stage II there is a one in two chance. It may also be advisable to inform patients that they are participating in part one (or two) of a two part trial. In this case special care has to be taken by the investigator to the use of the correct Informed Consent Form.

Selection of endpoints and use of surrogate endpoints and biomarkers

Adaptive trials need an early readout on which to base adaptation decisions; for some diseases / indications this is not possible and adaptive designs are not feasible because the time to reach an endpoint is too long in relation to the recruitment rate. This problem can be ameliorated if a good predictor that is highly correlated with the true endpoint is available, for example a surrogate endpoint or a biomarker.

Engaging regulatory agencies in early discussion of proposed surrogates is critical to assess their view of the validity and acceptability of the proposed surrogate. It may be possible to utilize a surrogate for decision making in the learning stage while relying on more traditional endpoints in the confirmatory stage of a trial.

Biomarker development is being undertaken by an industry consortium in collaboration with the FDA. The intention is to use the biomarkers to identify patients who have a greater likelihood of response to treatment. For practical purposes, the biomarker tests will also need to be easy to perform and widely available or they will not be useful.

Optimizing the trial design using simulation

Simulation can provide key insights into the optimum trial design to maximize the information required for decision making. For example, various scenarios or the behaviour of a trial can be simulated with respect to the type and timing of adaptations in relation to recruitment timelines, duration of observation period, and endpoints. These can be based on historical data on effect size, placebo responses, and variability. Simulation techniques can also be used to assess and define the most appropriate decision rules for the trial.

Concluding remarks

Although statistical methodology and simulation techniques are available to address many of the statistical complexities of adaptive trial designs, the success or failure of using these designs also depends on overcoming the operational issues of running adaptive trials. Adaptive trial designs when properly used can reduce the chance of getting an inconclusive outcome, they also have the potential to speed up development time and make safe and effective drugs available earlier. However; if interim analyses cannot be performed quickly after the last patient contributing to the interim analysis has reached the chosen endpoint, if there are any doubts about the integrity of the trial, or if investigators cannot manage the expectations of the patients who enter the trial, adaptive trials will not become routine. Only if the statistical and the operational challenges can be overcome will adaptive/ adaptive seamless trials become widely accepted.

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