# Practical Considerations for Adaptive Trial Design and Implementation

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## Chapter 12

# Implementation issues in adaptive design trials

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### Abstract

In this chapter we discuss operational challenges that are specific to adaptive trials (as well as complex non-adaptive trials): essentially, the need to validate the design; to control the trial centrally; to collect and analyze key data rapidly; to preserve the trial blinding and integrity; and to document all important adaptive decisions taken. We illustrate these challenges using an actual phase I trial in oncology, and argue that the issues can be addressed through proper planning, choice of experienced vendors and independent groups (coordinating center and DSMB), statistical teams with adequate expertise in the design chosen (randomization and CRM), recourse to efficient computer technology (IWRS, EDC, automated emailing), and oversight by a team that must be as flexible as the trial design!

### Keywords

Operational issues, CRM (Continual reassessment Method), IWRS (Interactive Web Response System), EDC (Electronic Data Capture), DSMB (Data and Safety Monitoring Board)

## 12.1 INTRODUCTION

The growing enthusiasm for adaptive design trials is sometimes abated by concerns about difficulties with their conduct (Quinlan et al., 2010). While it is undeniable that adaptive design trials are generally less straightforward to implement than classical, fixed sample size designs, potential difficulties can all be addressed prospectively (Krams et al., 2007). Regulatory guidance documents are essential background references (EMA, 2007; FDA, 2010). Sponsors who choose to conduct adaptive design trials will want to ensure that the providers with whom they partner to conduct the trial have adequate expertise in terms of statistical methodology as well as operational experience in terms of using advanced technology (IWRS, EDC) and dealing with multiple partners (DSMB, drug supply centers, investigational sites).

In this chapter we discuss implementation issues using a phase I clinical trial as a case study. This trial is in many ways more complex than larger-scale, later-phase adaptive design trials, but it is illustrative of many requirements that are common to all adaptive designs: the need to allow for sufficient planning of the trial design and implementation; to validate the design prior to starting the trial; to oversee the trial progress centrally; to monitor drug supply at all participating sites; to collect patient data in real-time; to clean essential data with minimal delays; to analyze the data in a timely fashion for appropriate adaptations to be possible; to revisit some of the design assumptions over the course of the trial if required; to preserve the trial blinding and integrity; and to document all important adaptive decisions taken over the course of the trial for future audits.

## 12.2 CASE STUDY

The case study used here is based on an actual trial, although details have been modified to preserve anonymity. An experimental drug for supportive therapy of cancer patients had to undergo phase I testing. The goal of the phase I trial was to find the maximum tolerated dose (MTD), defined as the dose of the drug for which the probability of dose-limiting toxicity (DLT) was equal to 33%. The experimental drug was added (with no expected interactions) to standard anti-cancer therapy.

### 12.2.1 Design Constraints

The design of the trial had to fulfill the following requirements specified by the sponsor:

- a continuous dose scale should be used over a pre-specified range of feasible doses;
- about 10 patients should be treated at the MTD;
- a placebo group of about 10 patients should be included;
- patients should be randomized in double-blind fashion with less patients randomized to placebo than to the experimental drug;
- the total sample size of the trial should be about 30-40 patients.

These conditions implied that a non-standard phase I design had to be worked out. It was decided to design the trial using the likelihood-based version of the continual reassessment method (CRM)

(O'Quigley and Shen, 1996) on a continuous dose scale (Storer, 2001). The trial was split in two stages: an initial dose-escalation stage and a model-guided stage. In both stages, patients were randomized to receive placebo or the experimental drug in addition to standard chemotherapy according to a 1:3 randomization ratio. The main reason for including the placebo group was to collect information about the background rate of a particular type of chemotherapy-related toxicity the supportive therapy was aimed at reducing. The information collected was intended to provide some idea about the potential effect of the therapy and could be used by the sponsor for planning (e.g., sample size calculations) of the next trials.

### 12.2.2 Initial CRM Design

Initially, the design of the trial was specified as follows. In the dose-escalation stage, consecutive patients were assigned to doses equal to multiples of a dose $d$, i.e., $0.5d$, $d$, $2d$, $3d$, $4d$, $5d$, $6d$, and $6.7d$. Already at this stage, randomization to placebo (with 25% probability) was implemented, i.e., the assignment of patients to the sequence of the pre-planned active doses was interleaved with a random assignment of placebo.

Upon observing the first instance of dose-limiting toxicity (DLT), the model-guided stage was to be initiated. Note that observing a DLT for placebo did not trigger the stage, nor were placebo-assigned patients used in updating the model.

In the model-guided stage, the hyperbolic-tangent dose-toxicity model was used for selection of the doses for consecutive patients. The model was of the form

$$\pi(x,\beta) = \{(\tanh x + 1)/2\}^{\beta},$$

where $\pi(x,\beta)$ is the probability of DLT for dose x .

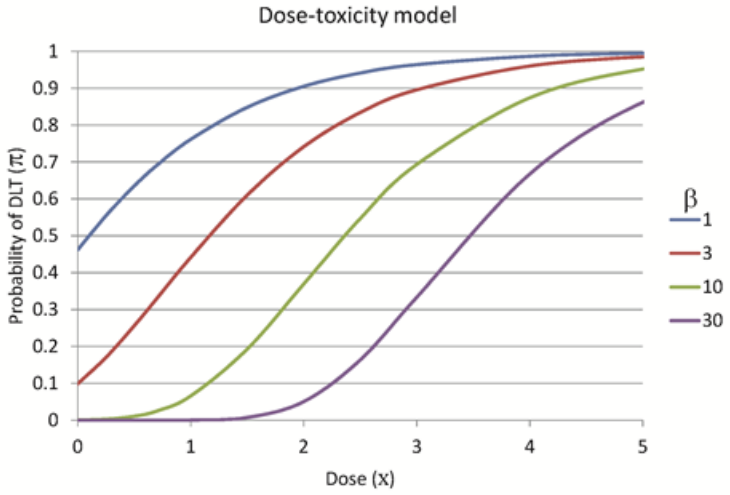


***Fig. 12.1*** *Probability of dose-limiting toxicity (DLT) as a function of dose (x). In the continual reassessment method (CRM), parameter β is re-estimated every time the outcome of a patient (DLT or no DLT) is observed.*

Upon observing the DLT status for a patient, the value of the parameter β would be updated based on all available data. Then, the next patient would be assigned the dose for which the probability of the DLT, based on the updated model, was equal to 33%. In this stage, doses would be chosen

on a continuous scale. That is, the dose with a DLT probability exactly equal to 33%, according to the updated model, would be selected. Section 12.3.6 describes how these continuous doses were managed. The following stopping rule was used for the model-guided stage: before assigning a dose, the probability of assigning the next four patients to a dose within $\pm(2/15)d$ relative to the last assigned dose was computed.

- If the probability was less than 90%, then the trial would continue.
- If the probability was equal to at least 90%, then the number of patients already treated at doses higher or equal to the last assigned dose minus $(2/15)d$ would be determined.
    - If 10 or more patients had already been treated at doses higher than or equal to the last assigned dose minus $(2/15)d$, the trial should be stopped.
    - If less than 10 patients had already been treated at doses higher than or equal to the last assigned dose minus $(2/15)d$, additional patients – maximally four – would be assigned to the last assigned dose in order to reach (if possible) the total of 10 patients, after which the trial would stop without reassessing the model.

If, according to the above rules, any additional patients were to be added to the group receiving the experimental drug, and if the placebo group contained less than 10 patients, up to two extra placebo patients could be included in the trial, so that the size of the placebo group would get as close as possible to 10 patients.

### 12.2.3 Design Modifications

During the conduct of the trial, several modifications to the design had to be made. In particular:

- After the trial started, it appeared from extensive simulations that the condition used in the stopping rule for the model-guided stage (at least 90% probability of assigning the next four patients to a dose differing by at most $(2/15)d$ from the last assigned dose) was too stringent and would result in too large a sample size. Thus, the condition was changed to: at least 80% probability of assigning the next four patients to a dose differing by at most $(3/15)d$ from the last assigned dose. For this condition, the expected number of patients receiving experimental drug would be equal to about 40. The modification was introduced by a formal amendment to the protocol.
- The results observed for an initial sequence of patients included in the initial dose-escalation stage suggested that the drug was safer than assumed and that the MTD could be higher than the initially-set maximum of $6.7d$. Hence, the margin of tolerance, used in the condition specified in the stopping rule, was changed from an absolute one to a relative one. In particular, the stopping-rule condition was changed to: at least 80% probability of assigning the next four patients to a dose differing by at most 10% relative to the last assigned dose.

Given that the initial results suggested that the drug was safer than assumed, changes to the initial dose-escalation scheme were introduced. First, the escalation of doses beyond the $6.7d$ was formally allowed. To this aim, a second protocol amendment was issued, which also included the

change of the margin of tolerance mentioned earlier and an update of the drug preparation and administration procedures implied by the increase of the allowed maximum escalated dose. Next, once the total dose of $10d$ had been reached, the basic increase of dose equal to $d$, adopted for the initial dose-escalation step, appeared to be much too small. Hence, the increase was changed to 20% of the last assigned dose. That is, the sequence of doses to be assigned in the initial dose-escalation stage was modified to $10d$, $12d$, $14.4d$, $17.28d$, etc. Moreover, the maximum dose to be used in the trial was re-set to $66.7d$. These modifications were introduced by a third protocol amendment, in which additional updates of the drug preparation and administration procedures had to be made.

### 12.2.4 Trial Conduct

The trial was conducted in five centers. The occurrence of a DLT was assessed during a 5-day period. The DLT status of each patient was reviewed by a Data Safety and Monitoring Board (DSMB), based upon all adverse event data provided by the clinical sites. The DSMB was also charged with the approval of the next dose assignment within the model-guided stage. Hence, the role of the DSMB extended well beyond the traditional role of monitoring safety, adding to it the roles of an adjudication committee and a trial steering committee (Ellenberg et al., 2002; DeMets et al., 2006; Herson, 2009; also see Chapter 14 of this book for further discussions).

The study took about one year until completion. Eventually, the trial never reached the model-guided stage, as not a single DLT was observed. The assumed level of toxicity of a new drug may in fact be overestimated in phase I trials, which calls for flexibility in the range of doses that are planned to be studied (see, e.g., Paoletti et al., 2006). In this trial, the accrual was stopped with a last assigned dose of the experimental drug equal to $62d$, i.e., close to the (updated) maximum of $66.7d$. The total number of patients included in the trial was equal to 28, with 7 patients assigned to placebo.

### 12.2.5 Challenges

The implementation of this trial raised a number of challenges. These included the need for implementing randomization and blinding, which are not standard practices in a phase I study. The randomization system had to be linked to a drug supply system that monitored the treatment kits available at each of the 5 sites. The DSMB had to accept or over-rule the dose of each patient randomized to receive the experimental drug. The DSMB also had to adjudicate the outcome of each patient, and decide whether a DLT had been observed or not.

The conduct of this trial was further complicated by the additional design modifications made during the conduct of the study, which implied modifications to the system used for randomization and assignment of the doses to the patients. All of these challenges are discussed in more detail in the next sections. Admittedly some of the challenges are peculiar to our case study, such as major design modifications that are typically not be permitted in later phase trials but are to be expected in first-in-man trials. However, this case study is of interest because many of the solutions adopted to address the adaptive nature of the trial are generic and can be implemented identically for simpler adaptive designs of later phase trials.

## 12.3 IMPLEMENTATION

The flowchart of Figure 12.2 summarizes, in simplified form, the way in which this phase I trial was implemented.

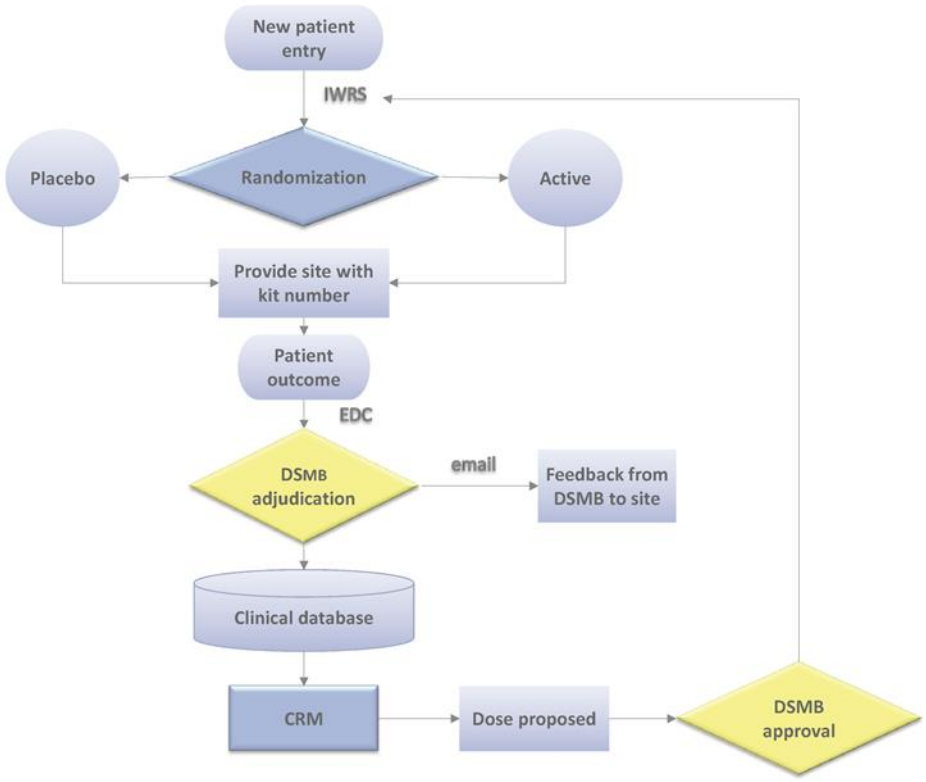


***Fig. 12.2*** *Flow chart showing implementation of phase I design (Abbreviations: IWRS, Interactive Web Response System; EDC, Electronic Data Capture; DSMB, Data Safety and Monitoring Board)*

Clearly, implementation of such a design requires integration of several computer systems (Gallo et al., 2006). An interactive web response system (IWRS) was used for patient randomization and for drug supply management and an electronic data capture (EDC) system was used to enter clinical data (case report forms). An automated emailing system was used to send messages from the coordinating center to the DSMB and to the 5 clinical sites where patients were being treated. Documents were stored in, and shared through, a web portal that gave different access privileges to the individuals involved in the trial conduct.

### 12.3.1 PLANNING

The planning phase is of key importance to ensuring the successful implementation of an adaptive design (Quinlan and Krams, 2006). Because the design is non-standard, custom software must usually be developed, tested, and validated. The various functionalities required for the trial conduct, as outlined in the next sections, usually involve different departments (typically, information technology, data management, biostatistics, and clinical operations). An "adaptive design team" dedicated to the trial should be put in place by the trial sponsor (Fardipour et al.,

2009a). This team is responsible for choosing the various technologies required for the trial conduct (IWRS, EDC, CRM or other adaptive statistical module, communication system), as well as any other vendors and the committees involved in the trial (DSMB, drug supply center, independent statistical center). In our example, the adaptive design team was based at the coordinating center of the trial, which also served as the independent statistical center. Adaptive trials have been reported in which two independent statistical centers were put in place in order to fully protect the blinding of interim data (Fardipour et al., 2009a). Generally speaking, blinding is a key consideration in planning adaptive trials (Gallo, 2006), especially those in which part of the trial is confirmatory and is intended to be used for registration, such as in seamless II/III designs (Maca et al., 2006).

### 12.3.2 Randomization

Having a correct and validated randomization system is essential for any randomized trial. A centralized randomization is essential for an adaptive trial where the randomization depends on the totality of the current data. This may sound trivial but a number of trials have failed or have raised serious questions about how patients were randomized. There are several aspects to this issue: first and foremost, does the vendor implementing the randomization system have adequate statistical competence? There exist a number of classical randomization methods (permuted blocks with or without stratification, minimization, etc.), and the choice of a method as well as the details of its implementation are among the most important features of any randomized trial. This is also true when outcome-adaptive randomization is chosen, whereby the probability of treatment allocation varies over the course of the study depending on the observed patient outcomes. Second, is the integrity of treatment allocation ensured, and how? Third, are measures in place to address deviations, such as patients not taking the medication allocated to them? Fourth, is the randomization monitored over time, to ensure that the system does what it is supposed to do? For all these reasons, it may be desirable to choose a vendor that has a proven system and a track record of successful randomization implementations. Chapters 9 and 10 of this book provide details about points to consider regarding randomization in adaptive trials.

### 12.3.3 Continual Reassessment Method (CRM)

Special-purpose software (a SAS macro) was developed for this trial to implement the CRM method described in Sections 2.2 and 2.3. The software was qualified by running extensive simulations aimed at checking the operational characteristics of the design, including the identification of the MTD and the expected sample size. One unusual feature in this trial was the major design changes that occurred during trial conduct, and required software changes and re-validation. The statistician responsible for the trial attended the DSMB meeting during which all relevant data were reviewed. Once the DLT status of a patient was confirmed by the DSMB, the statistician was responsible for including the information into the randomization system. Also, in the model-updating stage, the statistician was responsible for running the CRM module. However, as has already been mentioned, the trial did not reach this design stage.

### 12.3.4 Interactive Web Response System (IWRS)

The availability of a flexible Interactive Web Response System (IWRS) was essential to manage the complexity of this adaptive design. The trial was designed to go through two distinct stages, each stage being substantially different from the previous one in terms of the randomization features. The IWRS was also designed to generate information to, and integrate information from, the DSMB, to provide a treatment kit number to the unblinded pharmacist at each site, to control the opening and closure of recruitment at each participating site, and to monitor investigational product needs at each site, taking into account the subjects and site history, as well as the current trial status.

As stated above, the DSMB involvement was continuous in so far as they had to approve the dose to be administered to every patient randomized to the experimental drug. This is unusual and had implications on the choice of DSMB members as well as on the DSMB Charter, which contained clear explanations about the flow of information between the different parties involved in the trial. Every effort was made to keep all processes as simple as possible for DSMB members. They did not have to log into the IWRS; rather, they had stated their preference to send a fax with their decision to the coordinating office which entered the necessary information into the IWRS. All other communications to and from the DSMB were done via emailing system, which was largely automated to minimize both the time required and the opportunity for errors.

The sites were informed automatically and in real-time of the trial status. This was important since the randomization was stopped and started before and after each DSMB meeting. They needed to know at every moment whether the randomization was open or closed so that they knew when they could randomize patients.

### 12.3.5 Electronic Data Capture (EDC)

The EDC system in this trial was used to collect key data for the IWRS to act as a central control system. The EDC captured real-time information on the subject treatment and outcome (in this case any dose-limiting toxicity). This information was fed to the clinical database, and was to be used by the CRM for dose selection, and reviewed by the DSMB for dose approval (Figure 12.2).

### 12.3.6 Drug Supply Management

The drug supply process can be complex in adaptive trials, especially when the trial proceeds in stages with different types of supplies (product, dose, formulation, etc.) It is important to test the product dosage, packaging, distribution, storage or usage before trial start, and to monitor these features closely during the early phases of the adaptive design trial. When changes in any of these parameters are mandated by the trial design, all possible scenarios must be simulated to estimate the quantities of the product required, where and when. Further discussions of points to consider for the drug supply process in adaptive trials can be found in Chapter 15 of this book.

An experimental product never comes in unlimited quantities and is often quite expensive; the shipments can have significant costs; storage conditions are not always ideal; product shipments may not arrive immediately. Having these restrictions in mind is key in order to put in place the drug supply process including mechanisms that will help make appropriate real-time decisions in

case of unexpected events with drug supply. A challenge that is specific to adaptive trials is to optimize drug supply across all scenarios allowed by the adaptive design. Whenever possible, the product formulation or packaging should ensure that there will be no need for additional product regardless of the scenario that actually takes place, for example in designing the product kits in such a way that all possible doses can be reconstituted with a given number of kits. This not only reduces the cost of drug supply, it also ensures the integrity of the trial blind after adaptation.

For the study described above, the treatment was given as an infusion so there was flexibility in modifying the dose. Since this was a double blind study, the investigator could not be aware of the treatment being given so the syringes were prepared by an unblinded pharmacist. The pharmacist prepared two syringes by drawing the appropriate amount of study drug and adding the appropriate amount of sterile water for injection in order to get the final volume needed. The IWRS system provided detailed instructions to the pharmacist on the size of the syringe, how much active drug and how much saline solution to combine in each syringe. All of this information was dynamic and depended on which dose was to be given. This was defined at the beginning of the study, and then modified and revalidated when the protocol increased the maximum possible dose as the IWRS system had to foresee all possible doses.

### 12.3.7 Data Safety and Monitoring Board (DSMB)

Adaptive designs, by definition, include interim analyses which may or may not trigger adaptations. Our phase I design is an extreme example in which the outcome of every patient receiving experimental treatment could potentially change the dose for the next patients entered in the trial. In traditional open-label phase I dose escalation trials, the investigators themselves review the interim data to decide on the next dose to be administered, but in the double-blind trial discussed here the interim analyses were reviewed by an independent DSMB, just as they would be in most other adaptive design trials. The independence of the DSMB was felt essential to maintain the blinding and prevent operational bias from entering the trial post-adaptation, had the investigators and/or the sponsor been aware of interim trial outcomes.

Regulatory guidance documents (EMA, 2005; FDA, 2010), as well as several books (Ellenberg et al., 2002; DeMets et al., 2006; Herson, 2009) discuss requirements for the composition and role of DSMBs, and provide templates for DSMB Charters. The role of DSMBs in adaptive trials is covered in detail in Chapter 14 of this book. The most important role of DSMBs is to ensure the protection of the patients entered in the trial, which entails not only a careful and regular review of safety data, but also a close scrutiny of the trial conduct. As stated above, DSMBs are typically independent from all other parties involved in the trial conduct and the integrity of the trial data is ensured by restricting access to interim trial outcomes to DSMB members only. In our phase I example, the algorithm for dose escalation was fully pre-specified and the DSMB acted mostly as a safeguard against unexpected drug effects. In late-stage adaptive designs used for confirmatory trials, it is also essential that the DSMB have complete independence. In some situations, however, *e.g.* in early-stage adaptive design trials, the sponsor may find it difficult to leave important adaptations to a completely independent committee, no matter how carefully chosen. Leaving aside the sponsor's financial interest, it may be the case that the sponsor has access to important

information not available to the DSMB, so that it may be in the best interest of the trial that the sponsor be involved in the decision making. If the sponsor needs to be represented at all in the decision making, the PhRMA Working Group on Adaptive Trial Designs (Gallo et al., 2006) recommends that the rationale for this be documented, that the sponsor representatives who receive access to interim results be adequately distanced from the trial conduct, and that their number be limited to the bare minimum. Table 12.1 lists essential conditions under which sponsor involvement may be considered in adaptive decisions.

**Table 12.1**: Conditions under which sponsor involvement may be considered in adaptive decisions

| Condition | Details |
|---|---|
| Rationale for involvement | There is a strong and documented rationale for a few sponsor representatives to be involved, either to reach the best decision for the trial itself, or to secure further funding for the remainder of the trial (*e.g.* if a sample size increase is considered) |
| Complete independence from trial conduct | The sponsor representatives are not involved in trial operations, and clearly understand the issues and risks associated with knowledge of interim results (*e.g.* operational biases) |
| Minimal data shared | The sponsor representatives receive "minimal" pre-specified interim data, i.e., *only* at the adaptation point, and *only* the data required to reach a decision (unlike a DSMB who has a broader role, and may therefore see more extensive interim data) |
| Documentation | Any release of information to sponsor representatives is duly documented and tracked using a secure electronic system |
| Adequate blinding | Adequate firewalls are put in place to guarantee blinding for all individuals other than those involved in adaptive decisions |

It should be emphasized that even if all necessary precautions are taken to maintain interim results blinded, adaptations will often convey indirect information on the treatment effects – for instance, when doses are dropped for lack of efficacy. For a detailed discussion of this issue, see Gallo (2006).

One problem that occurred in the trial described above, but also frequently in other trials, is that the DSMB may see data that raise serious questions about the adequacy of the design assumptions. To protect against unwarranted consequences of such problems, it is useful to put in place a trial Steering Committee, involving all parties concerned, and to pre-specify rules for any required interactions between the Steering Committee and the DSMB (Fardipour et al., 2009b). The fact that a trial is planned to be adaptive does not imply that any type of data-derived design changes are feasible; in fact, a well-designed adaptive trial must pre-specify what specific adaptations will be considered, and under what conditions. However, the set-up of an adaptive trial ensures that mechanisms are in place to discuss other design changes that might be required, as in our example, whilst preserving the trial integrity.

### 12.3.8 Communication System

As is clear from Figure 12.2, the various parties involved in the conduct of the trial (coordinating center, drug supply center, DSMB, participating sites) had to be informed quickly and consistently of new events triggering further actions. This was made possible through implementation of an automated emailing system between these parties, which was felt to be more reliable than an emailing system triggered by human intervention. Such a system also provided an unalterable record of the sequence of events throughout the course of the trial. In addition to this emailing system, a dedicated web portal was built specifically for the trial, with access privileges tailored to each individual involved in the trial conduct.

## 12.4 QUALITY ASSURANCE

### 12.4.1 Systems Validation

All systems put in place to help conduct a trial (CRM, IWRS, EDC, drug supply) need to be fully validated, whether for an adaptive or non-adaptive trial. The testing required for systems validation is more challenging for an adaptive trial, and can become a hefty mission when the number of potential scenarios is large. However the systems validation provides a unique opportunity not just to test the systems, but also to revisit the assumptions underlying the design and the plausible scenarios arising from it. Unsuspected flaws can be uncovered during testing, in which case amendments to the design may prove necessary. Finally, the systems validation brings added value because it involves a number of real trial actors and offers an opportunity to identify bottlenecks or obstacles and fine tune all processes and communication lines.

### 12.4.2 Simulations

When an adaptive design is implemented, it is essential to investigate the various potential outcomes of the trial under a range of plausible scenarios. From a statistical point of view, the operating characteristics of simple designs can be derived analytically, but for complex designs such as the phase I design discussed here, simulations must be used. If custom-made software is used to implement the design, its validation usually includes simulations aimed at showing that the design and the software deliver the intended outcomes. When we conducted such simulations in our phase I trial, they indicated that the initially-proposed stopping rule for the CRM design would result in too large a sample size. Consequently, the stopping rule was modified. For detailed points to consider on trial simulations, see Gaydos et al. (2009).

### 12.4.3 Documentation

An adaptive design requires more documentation than a traditional design. Unless the design has been described in a peer-reviewed publication, its operating characteristics will need to be documented in detail. The advantages of the chosen design will need to be demonstrated, in comparison to simpler, non-adaptive, designs. The simulation report, in an adaptive design, may be considered a regulatory document alongside the statistical analysis plan. For detailed points to consider on documentation, see Gaydos et al. (2009), and Chapter 14 of this book.

## 12.5 OTHER OPERATIONAL CONSIDERATIONS

### 12.5.1 Coordinating Center

The coordinating center must have statistical expertise in adaptive designs, as well as relevant experience in managing adaptive trials. Although adaptive designs can have a wide range of purposes (dose finding, seamless transition from phase II to phase III, sample size increase, population enrichment, etc.) with different operational implications, we have tried throughout this chapter to discuss issues that are common to most adaptive trials. As a matter of fact, coordinating centers having experience with sophisticated non-adaptive trials (e.g. trials with complex randomization schemes and trials using sequential or group sequential designs) will already have in place a number of key components discussed above (e.g. IWRS and DSMB experience), hence they will find it easier to extend their capabilities to address specific requirements of adaptive trials. In addition to relevant experience, such a coordinating center needs to have a help desk available to all users at all times. Adaptive designs have more parts that can require assistance for the sites, so it is important for them to be able to call someone to get help whenever needed. Since most trials are now worldwide, this help desk should be reachable 24/7 – ideally either by e-mail or by telephone.

### 12.5.2 Change Management

The sponsor of an adaptive trial, and even more so the coordinating center in charge of the trial conduct, must be prepared to implement change management. In a survey of 13 large and medium-sized pharmaceutical companies and 3 statistical consultancy groups, change management was mentioned as a major stumbling block against broader adoption of adaptive designs (Quinlan et al., 2010). Appropriate education and training are both key, but it is equally important for the coordinating center to maintain a spirit of openness, flexibility and critical thinking rather than over-reliance on a rigid set of Standard Operating Procedures (SOPs). Although project-specific SOPs can be useful in most situations, the personnel involved in the project must be adaptive – i.e. prepared to face unexpected events and changes gracefully and efficiently.

### 12.5.3 Institutional Review Boards

Because of their inherent complexity, adaptive designs will often need to be explained in detail to Institutional Review Boards (called Ethics Committees in Europe) charged with their approval for local use. Similarly, more time may need to be devoted to develop Informed Consent Forms that are truly informative about the nature of the trial design as well as understandable by patients (and investigators). Although the statistical details of the adaptation can be technically challenging, such details are unnecessary to understand the essence of the design, and in fact are best kept hidden from the trial participants, in order to avoid any operational biases that might arise from such in-depth knowledge. A typical example is the randomization method used to allocate treatments to patients. Although the method must be fully described in the technical documentation of the trial, it should not be described in any detail in the documents that are publicly available (*e.g.* the trial protocol or the trial summary posted in clinicaltrials.gov).

## 12.6 CONCLUSIONS - SUCCESS FACTORS FOR ADAPTIVE TRIAL IMPLEMENTATION

Our example illustrates that implementing an adaptive design does require careful planning and creates an operational overhead which adds to the overall costs of the trial (Quinlan and Krams, 2006). We discussed a phase I dose-finding trial in cancer, but many of the operational difficulties would be similar in other adaptive dose-finding trials (Shen et al., 2011). In return for such careful planning of adaptive trials, it is important to emphasize that many of the risks associated with the trial design and execution will have been fully addressed prior to starting patient accrual in an adaptively designed trial, which is fully in line with the recent guidance documents on risk based quality management from the European Medicines Agency (EMA, 2011) and the US Food and Drug administration (FDA, 2013). A dialogue with the agencies is less essential for early phase trials, where there are fewer regulatory concerns about adaptive designs, but for later phase trials an early interaction with the agencies is highly recommended (Chow and Chang, 2008).

All in all, the challenges of implementing adaptive designs may be well worth the effort. From an operational point of view the following issues should be considered:

- The vendors in charge of implementing the trial should have knowledge of, and experience with, adaptive and complex designs, which requires both statistical and operational (randomization) expertise;
- The vendors should be involved in the trial as soon as possible, preferably at the design stage;
- The members of the DSMB should have adequate expertise and availability to effectively monitor the trial;
- The key events and transitions between the different stages of the adaptive design should be clearly outlined, all operations (automated/semi-automated/manual) defined, and all actors identified prior to trial start;
- The computerized system (see Figure 12.2) should be fully implemented, tested and validated, and re-validated in case of major design changes;
- Extensive simulations should be carried out to cover all possible scenarios dictated by the adaptive design, with active involvement of all key actors in ‘dummy runs’;
- Proper documentation must be available to address any question that might be raised during or after the trial.

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## References

1. Chow, S.C., Chang, M.: Adaptive design methods in clinical trials – a review. Orphanet J. Rare Dis. **3**, 11 (2008).
2. DeMets, D.L., Furberg, C.D., Friedman, L.M. (eds.): *Data Monitoring in Clinical Trials: A Case Studies Approach*. Springer, New York (2006). ISBN 0-387-20330-3
3. Ellenberg, S.E., Fleming, T.R., DeMets, D.L.: *Data Monitoring Committees in Clinical Trials: A Practical Perspective*. Wiley, Chichester (2002). ISBN 0-471-48986-7
4. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP): Guideline on Data Monitoring Committees. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003635.pdf (July 2005). Accessed 30 Sep 2013
5. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP): Reflection Paper on Methodological Issues in Confirmatory Clinical Trials Planned with an Adaptive Design. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003616.pdf (October 2007). Accessed 30 Sep 2013.
6. European Medicines Agency: Reflection paper on risk based quality management in clinical trials. EMA/INS/GCP/394194/2011. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500110059.pdf (February 2011). Accessed 30 Sep 2013
7. Fardipour, P., Littman, G., Burns, D.D., et al.: Planning and executing response-adaptive learn-phase clinical trials: 1. The process. Drug Info. J. **43**, 713-724 (2009a).
8. Fardipour, P., Littman, G., Burns, D.D., et al.: Planning and executing response-adaptive learn-phase clinical trials: 2. Case studies. Drug Info. J. **43**, 725-734 (2009b).
9. Gallo, P.: Confidentiality and trial integrity issues for adaptive designs. Drug Info. J. **40**, 445-450 (2006).
10. Gallo, P., Chuang-Stein, C., Dragalin, V., et al.: Adaptive designs in clinical drug development – an executive summary of the PhRMA Working Group. J. Biopharm. Statist. **16**, 275-283 (2006).
11. Gaydos, B., Anderson, K.M., Berry, D., et al.: Good practices for adaptive clinical trials in pharmaceutical product development. Drug Info. J. **43**, 539-556 (2009).
12. Herson, J.: *Data and Safety Monitoring Committees in Clinical Trials,* Chapman & Hall/CRC, Boca Raton FL (2009). ISBN 978-1-4200-7037-8
13. Krams, M., Burman, C.F., Dragalin, V., et al.: Adaptive designs in clinical drug development: opportunities, challenges, and scope. Reflections following PhRMA's November 2006 Workshop. J Biopharm. Statist. **17**, 957-964 (2007).
14. Maca, J., Bhattacharya, S., Dragalin, V., et al.: Adaptive seamless phase II/III designs -

background, operational aspects, and examples. Drug Info. J. **40**, 463-473 (2006).

15. O'Quigley, J., Shen, L.Z.: Continual reassessment method: a likelihood approach. Biometrics **52**, 673-684 (1996).
16. Paoletti, X., Baron, B., Schöffski, P., et al.: Using the continual reassessment method: lessons learned from an EORTC phase I dose finding study. Eur. J. Cancer **42**, 1362-1368 (2006).
17. Quinlan, J., Gaydos, B., Maca, J., Krams, M.: Barriers and opportunities for implementation of adaptive designs in pharmaceutical product development. Clin. Trials **7**, 167-173 (2010).
18. Quinlan, J.A., Krams, M.: Implementing adaptive designs: logistical and operational considerations. Drug Info. J. **40**, 437-444 (2006).
19. Shen, J., Preskorn, S., Dragalin, V., et al.: How adaptive designs can increase efficiency in psychiatric drug development: a case study. Innov. Clin. Neurosci. **8**, 26-34 (2011).
20. Storer, B.E.: An evaluation of phase I clinical trial designs in the continuous dose–response setting. Statist. in Med. **20**, 2399-2408 (2001).
21. U.S. Department of Health and Human Services. Food and Drug Administration: Guidance for Clinical Trial Sponsors - Adaptive Design Clinical Trials for Drugs and Biologics. http://www.fda.gov/downloads/Drugs/.../Guidances/ucm201790.pdf (March 2006). Accessed 30 Sep 2013
22. U.S. Department of Health and Human Services. Food and Drug Administration: Guidance for Industry - Establishment and Operation of Clinical Trial Data Monitoring Committees. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf (March 2006). Accessed 30 Sep 2013
23. U.S. Department of Health and Human Services, Food and Drug Administration: Guidance for Industry: Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf (August 2013). Accessed 30 Sep 2013