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Adaptive Methods: When and How Should They be Used in Clinical Trials?

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Abstract – Adaptive clinical trial designs are defined as designs that use data cumulated during trial to possibly modify certain aspects without compromising the validity and integrity of the said trial. Compared to more traditional trials, in theory, adaptive designs allow the same information to be generated but in a more efficient manner. The advantages and limits of this type of design together with the weight of the constraints, in particular of a logistic nature, that their use implies, differ depending on whether the trial is exploratory or confirmatory with a view to registration. One of the key elements ensuring trial integrity is the involvement of an independent committee to determine adaptations in terms of experimental design during the study. Adaptive methods for clinical trials are appealing and may be accepted by the relevant authorities. However, the constraints that they impose must be determined well in advance.

1. Introduction

The adaptive trial concept recently generated considerable interest both in biostatistical literature (special editions of the Journal of Biopharmaceutical Statistics in 2005 and the Biometrical Journal in 2006, literature reviews),[1–5] and with regulatory agencies.[6–8]

According to the authors, this concept can group together extremely different ideas. A rather detailed taxonomy was put forward within the scope of think-tanks organized by the PhRMA[9] group and an adaptive design is now generally defined as an experimental design in which data cumulated during the trial are used to possibly modify certain aspects without compromising its validity and integrity. This is the definition used in the Food and Drug Administration (FDA) project guidelines.[8] The term trial validity means that statistical inference must be correct in terms of estimation and testing (especially controlling for type I error), consistency must be maintained between the various stages of the trial and that operational bias must be minimized. In the broadest sense of the term, integrity refers to the acceptability of results by the scientific community, especially the relevant authorities. This primarily involves planning adaptations in advance as much as possible and maintaining data confidentiality during the trial. The options for adapting the experimental design are extremely broad. Possible adaptations include trial eligibility criteria, randomization rules (modifying the allocation ratio of each treatment), the sample size (including early trial discontinuation), treatment (dose, duration, etc.), endpoints (including the primary endpoint, for instance, in the case of a composite criterion) and the statistical methods for data analysis method, etc. The various types of adaptive designs can be summarized as shown in table I, not to mention the detailed taxonomy above.

According to the definition selected, a trial whereby the experimental design is modified solely on the basis of outsourced trial data, does not follow an adaptive design. Conversely, a group-sequential trial in which early discontinuation on trivial grounds or due to efficacy is provided for after one or more interim analyses, fits the adaptive design concept (according to some authors, these trials where the adaptive component is fully specified in advance are not, however, entirely adaptive).[10] Adaptive designs also include methods for the blind re-assessment of the number of subjects required based on aggregated data. In the latter case, a nuisance parameter such as variance of the endpoint, is estimated

⋆ For the list of participants, see end of article

Table I. Key adaptive designs.

Type of adaptive trial	Adaptations
Group-sequential trial	Early study discontinuation.
Re-evaluation of the number of subjects required for blind status (re-estimation of the variance, etc.)	Modification of sample size
Phase 1 dose escalation modified CRM	Choice of the next dose
Phases 1-2 incorporated	Choice of the next dose
Phase 2 adaptive dose-finding	Change of randomization ratio
Re-evaluation of the number of subjects (non-blind status, on efficacy endpoints)	Increase in sample size
Extending the population	Modification of inclusion criteria, population for analysis, sub-groups
Seamless phase 2-3 trials	Dose selection, etc.

CRM: Continual Reassessment Method

during the study to revise the value used in calculating the required number of subjects during the planning stage and to modify, if need be, this number of subjects in order to maintain study power. Both types of adaptive designs have long since been used, the statistical methods are well developed and their use does not appear to raise any particular issues about regulatory agencies. The adaptive designs have therefore been separated to form two distinct entities – those that are well controlled or well understood and those that are less well understood.[8] The work of the Round Table has focused specifically on these less well-known designs, overlooking group-sequential trials, for example.

Compared to traditional designs where the entire experimental design is determined before the study begins, adaptive designs allow the same information to be obtained but more efficiently, *i.e*. within a shorter timeframe or with fewer subjects. Their flexibility also increases the probability of achieving trial objectives or improving the knowledge of treatment effects by leading, for instance, to a more accurate estimation of the dose-effect relationship or of the success rate at the dose selected by treating more patients at this dose. However, the use of this type of design could be sometimes associated with extremely rigid constraints, which are summarized below, and which may prove risky for a trial sponsor. The compromise between the potential advantages and the impact of these constraints and risks varies depending on whether the trial is exploratory or confirmatory with a view to registration.

In the rest of this paper, we will briefly outline a few significant methodological concepts in adaptive designs. We will then describe the types of design suitable for exploratory and confirmatory trials in chapters 3 and 4, respectively, along with their advantages and disadvantages. Chapter 5 describes the role of the various key players focusing in particular on the independent committee. The constraints imposed by adaptive designs and the risks associated with their use are finally set out in detail followed by a succinct conclusion.

2. Basic concepts

The concepts that underlie adaptive methods and the statistical approaches used differ depending on the type of adaptive trial. However, the definition of an adaptive trial presupposes a sequential trial procedure with one or more interim analyses in order to adapt the experimental design according to the data observed. This concept is therefore central and a key element in any type of adaptive trial, which can be viewed as a sequential trial with the extra option of adaptation. An adaptive design therefore corresponds to an extension of the role of the interim analysis. The very definition of an interim analysis is also extensive in the case of adaptive designs compared to the usual structure, *i.e*. an analysis intended to compare the treatment arms in terms of efficacy or safety.[11] For an adaptive design, any analysis of trial data whilst the trial is in progress is considered an interim analysis, regardless of the data examined or the purpose of this evaluation. The crucial point is to establish whether or not this analysis has been carried out entirely without knowledge of treatment.

The aim of this paper is not to go into detail about all of the statistical methods employed in adaptive trials but to leave the reader wanting to expand his/her knowledge by looking at some of the recently published reviews on this topic.[3,4] We nevertheless felt that it was important to summarize here some of the key concepts to be found in adaptive trials.

2.1. Controlling type I error and the conditional invariance principle

Rigorous monitoring of the risk of type I error is essential in confirmatory studies so as not to challenge the validity of the conclusions. Any trial without strict control of the type I error rate is therefore deemed to be exploratory. Conversely, despite type I error control, an excessive number of adaptations, an inadequate

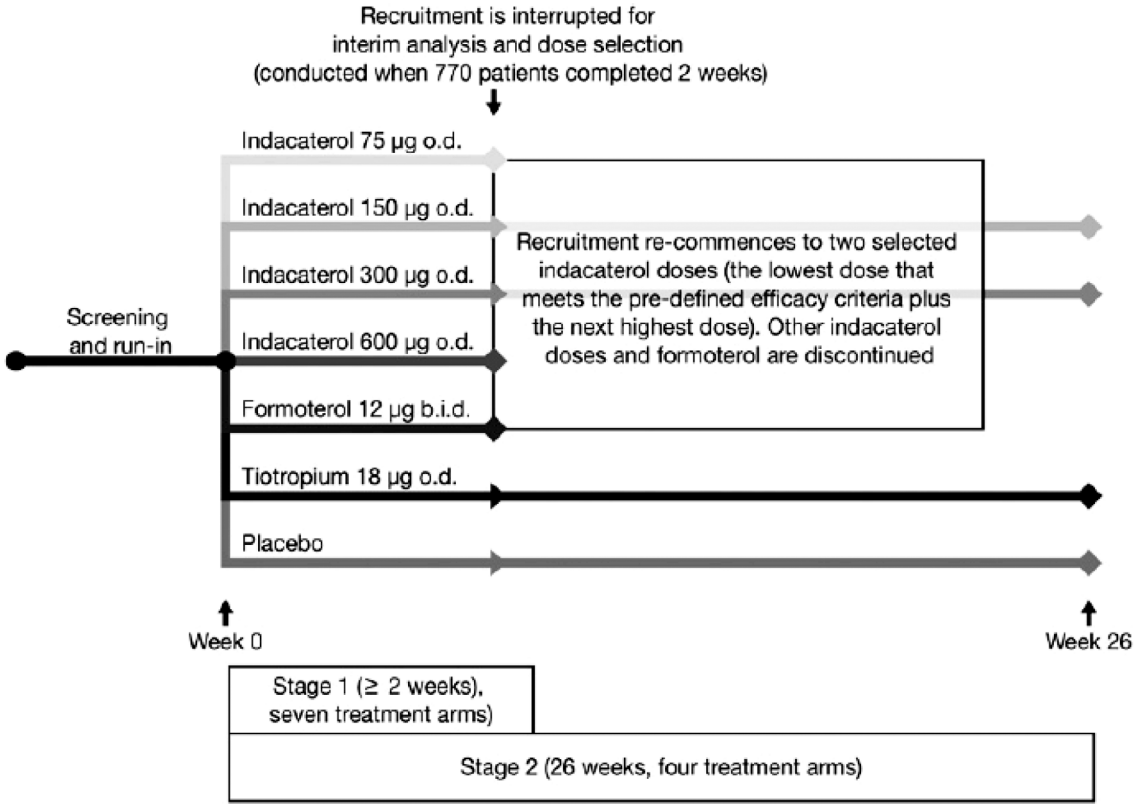

Fig. 1. Design of a seamless phase 2-3 trial (according to Donohue *et al.* 2010 with authorization of American thoracic society).[29]

sample size or too many endpoints will lead to some uncertainty in terms of trial validity.

Adaptive designs respond to a conditional invariance principle[12] in order to control the type I error rate. Let us assume that, without making any change to the experimental design, the final test can be expressed in terms of a combination of test statistics calculated at different stages in the trial (*i.e.* using data collected between the various interim analyses) and that the deciding rule regarding this test statistic ensures a type I error rate to predefine α. Any modification to the experimental design that keeps distribution under the null hypothesis of test statistics of each stage depending on what has been observed to date, globally preserves α provided that the test statistics are combined, as initially specified.[13,14] An experimental design can thus be adapted insofar as its modification retains the initial conditional type I error.

Several methods can be used to pool the information acquired during the various stages. The first studies on this subject used combination tests obtained by combining the degrees of significance (p) obtained at each stage.[13] Other methods are based on the conditional error function.[15] Although technically different, all of these approaches are connected and may prove equivalent in some cases.[16]

2.2. Multiple testing

Numerous adaptive designs use the several null hypotheses test as shown in the case illustrated in figure 1. The correction of tests to control the overall risk of a type I error therefore becomes crucial. Let's take the case of an adaptive dose-finding trial where, of all the various treatment doses initially considered, only some will be selected after interim analysis. This provides a series of null hypotheses corresponding to the effect of each of the doses in comparison to the control arm. A method must therefore be used that will test these null hypotheses by controlling the overall risk of type I error and taking into account the fact that the data used to test these hypotheses will not necessarily be available at each stage, for example when one of the doses has not been selected for the second stage. The methods used are based on the principle of closed testing procedures,[17] which control the type I error rate for all of the hypotheses tested.

2.3. Bayesian methods

The principle of Bayesian inference is based on a combination of the distribution *a priori* of parameters of interest and data

collected during the trial in order to obtain a distribution *a posteriori* of this distribution that represents the current level of knowledge about these parameters. The use of Bayesian methods does not necessarily imply the use of an adaptive design. Nevertheless, the Bayesian approach is particularly suitable to a sequential approach in that re-updating parameter distributions in a Bayesian setting does not lead to any increase in terms of error risk.[18] Although this type of inference has mostly been used for exploratory trials,[19,20] the use of Bayesian methods has been proposed for trials of a more confirmatory nature with methods to re-evaluate the number of subjects or for phase 2-3 trials.[21,22]

2.4. Pre-specification, operational characteristics and independence of the decision

In confirmatory trials, proof of trial integrity is of paramount importance and must be provided by the sponsor. Several points are important in order to ensure this integrity.

The first point is the pre-specification of the adaptive nature of the trial and the adaptations considered. On the one hand, the trial must have been planned as an adaptive trial with a limited number of adaptations. On the other hand, if an experimental design has to be adapted to cope with an unforeseen situation, without having been planned initially, it is absolutely essential that the decision is taken prior to any analysis. The first stage experimental design and the rule for combining information gleaned at different stages must be determined in advance as this will ensure the strict control of type I error. Moreover, adaptations that do not directly affect this risk of error must also be determined in advance if possible. The impact of interim decision-making rules on estimating treatment effects is therefore assessed using extensive numerical simulations covering a wide range of situations.

The second point is to ensure the sponsor's blind status in terms of trial results when taking adaptation decisions. These decisions based on trial results must be taken by an independent committee. The role of this committee and its relationship with the sponsor will be discussed in more detail further on.

3. Adaptive designs for exploratory trials

3.1. Phase 1 dose-finding trials

The purpose of phase 1 trials is to determine the maximum tolerated dose of a new treatment. In oncology, they are specifically carried out in patients given the severity of the potential toxicity of the treatments involved. The conventional design of these trials, namely "3+3", comprises the sequential allocation of scheduled doses of treatment to cohorts of three patients. Once three patients have been treated with one dose, the next three patients are treated at a higher dose if no toxicity is observed and at the same dose if one case of toxicity is observed. If two or more cases of toxicity are observed for the same dose of treatment, an intolerable dose has been reached, and a lower dose will be recommended or the trial is stopped.

An alternative continual design for carrying out and analyzing such trials (the Continual Reassessment Method or CRM) has been proposed.[19] It is based on the parametric modeling of the dose-toxicity ratio with dose allocation and sequential estimation of the model parameter up to the inclusion of a pre-set fixed number of subjects. This method has led to numerous studies that have corrected most of the limits. Nowadays, most applications use the modified CRM.[23,24] Inference in this type of design can be Bayesian or frequentist. Although this design was developed more specifically for oncology trials, it has also been used in other domains such as pediatrics, for instance.

The advantages of modified CRM compared to the "3+3" design include improved estimation of the maximum tolerated dose and faster allocation of the correct dose. It also exposes fewer patients to excessively toxic or ineffective doses. Conversely, this method appears to be rather sensitive to toxicity observed at the first dose, especially in the case of Bayesian inference. The use of this type of design can be recommended.

One example of using modified CRM concerns a dose-finding study to establish the maximum tolerated dose of subcutaneous homoharringtonin in patients with acute myeloid leukemia.[25] In this trial, five dose levels were initially planned and the maximum tolerated dose (5 $mg.m^{-2}$/day, *i.e.* the fourth dose level) was selected after including 18 patients eligible for assessment in cohorts of three. However, 12 of these patients received the dose that was finally selected, *i.e.* twice the number of patients who would have received that dose with a conventional trial design.

3.2. Integrated phase 1-2 trials

Dose-finding trials using a combination of safety and efficacy criteria have also been proposed. These are referred to as seamless phase 1-2 trials.[22,26] In terms of general methodology, these trials resemble the designs used in the afore mentioned phase 1 dose-finding trials.

The advantage of these designs is based on a combined safety and efficacy evaluation to select the dose with less chance of ruling out interesting doses compared to traditional methods. However, this type of trial requires a response in terms of efficacy in order to

establish the dose to be allocated to the next patient cohort. In oncology, for example, safety is assessed over a period of about one month but efficacy is rarely assessed before three or four months. Hence, there is a significant delay before the right dose is found. Furthermore, this approach limits the feedback needed to highlight late toxicity and reduces knowledge of mid-term tolerability compared to development in separate phases.

The last point has been deemed crucial. This type of design is considered to be less appropriate for testing little known molecules or a combination of molecules. When used, it is recommended for single therapy.

3.3. Phase 2 trials

Phase 2 trials are exploratory trials to assess treatment efficacy. Depending on the domain, the state of the art or the number of molecules to be tested for the disease in question, numerous adaptive designs responding to various questions and constraints have been used. These questions may, for instance, focus on dose-finding or prioritizing several treatments. Adaptive dose-finding studies where the patient allocation ratio between the different doses is adapted depending on the responses observed are essentially rather widespread.[4,20,22]

This type of design offers several advantages. For example, they allow a larger number of doses to be investigated and a smaller number of patients to be included. They can also treat more patients at the selected dose. Nevertheless, this type of design presents certain limitations such as the heavy logistics requirement and a certain methodological complexity. Finally, they are not applicable if the primary outcome is assessed late in terms of the trial recruitment pace. The Round Table has nevertheless approved the use of these methods where possible.

4. Adaptive designs for confirmatory trials

4.1. Seamless phase 2(b)-3 trials

One of the adaptive designs that has led to numerous studies[1,5,27,28] and which has been considered as one of the most promising[2] is the seamless phase 2-3 design. This design combines two development phases traditionally carried out in separate trials in one single study. The first stage is generally used to select one or more doses of treatment, which will then be selected for the second stage. The final analysis thus focuses on patients included at two levels with methodology ensuring the validity of the conclusions (see above).

This type of design offers several advantages compared to development in two separate trials – one phase 2 trial and one phase 3 trial. Since recruitment is not interrupted, there is an overall saving in terms of time, which is accentuated by the steady pace of inclusions throughout the trial. Time is also saved in terms of patient follow-up since the first stage patients, *i.e.* "phase 2", are also included in the second stage efficacy analysis ("phase 3"). This type of design may also be considered to eliminate uncertainty with regard to the dose or variability of the endpoint, still under the confirmatory trial approach. Finally, this design completes safety data at different doses. It should, however, be noted that the lack of feedback between the two phases can be viewed as a disadvantage.

A heavy logistical framework is the price to be paid for this flexible, time-saving approach. Whereas the in-depth planning of a trial based on extensive simulations of clinical situations bears testimony to careful planning, a great deal of time and thought are required upstream of the trial. The use of this type of design calls for scientific competence and negotiations with the relevant authorities. Trials with this type of design are, however, approved, case-by-case, by these authorities if the adaptive nature and adaptations are specified in advance, if the methodology used is rigorous and the choice of the approach well supported. If it is to be carried out as a confirmatory trial, a seamless phase 2-3 trial will also need compliance with pre-clinical requisites from the beginning of the "phase 2" section of the trial along with definitive pharmaceutical forms for all treatment doses considered. Its methodology must be based on a valid replacement criterion in order to make appropriate decisions regarding the dose selection to be retained during the interim analysis.

This type of design is therefore justified if the sponsor has good reason to accelerate the development process, e.g. in the case of an important therapeutic need. It should also be noted that a shorter timescale does not necessarily imply a gain in terms of the number of subjects to be included. Lastly, this type of design is not suitable for unfamiliar situations fraught with uncertainty. A trial in which too many parameters are adapted is likely not to be considered as confirmatory.

The example shown in figure 1 uses this type of design for seamless phase 2-3 trials.[29] This confirmatory study has, in fact, been carried out in two combined stages using an adaptive design. During the first stage, the patients randomly received the following medication double-blinded: 4 doses of indacaterol 75, 150, 300 or 600 μg /d, formoterol (12 μg twice daily) or a placebo, or open-labelled, tiotropium (18 μg /d). An interim analysis planned at the end of the first stage allowed an independent committee to select two doses of indacaterol on the basis of safety and efficacy data cumulated over the first two weeks using pre-defined efficacy criteria. During the second period, the two doses of indacaterol selected were compared to tiotropium and placebo over a 26-week period.

4.2. Sample size reassessment

Methods for so-called blinded sample size reassessment are already used and do not pose any specific problems in terms of acceptability. On the other hand, methods to re-evaluate the sample size using unblinded data, *i.e.* formal group comparison [30] have met with major controversy in the literature, which has since continued during round table debates. With these methods, nuisance parameters and occasionally the difference in efficacy to be highlighted can be revised on the basis of data observed during an interim analysis. The main critique leveled at these methods is their lack of efficiency compared to group-sequential trial. [31,32] In cases where the sample size is re-evaluated, the trial starts out with a rather small cohort with the option of increasing numbers of patients if the results look promising. Conversely, a group-sequential trial initially plans to include a larger number of subjects but enables to early discontinue subject recruitment. Furthermore, estimators of variance or of treatment effect during the first interim analyses were hardly stable, which could result in substantial increases in the number of subjects and the risk of incorrectly modifying a trial that was initially planned correctly. [33,34] Therefore, this type of adaptive trial has not been generally recommended although such trials have been accepted by the relevant authorities.

4.3. Sub-group selection

The determination of a patient sub-group with an effective treatment assessment may prove important. Although a biomarker that can be related to treatment efficacy is available, adaptive designs, so-called enrichment designs, have been proposed. [35,36] They allow the trial to be started in the general population with the option of restricting inclusions to a sub-group following interim analysis if the results indicate that the treatment is effective only in this sub-group.

This type of design does not raise any particular problems if the marker defining the sub-groups is specified in advance. However, if this marker is not defined in advance, its use must be justified independently of the trial. It also seems useful to recommend that adaptation methodology should be determined before analyzing any trial data.

5. Role of the independent committee and key players

5.1. Independent data monitoring committee (IDMC)

In order to ensure trial integrity, adaptations to the experimental design during interim analyses must be recommended by the sponsor's independent committee without the sponsor having any access to the data. With an opportunity to adapt the experimental design, the independent data monitoring committee (IDMC) now has a bigger role than it did in more conventional trials in which it generally monitored safety. To maintain the integrity of the results, it is essential that the information networks are secure to prevent any attempts to lift the blind status. In particular, a statistician working separately from the sponsor and IDMC, is sometimes involved in certain adaptive designs. This statistician, interfacing with the latter, is responsible for carrying out analyses required by the IDMC.

The IDMC per se does not make decisions regarding adaptations but sends recommendations based on trial results, which may relate to safety and efficacy data or to any other source of external data, which, in the committee's opinion, should be taken on board. Adaptation decisions must, however, respond to the sponsor's development strategies. However, the sponsor cannot examine data on which adaptation decisions are based. The sponsor is therefore advised to send a charter to the independent committee in which it outlines the situations initially envisaged and the decisions that it wishes to take depending on interim results. Nevertheless, it seems that part of the decision-making process should be left to the independent committee, essentially with regard to dealing with situations not included in the charter.

To face these unexpected situations, some have considered limited intervention for the sponsor's representatives not directly involved in the study in decisions taken by the IDMC. [3] To our knowledge, at least one trial has adopted this strategy. However, there is no precedent and the risk of requalifying the trial as an "exploratory" study is too great to recommend this approach.

5.2. Relations with the relevant authorities

The relevant authorities pay particular attention to confirmatory trials carried out with adaptive designs and specific interactions between the sponsor and the authorities are expected. Upstream of the trial, the adaptive element can be discussed and the sponsor is advised to request scientific approval from the registration authorities. For instance, with regard to this topic, the FDA gave its non-binding approval to adaptive designs having, by definition, innovative methodology. The authorities also are the recipients of the chart that the sponsor forwards to the independent committee and listen to the recommendations made by this committee during the trial. If the sponsor were to disregard these recommendations, the relevant authorities would probably refer to the independent committee and possibly suspend the trial as a conservatory measure.

6. Constraints: logistics and risks

We have seen that adaptive designs generate constraints, particularly from a logistics standpoint. Furthermore, it seems important to assess the risks associated with the use of such designs in terms of the advantages that they may bring.

6.1. Constraints and logistics

Adaptive designs generally warrant more in-depth planning than conventional trials. For example, early trials described in paragraph 3.1 are based on a parametric model of the dose-toxicity ratio, which must be determined and justified in advance. For the phase 2-3 trials described in paragraph 4.1., the pre-planning requirement calls for consideration of a large number of situations and corresponding adaptations in advance. In many cases, the operational characteristics of the designs used are assessed *a priori* by numerical simulations insofar as they are not known analytically in advance.

These designs also lead to larger, more numerous consultation meetings sometimes involving more upstream players than usual. For example, it may prove necessary to meet with representatives of the relevant authorities and to involve trial committee members more extensively (scientific committee, independent committee, etc.). In a phase 2-3 trial, the pharmaceutical-technical managers will be involved at a much earlier stage than in conventional development. Finally, in-house teams and service providers as well as investigators must be trained in unfamiliar trial methodology.

In terms of product logistics, the commercial form may need to be available earlier, as considered previously. A larger number of doses tested in a phase 2-3 trial may also call for the development of "flexible" pharmaceutical forms such as mini-tablets, for instance. The flexibility of the experimental design also impacts upon procurement and inventory management systems.

Lastly, constraints affect the management of trial data, which must be both secure and valid. Valid data must be available rapidly so as not to delay adaptation decisions. The data must, therefore, be monitored continuously. Finally, data flows must be secure, as mentioned earlier. This also imposes fresh constraints.

6.2. Risks

Several types of risks can be considered. For the trial and therefore the sponsor, the greatest risk involves the validity and integrity of results, which would lead to a confirmatory trial being requalified as an exploratory investigation by the relevant authorities.

As for these authorities, they are somewhat reluctant, to authorize a trial without access to data from the previous phase, *i.e.* to authorize a phase 3 trial without phase 2 results or a phase 2 trial without phase 1 results. This reluctance is based on concerns regarding a lack of feedback between phases resulting in a loss of information vis-à-vis mid-term safety.

Conversely, as far as patients are concerned, apart from this possible shortage of feedback in seamless phase 1-2 or 2-3 trials, there are apparently fewer risks in adaptive phase 1 or 2 trials since these designs tend to actually lead to a larger number of patients being treated with an optimum dose. Patients can also be monitored for longer during a clinical trial with improved follow-up in phase 2-3 trials than in separate phase 2 and phase 3 trials.

Last but not least, the sponsor must also be able to provide the logistics resources and to conduct the trial through to its conclusion regardless of any adaptation decisions taken during interim analysis.

7. Conclusion

Compared to conventional designs where the experimental design is determined in advance, adaptive methods offer an appealing approach from a scientific and pragmatic perspective. Their main interest lies in the ability to provide anticipated information more quickly and more efficiently. The various situations approached during this review show that these methods can often be used during the exploratory or confirmatory development stage and are accepted by the relevant authorities provided that trial integrity and validity are ensured. To this end, there are multiple financial and logistical constraints, and these must be anticipated. In confirmatory trials in particular, the use of these methods calls for a rigorous approach, anticipation in terms of both planning and implementation, dialogue with the relevant authorities and the presence of an independent committee. If all of these conditions are met, the use of adaptive methods must be encouraged.

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