

Adaptive Designs: A challenge for the future of clinical research

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In the past few years, we are witnessing an exponential increase in costs for research and the development of new drugs: it has been estimated that the average expenditure in R&D for new drugs has duplicated in the last decade. This increase in costs, combined with a slower approval process, has resulted in a drastic reduction in the percentage of new drugs that are successfully brought to market.

According to pharmaceutical companies, the two aspects most problematic for clinical studies are excessive study lengths and the high probability of failure. Often, in cases of failed studies, the conviction of those involved is that if some aspects were managed differently, the program could have been saved and the potential of the therapies demonstrated.

Consequently, the question pharmaceutical companies continue to face is: *“How can we make a study more efficient while maintaining the validity and integrity?”*. Sponsors, clinical researchers and biostatisticians are becoming more interested in designs with greater flexibility than the standards and procedures that anticipate “go/no-go” decisions. In light of these objectives, it is of utmost importance to make modifications to a study while in process on the basis of new information pulled from accumulated data. In this aspect lies the fundamental feature of adaptive designs.

Within the definition of “Adaptive Design”, comes many different possible approaches, some simple and of relatively common use, others more sophisticated, and in certain aspects, controversial. All of these designs, however, have in common the use of collected data to modify several aspects of a study already in progress, without compromising the validity or integrity. It should be emphasized that modifications are not a remedy for inadequate planning, but must be pre-defined and justified in the study protocol.

The modifications include changes in sample size, in the criteria for inclusion/exclusion, in the doses or treatment regiment, in the study endpoints, in the elimination or addition of treatment groups, or in the early closure of the study for efficacy/futility.

Developed statistical methodologies permit the application of these modifications to a study in progress, while keeping under control the probability of error associated with hypothesis testing.

The European Regulatory Authority (EMA) has also faced the argument of adaptive designs in a document *“Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design”* (18 October 2007).

Depending on the type of changes foreseen, adaptive designs distinguish themselves into “group sequential design”, “designs with numerous adjustments” (N-adjustable design), “adaptive seamless Phase II/III design”, “adaptive randomization design”, and more.

While it is known that there is a possibility to re-estimate the number of patients needed for a study based on observed data in interim analysis, it is less known, but of great interest, that design can allow objectives to be achieved in one study that would normally require the scheduling of two distinct studies in phase IIb and III. An adaptive study in phase II/III combines two sequential and separate studies into one study and allows the use of collected information in the first stage to adapt the design in the second phase (Figure 1). The advantages of this design are, above all, a reduction in the overall time in the development of a drug, fewer patients required and the early availability of long-term safety data.

As an example of the application of designs in phase II/III, let's consider a recent study we are in charge of planning. In the first stage, corresponding to phase II, there are three legs of treatment expected: two different experimental treatment doses (indicated with A and B in Figure 2) and standard treatment. In the second stage, corresponding to phase III, there are only 2 legs of treatment expected: the experimental treatment dose, selected based on observed results in the first stage, and standard treatment. The selection of dosage depends on the observed success rates in the treatment groups at the end of phase II, according

to the decision rule defined in Figure 2. We can note that, in the case of a lack of efficacy of both doses of the experimental treatment, there is also the possibility to stop the study. It is clear in this example that adaptive designs have flexibility.

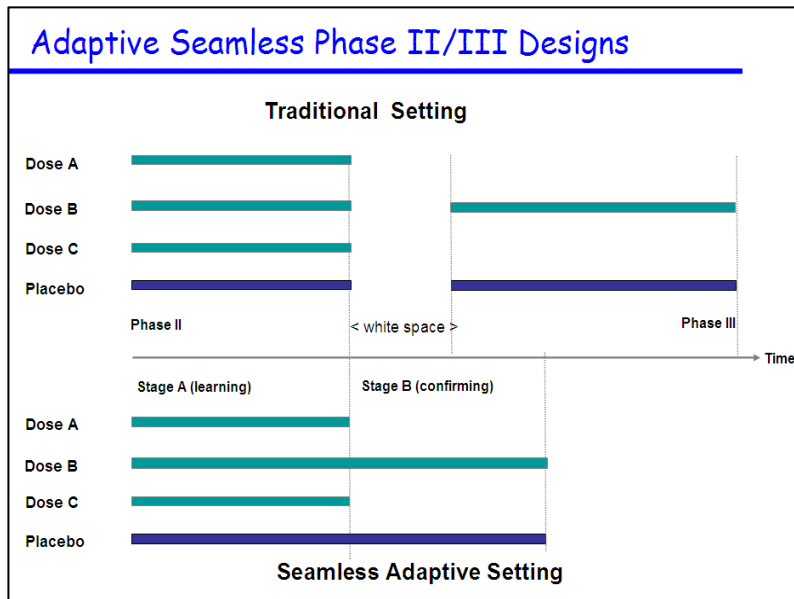


Figure 1

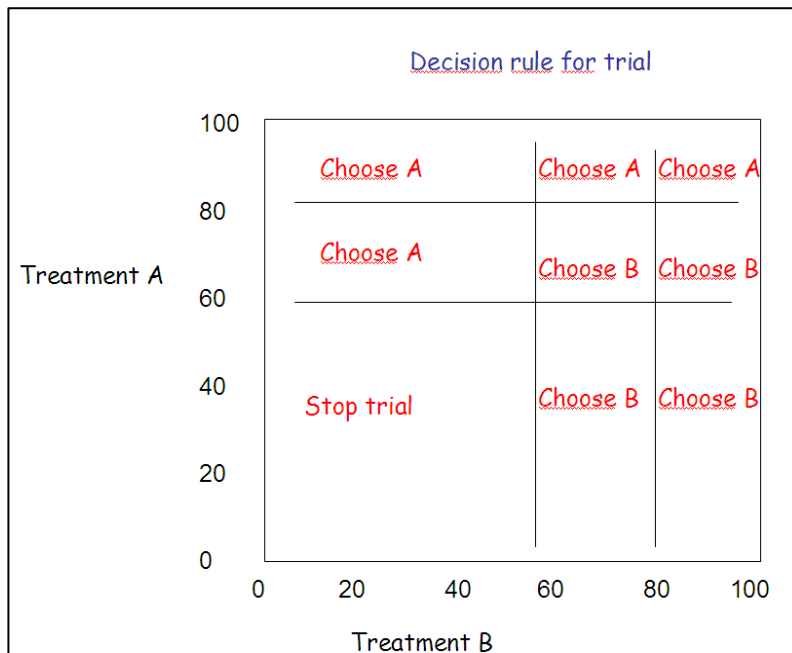


Figure 2

Based on our experience, the advice we would give a pharmaceutical company that is considering this type of design is as follows:

- Budget more time for the planning of an adaptive design as compared to a standard design
- Interact with regulatory authorities already in the planning phase, especially for phase II/III studies
- Define the decision rules for interim analyses and provide statistical justification to support the study design.
- Use simulations to calculate the power of the sample size and the probability of success in the study.
- Evaluate whether or not to stop the recruitment of patients for the interim analyses.

- Take into consideration the use of electronic files to manage data efficiently and rapidly for the interim analyses.
- Use independent statisticians to perform the interim analyses and Independent Committees to review the results of the analyses.
- Schedule frequent monitoring visits in order to provide as much data as possible for the interim analyses.
- Inform in advance those who are responsible for supplying the drug on the type of design, and take into consideration, for randomization, the possibility of an interactive centralized system.

In conclusion, adaptive designs have the potential to change the way in which we conduct clinical research, taking into consideration however, that the flexibility allowed in comparison to traditional designs requires a greater effort in the initial planning stage of the study.

About the Authors

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CROS NT Group, an international Contract Research Organisation (CRO), with headquarters in Verona, Italy, has built a strong heritage in biostatistics as well as providing clinical data management, medical communication, pharmacovigilance, and technology solutions to the life science industry. Founded in 1992, CROS NT is well-established in delivering quality, timely delivery, and cost effective service.