EMA AND FDA - ADAPTIVE CLINICAL TRIALS DESIGN

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ABSTRACT

Although research and development expenditure in the pharmaceutical industry is constantly increasing, the number of medicinal products put through clinical development up to marketing authorization is not increasing in equal measures. In fact, a decline in marketing approvals can be seen. On the other hand, there are still a lot of therapeutic areas where adequate treatments are still not available, thus a high unmet medical need exists. This circumstance led the FDA (Food and Drug Administration) to launch its "Critical Path Initiative" in 2004. This initiative included the "Critical Path Opportunities List" that was set up to foster clinical development and help sponsors in identifying opportunities to accelerate drug development. One of the items listed here is adaptive trial design as a means to streamline clinical trials and enhance drug development. With the EMA (European Medical Agency) releasing its "Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design" in 2007 and the FDA following with its draft guidance on adaptive design clinical trials in 2010, a first step towards encouraging pharmaceutical industry as well as other researchers to implement adaptive features into the clinical development of their compounds has been taken. Since then a slight increase in the usage of adaptive design clinical trials can be observed, either in the review of recent marketing authorization applications as well as in the number of medical publications referring to this topic, but vast experience is still lacking. The present article provides an overview of the different types of adaptive design clinical trials as well as their classification and assesses the inherent risks and opportunities. It elaborates that adaptive designs are not feasible for all types of clinical trials, but rather exhibit their advantages in specific settings, for example in trials with IMPs with an immediate treatment effect, where dose flexibility is
given (for example trials with liquid IMPs), in trials with a limited number of sites or for trials where data cleaning can be easily performed. This article additionally contains an evaluation of how and to what extent adaptive design clinical trials are currently adopted by pharmaceutical industry and accepted by the two major regulatory authorities EMA and FDA. Beside the results of a recent survey by the ADSWG, it also provides an overview on which recent marketing authorization applications were based on one or more clinical trials incorporating an adaptive design feature including the EMA´s and/or the FDA´s assessment of the trial design. The results suggest that regulatory authorities encourage sponsors to make use of adaptive design features, but also ask for early and intensive dialogue between authority and sponsor. The evaluation reveals that until now not much practical experience with adaptive clinical trial designs appears to be available and both pharmaceutical industry and regulators are still on the learning curve. However, the concluding outlook presented in this thesis suggests that the increasing transparency on clinical trial data that regulatory authorities are currently promoting might eventually foster consideration and usage of adaptive designs as it provides a basis for mutually sharing experience with adaptive designs.

KEYWORDS: FDA, EMA, ADSWG, IMPs.

1. INTRODUCTION

1.1 Evolution of Adaptive Design Clinical Trials

In today´s pharmaceutical industry, it is becoming more and more challenging to advance compounds through clinical development and onto marketing authorization approval. This can be attributed partly to the fact that there is often one or more safe and effective treatment already available on the market for any major diseases. Thus, new treatments have to be compared to existing treatment options and to at least show non-inferiority. Furthermore, regulatory requirements are also increasing and are becoming more stringent. As it is still critical to develop new treatments and make them accessible to patients, the United States Food and Drug Administration (FDA) launched its Critical Path Initiative in 2004 to foster clinical development and to help sponsors in identifying opportunities to accelerate drug development (US-FDA., 2004; 2006). In this context, the FDA later on released its —Critical Path Opportunities Listl in 2006 which specifically mentions adaptive trial design as a means to streamline clinical trials and enhance drug development under the topic —Creating Innovative and Efficient Clinical Trials…l. The first agency to release a guidance on adaptive design clinical trial was the European Medicines Agency (EMA) (EMA., 2007), whose
Committee for Human Medicinal Products (CHMP) adopted in 2007 the —Reflection Paper on Methodological Issues in Confirmatory Clinical Trials Planned with an Adaptive Designl. The FDA followed in 2010 with the release of their —Draft Guidance for Industry – Adaptive Design Clinical Trials for Drugs and Biologicsl. The first papers to introduce the concept of adaptive design were published before the aforementioned guidance were released, however since then the topic of adaptive design and its application in drug development has attracted a lot more attention likewise in pharmaceutical industry, academic research as well as amongst regulators. Although experience with adaptive design clinical trials is growing, there are still —grey areasl in this field where mainly statistical methods are not yet fully established to make full use of adaptations.

1.2 Definition of adaptive design vs. conventional design

In a conventional clinical trial design setting all key trial parameters are defined \textit{a priori} in the clinical trial protocol and they are kept constant during the execution of the trial. As several uncertainties may exist before the initiation of a trial (e.g. target population, optimal dose, treatment duration, active comparator, etc.) a conventional clinical trial might fail even though a treatment is actually effective, due to wrong assumptions taken in the design phase.

An approach to overcome this risk is the so-called adaptive design. In their —Draft Guidance for Industry – Adaptive Design Clinical Trials for Drugs and Biologicsl. The FDA defines an adaptive design clinical study as “…\textit{a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypothesis based on analysis of data (usually interim data) from subjects in the study}.‖. According to the CHMP an adaptive design involves —...design modifications based on the results of an interim analysis.l wherein —the interim analysis and the type of the anticipated design modification (change of sample size, discontinuation of treatment arms, etc) would need to be described and justified in the study protocol.l. A third definition is given by the Pharmaceutical Research and Manufacturers of America (PhRMA) working group on adaptive designs: —Adaptive design is defined as a multi-stage study design that uses accumulating data to decide on how to modify aspects of the study without undermining the validity and integrity of the trial.l. Although there are slight differences amongst various definitions, there are two main aspects that are in common: changes to a clinical trial under the adaptive design approach are.

1.) Prospectively planned
2.) Based on accumulating data obtained from interim analysis of the clinical trial. Almost all clinical trial protocols undergo changes while the clinical trials are on-going. Changes are introduced via protocol amendments in a conventional setting. The difference in an adaptive setting is that these changes are anticipated and prospectively included in the protocol and/or statistical analysis plan. The second characteristic of adaptive designs is that the revisions to the clinical trial are based on study-internal information gained during the conduct of the trial, and not from information that arises from external sources, such as results from other studies. What is emphasized in the PhRMA Working Group’s White Paper is that the validity and integrity of the trial must not be negatively affected by these adaptations. To maintain the validity of the trial means that the trial, despite the adaptations applied during the conduct of the trial, still delivers correct statistical inference. To achieve this, operational bias needs to be minimized and certain statistical adjustments are necessary (i.e. adjustment of p-values or confidence intervals) that help control the Type 1 error. The integrity of a trial is being preserved mainly via maintaining the blind as much as possible, but also by the prospective nature of the adaptations. Different types of adaptive design are discussed in the following section.

2. Types of adaptive design

Adaptive design can be implemented in clinical trials in many different ways. While the Executive Summary to the PhRMA’s full White Paper specifies only three different types of adaptive designs (adaptive dose finding, seamless Phase II/III designs and sample-size re-estimation), the article by Dragalin, which is also included in the PhRMA’s full White Paper, rather classifies adaptive designs by the rule that the adaptation interferes with after interim data are available (US-FDA., 2010). The four different rules are summarized in the following table.

Table 1 - Rules that can be affected by adaptations

<table>
<thead>
<tr>
<th>Rule</th>
<th>Changed features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation Rule</td>
<td>Adaptations in how patients are assigned to different treatment arms</td>
</tr>
<tr>
<td>Sampling Rule</td>
<td>Adaptations in how many patients are accrued in the next stage of a trial</td>
</tr>
<tr>
<td>Stopping Rule</td>
<td>Adaptations in when a trial will be stopped</td>
</tr>
<tr>
<td>Decision Rule</td>
<td>Further adaptations not following any of the above rule</td>
</tr>
</tbody>
</table>

EMA’s reflection paper also mentions different types of adaptive designs, but doesn’t really classify these into different groups. Last but not least, the FDA proposes another approach to differentiate between various types of adaptive designs: the methods that are summarized as
well-understood on the one hand and the ones that are less well-understood on the other hand. While for the well-understood adaptive designs regulatory experience is already broadly available and control of the Type I error rate is ensured considering that relevant statistical methods are existing, both aforementioned characteristics are not applicable to the less well-understood adaptive designs. The group of well-understood adaptive designs mainly does not involve un-blinded interim analysis, but rather make use of the examination of baseline data, blinded interim analysis or accruing data that is not related to treatment-related efficacy. Examples are changes to the eligibility criteria based on an evaluation of pre-treatment data or sample size re-estimation after blinded interim analysis. A further design that is considered to be well-understood is the group-sequential design. The well-understood adaptive designs distinguish themselves from the less well-understood designs in that they are considered to enhance efficiency, but generally do not increase the risk to introduce statistical/operational bias or negatively impact the study results’ interpretability. The less well-understood adaptive designs on the other hand always include an un-blinded interim analysis that estimates treatment-related effects and thus bear the risk to introduce statistical and operational bias. Since statistical approaches for these designs are not yet fully developed and/or regulatory experience is not broadly available, their practical implementation is to be done with great caution and should rather be incorporated into exploratory clinical trials where the question of concern cannot be adequately answered with better understood designs (Lewis RJ., 2012).

The following section provides an overview of different types of adaptive designs, their main features and some consideration on how they may be implemented in drug development.

2.1 Adaptive Randomization
In a conventionally designed clinical trial patients are allocated to the different treatment arms according to a pre-determined rule. For example 50% patients are treated with the test drug and 50% are treated with the comparator. In an adaptive clinical trial design setting the probability of a patient to be assigned to a specific treatment arm can change based on the analysis of the treatment effect of previously enrolled patients. That means that when one arm shows a greater treatment effect, more patients are allocated to this treatment (—play the winnerl approach).
The above figure is a simplified illustration of adaptive randomization, as usually the treatment allocation of a further patient is continuously calculated based on all available outcomes of previously enrolled patients.

The principle of adaptive randomization is beneficial especially in exploratory studies. For example, in studies evaluating the dose-response relationship you may start with several doses and in the course of the study concentrate the allocation of patients to those doses that show a greater treatment-related response or fewer adverse events, i.e. fewer patients are assigned to those doses that are less relevant for the generation of the dose-response curve (for example due to small response or occurrence of severe adverse events). This form of adaptation is known as adaptive dose finding and is described in more detail in 2.4.

However, clinical trials with adaptive randomization might lose statistical power when there is a huge difference in patients allocated to the different treatment arms. For a placebo-controlled trial it is therefore of importance to allocate enough patients to the placebo group to ensure statistical power. A further issue with adaptive randomization can be observed due to misleading early outcomes. Assuming one arm shows a few treatment failures in the early stages of a clinical trial, following randomization of further patients will favor the other treatment arms, so that the arm with the early treatment failures cannot rehabilitate.

2.2 Sample Size Re-assessment
Calculating the required sample size in the planning stage is important: on the one hand the sample size shouldn’t exceed what is actually necessary for ethical reasons, i.e. not to treat
more patients with an inferior treatment than needed, but should also be large enough for the trial to detect a statistically significant treatment effect. Sample size calculation is based on different variables: the expected effect size, the type of hypothesis testing, the statistical test, the desired error control and power of the test and the variance of the effect size. The variance estimate is usually based on observations made in previous clinical trials. However, the variance might be influenced by external circumstances specific to the trial that is being planned, for example by patient population, treatment modalities or further procedural aspects. An underestimation of the variance in the planning stage would lead to a significant loss of power of the trial. To account for a higher trial specific variance detected in an interim analysis during an on-going trial, the sample size may be re-assessed and increased to maintain the required power of the study.

There are two types of sample size re-adjustments: It can be based on either blinded or un-blinded interim analysis. If a blinded interim analysis of the observed treatment effect or variance of the treatment effect is utilized to increase the initially determined sample size, the Type I error is usually under control and statistical bias is not introduced.

A decrease in sample size based on observations in early interim analysis is usually not recommended, as the variability of treatment effect and variance can be high when only a small fraction of the patients have been treated. The principle of sample size re-assessment with un-blinded interim analysis is essentially the same, but usually results in inflation of the Type I error which needs to be statistically adjusted in the final analysis. This can be either done by reducing the alpha level or by maintaining the alpha level, but weighting the data from before and after the interim analysis unequally (Pocock SJ., 1997).

2.3 Changes to Eligibility Criteria
Eligibility Criteria, or In-/Exclusion Criteria, define the population considered adequate for participating in a specific trial. If the eligibility criteria are vague, incomplete or inaccurate, the recruitment of the required number of patients to answer the study question and therefore the power of the study might be jeopardized. When changes to eligibility criteria are based on a blinded interim analysis and in case the treatment effect is expected to be nearly the same in different subsets of the patient population, then the Type I error rate is considered not to be increased with this adaptation. A different picture is seen with changes to eligibility criteria after an un-blinded interim analysis when certain sub-populations exert higher responsiveness to the treatment as others. The adaptation in eligibility criteria can be done in different ways:
on the one hand without a change to the overall sample size and with the entire study population being included in the final analysis. On the other hand, the final analysis could also only include those patients that reflect the population after the adaptation of the eligibility criteria. Both methods, however, bear the risk to inflate the overall Type I error and statistical adjustment is considered necessary (O’ Brian PC & Fleming TR., 1979).

2.4 Adaptive Dose-Finding
Inadequate dose selection for Phase III trials is one of the major pitfalls in drug development and may lead to the drug not reaching the primary endpoint in the pivotal trial. Therefore identifying the dose-response curve as accurately as possible in early development stages is essential. In an adaptive dose finding setting the rough location and shape of the dose response curve is explored with only a few patients allocated to many different doses. After an interim analysis more patients are assigned to those doses which seem to be of more interest for the dose-response curve, possibly with also introducing new doses that are between the doses of interest. Doses outside of the dose response range might be dropped completely. The result is that more outcomes will be available for the doses within the relevant dose response range and therefore the information that can be taken from the dose response curve is more accurate.

Fig. 1 Dose – response curve
2.5 Seamless Phase II/Phase III Design

In conventional drug development settings, Phase II and Phase III studies are typically conducted sequentially, with a period to evaluate the Phase II data in order to apply the learning to the confirmatory Phase III studies with the trials being statistically independent.

In an adaptive setting, Phase II and Phase III can be combined in a seamless way, meaning that they are conducted with one single, uninterrupted trial which is conducted in two stages. The learning stage (Phase II) is used to identify the treatment or treatment dose that is to be tested in the confirmatory stage (Phase III).

Two different scenarios are possible for seamless designs. One is the operationally seamless design, which mainly aims at saving the time that is needed in a conventional setting for the evaluation of the Phase II data as well as the planning and setting up of the Phase III trial. The other one is the inferentially seamless design where the final analysis is done on the complete population treated in both stages. There are statistical methods available to control the Type I error, however final analysis might be challenging when the objectives/endpoints in the two stages are different (for example dose finding for the Phase II stage and efficacy confirmation in the Phase III stage) (Follmann DA., 2007).

2.6 Group sequential design

Group sequential designs are used to allow stopping a clinical trial either for futility, safety or efficacy. The principle behind group sequential designs is to first only recruit a fraction of the initially calculated sample size. In a first interim analysis the treatment effect on this
subgroup will be determined. If the treatment effect is greater than the treatment effect that had been anticipated in the planning stage, the study might be stopped at this point with an early rejection of the null hypothesis. If, however, the treatment effect is much lower than anticipated, the trial might also be stopped for futility with accepting the null hypothesis, thus avoiding exposing further patients to a treatment that isn’t as effective as the comparator and spending money on a trial that will not reach its primary endpoint. In case the treatment effect is as large as anticipated, the second fraction of patients will be recruited until a further interim analysis. These steps will be repeated as pre-specified in the planning stage. A diagram depicting the flow of actions within a group sequential design is shown below.

To account for the multiplicity issue caused by the multiple correlated statistical tests within the trial, i.e. to control the overall Type I error, local significance levels for each single statistical test should be pre-defined. Various models for stopping boundaries can be found in literature. Early models published include the ones by Pocock and O’Brien & Fleming, respectively. The approach within these alpha spending functions is to allocate a certain fraction of the overall Type I error to the single interim/final analyses. For both above mentioned models the boundaries are dependent on the number of analyses. However, the model developed by Pocock involves the same significance levels for all interim/final analyses, whereas according to O’Brien & Fleming the local significance levels increase with each analysis.

![Diagram showing the flow of actions within a group sequential design.](image-url)

**Fig.3 Design Group sequential**
Table 1 p-values –Analysis

<table>
<thead>
<tr>
<th>Number of planned analyses</th>
<th>Interim Analysis</th>
<th>Local significance level according to Pocock</th>
<th>Local significance level according to O’Brien &amp; Fleming</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1</td>
<td>0.029</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.029</td>
<td>0.0048</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>0.022</td>
<td>0.0005</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.022</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.022</td>
<td>0.045</td>
</tr>
</tbody>
</table>

Looking at the above table it is obvious that you might come to a different conclusion regarding the stoppage of a trial when following the two different approaches. Assuming the p-value resulting from a second interim analysis in a setting with a total of three analyses is 0.018. According to Pocock you would reject the null hypothesis and stop the trial early, whereas according to O’Brien & Fleming you would continue to recruit further patients. It is therefore essential to determine the boundaries in the planning stage of the trial. Furthermore it is important to actually stop the trial, in case one of the stopping criteria is met (either for futility or efficacy). Otherwise interpretation of the final study results will be challenging (Scott. 2007).

2.7 End point Adaptations

The primary endpoint is defined as the outcome that evaluates the effectiveness of a treatment in clinical trials. For a wide number of indications specific guidelines are available that help trial designers to determine an acceptable primary endpoint for a clinical study in the planning stage. For other indications such guidance is not available and trial designers will have to rely on information gained in earlier stages of drug development. In some cases an interim analysis or external data might suggest, that previously made assumptions for the definition of the primary endpoint are invalid and/or that other clinical endpoints might work better in the setting of a specific clinical trial. In these cases the change of the primary endpoint might be possible, either by re-defining a secondary endpoint as the primary endpoint, by addition or removal of specific aspects of a composite endpoint or by introducing a completely new primary endpoint. As with other adaptive designs, making changes to the primary endpoint with data from an early interim analysis might bear the risk of making a poor choice on the newly defined primary endpoint, as interim data might be highly variable with only a small fraction of patients treated.

If a change of endpoint is based on un-blinded interim data, then operational bias as well as
inflation of the Type I error is likely and it will be difficult to justify the change. If, however, the endpoint change is considered due to external data (for example results of other trials or identification of new biomarkers), then this should be justifiable to ensure that the trial is still scientifically valuable.

2.8 Change in study objective

According to paragraph 29 of the Declaration of Helsinki, a new treatment should usually be tested against the currently best available treatment, i.e placebo-controlled trials should be avoided as much as possible and only be used in case of the absence of a proven therapy. Newly developed drugs should therefore be tested in trials comparing the new treatment with an active control. Two different scenarios regarding the study objective are possible: either showing that the new treatment is better than the active control (superiority) or that the new treatment is not less effective than the active control (non-inferiority).

For a non-inferiority trial, a maximum treatment difference δ and the respective confidence interval need to be pre-specified in the trial protocol, as the conclusion of the trial may be subject to bias, if these specifics have only been determined after the availability of trial results. In case the lower limit of the two-sided confidence interval lies above -δ, non-inferiority of the test drug compared to the active control can be inferred. If, however, the lower limit of the two-sided confidence interval even lies above 0, not only non-inferiority, but rather superiority can be statistically inferred. In this case the p-value has to be recalculated based on a test of superiority and then has to be used to determine if the null hypothesis can actually be rejected. As non-inferiority trials are conducted following strict
requirements (larger trials, parallel analysis of intention-to-treat (ITT) and per-protocol (PP) population, rigid adherence to protocol specifications), a switch to superiority is usually feasible if interim results suggest that the superiority can be shown.

A switch from a superiority to a non-inferiority design, on the other hand, is much more difficult to justify. The most important pre-requisite is that a non-inferiority margin $\Delta$ is already specified in the protocol, i.e. before the availability of any interim analysis data. Determining $\Delta$ only afterwards is difficult to justify, unless there is a generally accepted value available. Additionally, an equally balanced analysis of ITT and PP population needs to be performed, which is unusual for superiority trials where the main emphasize lies on the ITT analysis (Berry DA., 2012).

7 CONCLUSION AND OUTLOOK

When the EMA and FDA published their guidances on adaptive clinical trial designs in 2007 and 2010, respectively, a lot of hope was set in these types of clinical trial designs to enhance and fasten drug development. However, since adaptive design features are not feasible for all types of trial settings, but mainly exhibit their advantages in specific trials, for example with IMPs with an immediate treatment effect, where dose flexibility is given (for example trials with liquid IMPs), in trials with a limited number of sites or for trials where data cleaning can be easily performed, a certain disillusion can be felt within the pharmaceutical industry.

The present master thesis, however, suggests that adaptive design clinical trials bear several advantages compared to conventional clinical trials, if they are thoroughly planned and well conducted, and should therefore be seen as an opportunity for both pharmaceutical industry as well as regulatory agencies to shorten overall drug development time and to enable faster access to new medicines to patients in need. Statistical methodologies for several types of adaptive designs seem to be available already. However, as practical experience with adaptive design clinical trials is still somewhat limited, one should probably rather concentrate on the more well-understood adaptations at first, especially when it comes to the trial’s acceptability to support a future marketing authorization application. Experience with less well-understood designs on the other hand can be gained in earlier phase trials/exploratory trials where there is less regulatory concern, but more opportunities for adaptations due to more existing uncertainties, or for line extensions/extension of indications where already a lot of information on a given investigational medicinal product is available. As mentioned in the review, early and intensive dialogue with regulatory authorities is essential for the
acceptability of adaptive design clinical trials, but as Health Technology Assessment (HTA)/Reimbursement is becoming more and more important for the economic success of a medicinal product pharmaceutical companies should additionally involve HTA bodies in early discussions about an adaptive design clinical trial.

A further initiative which might influence the acceptance and usage of adaptive design clinical trials is the recent announcement of the EMA to publish all clinical trial reports that are submitted as part of a marketing authorization application under the centralized procedure after 1 January 2015. This will enable pharmaceutical industry as well as further researchers to gain more insight in the clinical development performed by other applicants, and in case of adaptive design clinical trials will also give insight in these specific features and their application since a clinical trial report usually includes details on the statistical approach applied during the course of a clinical trial.

If competitors eventually see the success of a marketing authorization application that is underpinned by an adaptive clinical trial, it will probably also encourage them to include adaptive design features in the clinical development of their compounds or at least gives them the opportunity to learn more about adaptive design. So the publication of clinical trial reports that contain adaptive design features will in any case be a means to spread experience with the usage of adaptive designs and will therefore probably also increase the acceptance and further application of such features in future.

The same will also be achieved with the entry into force of the new Clinical Trial Regulation in 2016 which obliges sponsors to submit data on any clinical trial to a newly set up EU database after its completion and a clinical summary report on an IMP after a decision on a marketing authorization application has been made in a member state.

As with anything that is new and not very well known to mankind, it will still take some time and a greater amount of experience until the advantages of adaptive design clinical trials are clearly seen, so that they will be given more consideration in the clinical development of medicinal products and actually be applied in those cases where their advantages are most compelling, thereby enhancing and fastening drug development.
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