Adaptive Design Clinical Trials

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List of abbreviations

CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CHMP	Committee for Human Medicinal Products
CPMP	Committee for Proprietary Medicinal Products
δ	Treatment difference
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HTA	Health Technology Assessment
HIV	Human Immuno-deficiency Virus
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IDE	Investigational Device Exemption
ITT	Intention to treat
NI	Non-inferiority
NTD	Neglected Tropical Disease
OS	Overall survival
PhRMA	Pharmaceutical Research and Manufacturers of America
PP	Per protocol
p-value	Calculated probability
rPFS	Radiographic Progression Free Survival
SA	Scientific Advice
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SPA	Special Protocol Assessment

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 [1]. In this context, the FDA later on released its "Critical Path Opportunities List" in 2006 [2] 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…". The first agency to release a guidance on adaptive design clinical trial was the European Medicines Agency (EMA), whose Committee for Human Medicinal Products (CHMP) adopted in 2007 the "Reflection Paper on Methodological Issues in Confirmatory Clinical Trials Planned with an Adaptive Design" [3]. The FDA followed in 2010 with the release of their "Draft Guidance for Industry – Adaptive Design Clinical Trials for Drugs and Biologics" [4]. The first papers to introduce the concept of adaptive design were published before the aforementioned guidances 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 areas" 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 *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 [5].
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 Biologics" the FDA defines an

adaptive design clinical study as *"…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*." [4]. According to the CHMP an adaptive design involves "*…design modifications based on the results of an interim analysis.*" 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.*" [3]. 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*." [6]. 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) [7], 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 [6]. The four different rules are summarized in the following table.

Table 1 - Rules that can be affected by adaptations

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

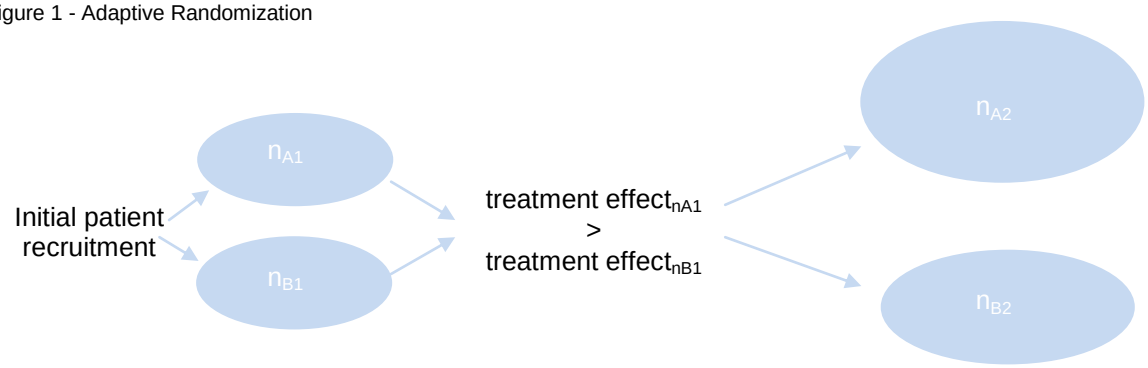
EMA´s reflection paper also mentions different types of adaptive designs, but doesn´t really classify these into different groups [3]. Last but not least, the FDA proposes another approach to differentiate between various types of adaptive designs: the methods that are summarized as well-understood on 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 do 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.

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 winner" approach) [4].

Figure 1 - Adaptive Randomization



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 [8]. 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 [9]. 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 [4].

2.3 Changes to Eligibility Criteria

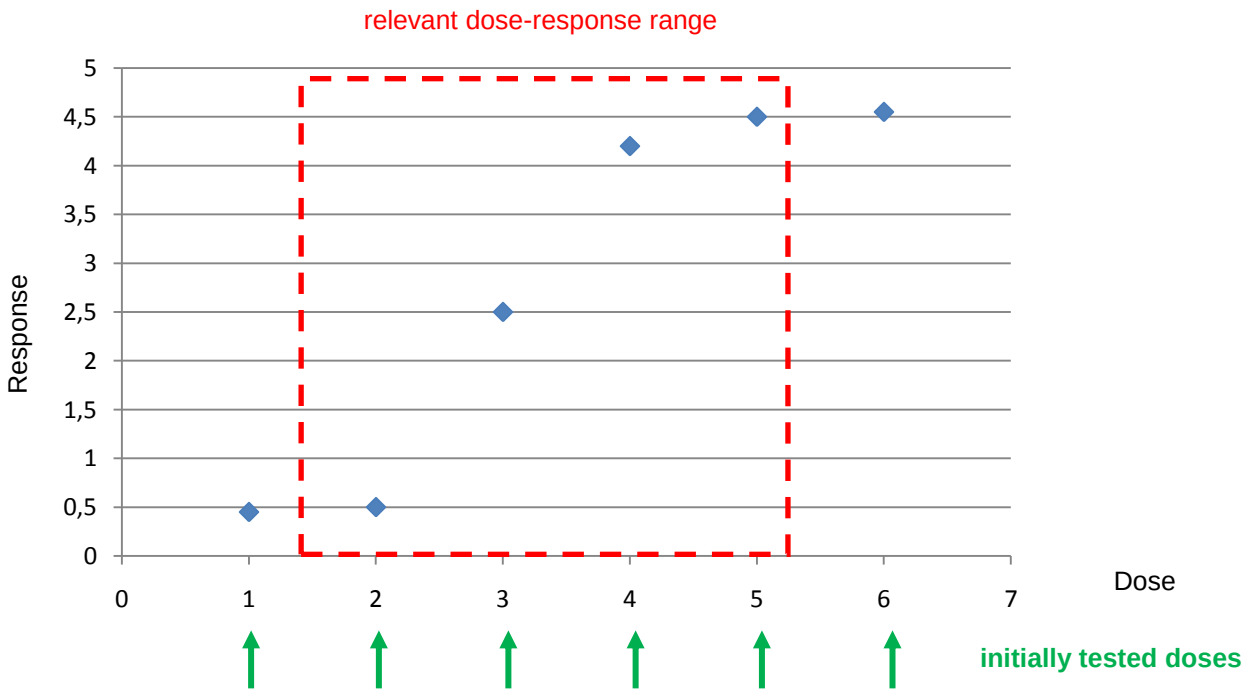
Eligibility Criteria, or In-/Exclusion Criteria, define the population considered adequate for participating in a specific trial. If the eligibility criteria are vague, incomplete or inaccurate, the recruitment of the required number of patients to answer the study question and therefore the power of 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 [4].

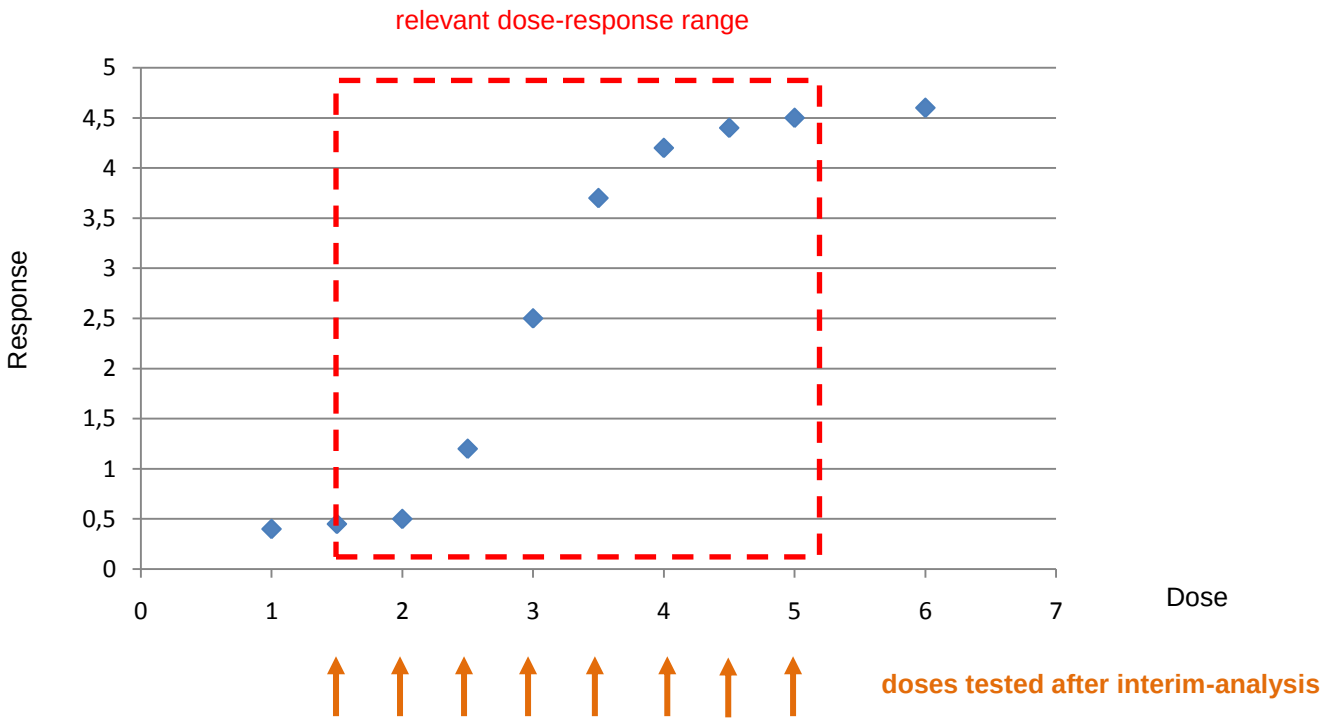
A different picture is seen with changes to eligibility criteria after an un-blinded interim analysis when certain sub-populations exert higher responsiveness to the treatment as others. The adaptation in eligibility criteria can be done in different ways: on the one hand without a change to the overall 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.

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.

Figure 2 - Adaptive Dose Finding



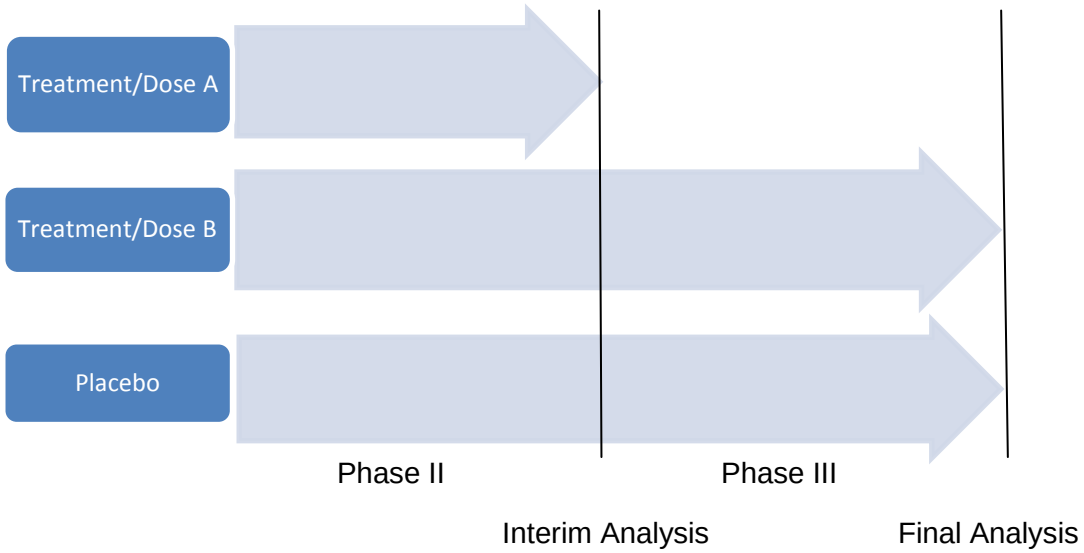


2.5 Seamless Phase II/Phase III Design

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).

Figure 3 - Seamless Phase II/III design

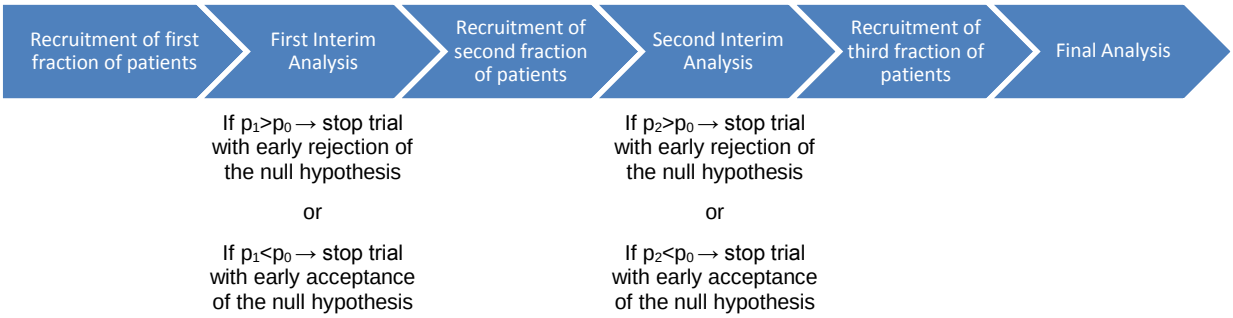


Two different scenarios are possible for seamless designs. One is the operationally seamless design, which mainly aims at saving the time that is needed in a conventional setting for the evaluation of the Phase II data as well as the planning and setting up of the Phase III trial. The other one is the 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) [10].

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.

Figure 4 - Group sequential design



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 [11] and O´Brien & Fleming [12], 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.

Table 2 - p-values according to Pocock and O´Brien & Fleming

Number of planned analyses	Interim Analysis	Local significance level according to Pocock	Local significance level according to O´Brien & Fleming
2	1	0.029	0.005
	2	0.029	0.0048
3	1	0.022	0.0005
	2	0.022	0.014
	2	0.022	0.045

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 [4].

2.7 Endpoint Adaptations

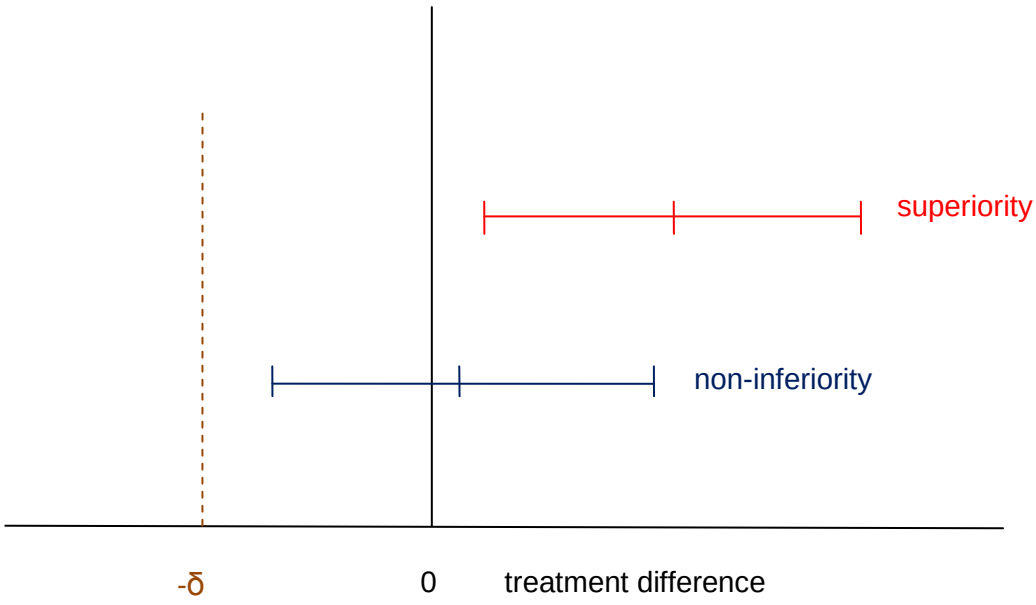
The primary endpoint is defined as the outcome that evaluates the effectiveness of a treatment in clinical trials [13]. For a wide number of indications specific guidelines are available that help trial designers to determine an acceptable primary endpoint for a clinical study in the planning stage. 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 [14].

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 [15]. 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).

Figure 5 - Superiority vs. 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 [16]. 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 re-calculated 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 –δ is already specified in the protocol, i.e. before the availability of any interim analysis data. Determining –δ 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. Furthermore, particular attention should be given to the accurate conduct of the trial as only then the sensitivity of the trial to reliably demonstrate non-inferiority is given.

3 Statistical considerations

3.1 Control of Type I error

One of the major concerns in adaptive design clinical trials is the control of the Type I error. A Type I error is the rejection of a null hypothesis that is actually true, that means deciding that a treatment is effective even though in fact it is not [17]. The inflation of the Type I error rate may derive from the fact that multiple statistical hypothesis are being tested, either because of performing multiple interim analyses, evaluating several endpoints (primary, secondary and/or composite endpoints), comparing multiple treatment arms, or analyzing subgroups. Both the Committee for Proprietary Medicinal Products´ (CPMP) "Points to consider on multiplicity issues in clinical trials" as well as ICH E9 require multiplicity adjustment of the Type I error rate. Closed test procedures are available to account for multiplicity issues. The closed test procedure was first introduced by Marcus, Peritz and Gabriel in 1976 [18] and has since then been further developed. The inflation of the overall Type I error rate in adaptive designs might also arise from the early rejection of a null hypothesis at an interim analysis. To account for that issue, group sequential analysis plans can be applied, as described in 2.6. Furthermore an inflated Type I error rate can also be caused by the adaptation of key trial design features and by the combination of information across trial stages. In this case a combination of p-values needs to be applied, e.g. Fisher´s combination test or inverse normal method [19].

3.2 Trial simulation

As mentioned in section 1.2 several uncertainties regarding critical trial features exist in the planning phase of any clinical trial. Furthermore, it has been said that any adaptation to the clinical trial design needs to be pre-specified. In order to be able to do so, extensive trial simulation should be done prior to fixing the complete design together with the planned adaptations. Clinical trial simulation is a model-based approach which allows the investigation of the influence of design characteristics on important aspects of clinical trials. It aids in understanding the impact that any adaptation will have on the overall clinical trial and its underlying mechanism. Due to the complexity of adaptive design clinical trials, trial simulation is very important to characterize how any adaptation will affect the overall Type I error, the study power or bias and it is also expected by authorities that the clinical trial protocol includes information on the trial simulation [4].

3.3 Statistical Analysis Plan

The definition of a Statistical Analysis Plan (SAP) of a clinical trial is given in ICH E9 as a document that is written in addition to the Clinical Trial Protocol which gives more detailed information on the statistical approach in the evaluation of the trial data. ICH E9 also specifies that for a conventional clinical trial the SAP should be finalized before any un-blinded analysis takes place or before database lock, respectively [9]. This approach generally also applies to adaptive design clinical trials, however it might be beneficial to complete the SAP well in advance of the un-blinding, i.e. at the time of the finalization of the study protocol. This is also an advice given in FDA´s Guidance for Industry on Adaptive Design Clinical Trials [4]. As one of the main features of adaptive design clinical trials is the pre-specified nature of any adaptation, the SAP already needs to include all prospectively planned changes that are intended for the clinical trial as per the protocol. Besides a description of the statistical methods that are going to be applied for the implementation of the adaptations, the SAP should also specify how the overall study result will be derived from the single interim analyses and by what means the overall Type I error will be controlled [4]. Finalizing the SAP at the time of the protocol finalization will not only ensure that statistical procedures for the adaptations are well thought out and ready for implementation in the course of the trial, it also provides an opportunity for the sponsor to discuss the statistical approach with the authorities in a Scientific Advice (SA) Procedure/Protocol Assistance in advance of the initiation of the trial, thereby ensuring that the agency agrees with a supposedly complex design.

As mentioned in 1.2 another main aspect of adaptive designs is that the adaptations occur without undermining the integrity of the trial. An early fixed SAP will also contribute to the demonstration that operational bias, that is usually possible when un-blinded interim analyses are performed, is not of concern, since the statistical analysis of the data is already pre-specified before the first interim analysis will take place. Should there be any reason to change certain aspects of the SAP after a first un-blinding has happened, it will be much more complicated to demonstrate that there was actually no leakage of un-blinded data to the individuals involved in the update of the SAP, i.e. that operational bias can be excluded.

4 Practical implementation of adaptive designs in clinical trials

4.1 General considerations on the feasibility of adaptive design clinical trials

The various adaptive clinical trial designs cannot be implemented for each and every clinical trial as several operational/organization aspects have to be considered first before being able to decide if the adaptive feature is on the one hand feasible and on the other hand of actual benefit for the sponsor.

Any interim analysis leads to having to halt recruitment ad interim in order to be able to evaluate interim data and to decide on the adaptation. In the case of a clinical trial where treatment duration is long or a treatment effect is only observed with delay, the temporary recruitment stop will even be extended because data on the treatment effects for the last included patients has to be awaited in order not to risk over-running of treatment effects. What needs to be considered as well is the fact that once recruitment for a clinical trial is temporarily put on hold, it is usually difficult to re-boost recruitment, which in turn might even prolong study duration. As study duration is critical for the cost and duration of clinical development and is by nature already long for Investigational Medicinal Products (IMPs) that require long treatment duration, adaptive designs seem to be more adequate if they include treatments that exhibit their effect after shorter treatment periods. On the other hand, an adaptive design does also not seem to be feasible in case the recruitment rate is high compared to the time to treatment effect. The problem in this scenario is that there will be little time for information gathering on treatment effect on a first cohort before an interim analysis which is needed for making any adaptation. It is suggested that recruitment duration is at least four times as long as the time required until the treatment effect can be observed [20].

A further aspect that needs to be contemplated upfront is the IMP itself. An adaptive dose finding design, for example, is more feasible in case of a liquid IMP, since formulation of further dosage strengths is usually not a problem, whereas development of additional dosage strengths of solid pharmaceutical formulations requires more time which results in additional cost. However, irrespective of the type of formulation it has to be taken into account that new doses that are intended to be used in an on-going clinical trial need to be put on stability before their introduction into a clinical trial, which again prolongs study duration. Adaptive design clinical trials additionally seem to be even more complicated when expensive IMPs are involved as stockpiling of IMP at sites will in this case often be limited to a minimum. However, the resulting need for re-packaging and site-to-site shipment generally raises concerns and also results in a delay of IMP availability at sites.

From an operational perspective, adaptive design clinical trials also bear the risk that the respective study teams for an on-going clinical trial might change since personnel usually cannot be held available during a temporary recruitment stop. After re-initiation of recruitment, the newly introduced personnel needs to be trained on the specifics of the respective clinical trial and beginner´s mistakes that possibly have occurred before the interim analysis might be repeated again. Adaptive designs might therefore be more suitable for clinical trials that are less complex and do not require specialty know-how in the conduct of the study.

4.2 Planning of the study

Due to the complexity of adaptive design clinical trials and the pre-specified nature of any adaptations that are envisaged to occur during the conduct of the trial adequate planning is critical. As with any other conventional study, a clinical trial protocol needs to be developed that specifically addresses the question that the trial is intending to answer. Not only statistical issues need to be considered in advance (refer to section 3), operational aspects also need to be evaluated upfront. Operational aspects specific to adaptive designs are manifold. For example, it has to be ensured that in-time drug supply to the sites will be possible even though pre-planning is difficult due to not knowing e.g. which doses will be continued/dropped after an interim analysis. Furthermore, a Data Monitoring Committee (DMC) has to be established which will be privy to un-blinded data. Therefore, it has to be ensured upfront that there is a firewall in place to prevent any un-blinded data leakage from the DMC to any other personnel involved in the conduct of the trial to eliminate the risk of operational bias. The planning stage also includes the development of the clinical trial protocol, which is the key document for a given trial. It is important to give as much attention to the elaboration of the protocol as possible, as implementation of a complex design is easier if it is clearly defined in the protocol. Some items should be included in the protocol in addition to what is usually required for a conventional clinical trial. This includes a justification why an adaptive design was chosen and what the advantages are based on Clinical Trial Simulations. Furthermore, a clear description of the adaptive mechanism should be included, the role of the DMC should be explained and additional discussion should be given with regard to the control of the Type I error, the calculation of estimates and confidence intervals. Some aspects might not necessarily be included in the protocol in full detail, but can also be part of the SAP [21].

In summary, the planning phase of an adaptive design clinical trial will usually be longer than that of a conventional clinical trial. This is not surprising considering the pre-planned nature of adaptations and the complexity of such a study that will also involve more resources, as

multiple functions will need to be included early in the set-up of an adaptive design clinical trial.

4.3 Interaction with Regulatory Authorities

Early discussion with regulatory authorities is essential for all types of clinical trials, especially for those that are envisaged to be included in the data package to support a marketing authorization. This is not unique to adaptive design clinical trials, but is even more important due to their complexity and due to the limited experience that agencies as well as the pharmaceutical industry have with this novel approach to clinical development. In the European Union Scientific Advice/Protocol Assistance are regulatory mechanisms available to get early agency feedback on a planned clinical trial design, whereas the US FDA mainly encourages sponsors to discuss adaptive design clinical trials in an End of Phase-2 meeting. This is due to the fact that the timelines applicable to Special Protocol Assessments might be too short for the FDA to adequately review the request [4]. What is important when seeking an authority´s agreement on an adaptive design is to provide them with as much information as possible. This should at least include the clinical trial protocol, the Statistical Analysis Plan, clinical trial simulation results as well as the operating principles of the DMC in order to allow the agency to critically review the proposed design.

4.4 Trial Monitoring

The purpose of trial monitoring according to ICH E6 is to "*verify that (a) the rights and well-being of human subjects are protected. (b) the reported trial data are accurate, complete and verifiable from source documents. (c) the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).*" [22]. However, the extent and nature of monitoring is at the discretion of the sponsor, depending for example on the questions that are being addressed in the clinical trial as well as the complexity of the study design (risk-based approach). In adaptive design clinical trials a Data Monitoring Committee (DMC) is usually established [23], which not only covers safety monitoring of the trial, but it also assessws study integrity and design features. A DMC consists of several experts independent of the sponsor of the study. In order to perform the tasks mentioned above the members of the DMC might be privy to un-blinded data during the conduct of the trial. As the DMC´s role is also to give recommendations to the sponsor regarding pre-planned modifications of the study, operational bias is of great concern. Therefore, it should be ensured that Standard Operating Procedures (SOP) are in place at the start of the clinical trial that have the ability to minimize the concern of operational bias, i.e. standardized procedures to prevent any un-blinded data leakage to any

persons that should not be aware of these data. Processes to monitor compliance with these SOPs should be established as well.

Despite comprehensive discussions between the DMC and the sponsor in advance of the initiation of a trial, there might be situations in the course of an adaptive design clinical trial where sponsor input is required after the DMC has seen un-blinded interim results. In this case, the following should be considered in order not to endanger trial integrity: a convincing reason for the need of sponsor involvement should be documented, any sponsor personnel that gets access to un-blinded interim results should not be involved in the further trial conduct, only the minimum necessary number of sponsor personnel should be involved and last but not least, only the minimum amount of information needed for making a decision should be provided to the sponsor personnel [21].

Further considerations on trial monitoring for adaptive design clinical trials relate to data quality. Due to the complexity of adaptive designs, data quality is of utmost importance to guarantee that the trial results are easily and unambiguously interpretable. In order to achieve high data quality, efficient and adequate monitoring is crucial. This does not only call for well trained personnel that is familiar with the complex clinical trial design and increased on-site monitoring, but could additionally involve the usage of electronic Case Report Forms (eCRFs). eCRFs provide the opportunity to not only ease data handling, but also to fasten data cleaning. This is especially important in case of adaptive design clinical trials, as the interim analysis needs to be performed on cleaned data and temporary halt of recruitment at the time of the interim analysis should be limited to a minimum.

4.5 Evaluation and Reporting of a completed study

In principal, ICH E3 “Structure and Content of Clinical Study Reports” [24] needs to be followed for adaptive design clinical trials as for any other conventional clinical trial. However, several aspects need to be additionally taken into account when preparing a clinical study report that encompasses adaptive features. In order for a regulatory authority to thoroughly review clinical trial results submitted as a basis for approval of a marketing authorization application, the following items should be provided along with the clinical study report or within the clinical study report, respectively:

- Information on how the pre-specified adaptation plan was adhered to and how the study integrity was maintained
- Information on the mitigating procedures in case of deviations from the prospective plan
- Minutes of the DMC´s or any other committee´s meetings that were involved in the decisions regarding any adaptation

- Results of the interim analyses that formed the basis for the decisions regarding any adaptation
- Assessment of the procedures to prevent data leakage of un-blinded interim results [4]

The above is to be seen as information that should be provided in addition to what is usually already provided to regulatory authorities in the planning stage to get their feedback on proposed adaptive design clinical trials. As mentioned in section 4.3, this includes the clinical trial protocol, the Statistical Analysis Plan, clinical trial simulation results as well as the operating principles of the DMC.

It is important to provide the regulatory authorities with as much relevant information as possible, and also to prepare the information in a way that eases the agency´s evaluation of the study. The FDA guidance on "Adaptive Design Clinical Trials for Drugs and Biologics", for example, suggests to depict the trial´s progress along with the adaptive plan and the decisions taken at certain points during the trial in a schematic way [4].

5 Adoption of adaptive designs in pharmaceutical industry and acceptance by regulators

5.1 Results of a recent survey by the ADSWG

The Drug Information Association´s Adaptive Design Scientific Working Group (ADSWG) has recently published results of their 2012 Survey on Perception and Use of Adaptive Designs in clinical trials. The article not only includes results of the ADSWG´s 2012 survey, but also compares the new results with those gained in their 2008 survey, with literature reviews as well as with further surveys performed by either the FDA or the EMA [25]. The survey was provided to 92 organizations worldwide within the pharmaceutical industry and academia. It consisted of 10 questions on the usage of adaptive design clinical trials and possible obstacles experienced. 18 organizations responded to the survey and reported 475 adaptive design clinical trials altogether. Of these, 65% used a form of adaptive design, that the FDA guidance specifies as well-understood, i.e. a standard group sequential design or a sample size re-estimation based on a blinded interim analysis. For the rest of the reported adaptive design clinical trials a so-called less well-understood design was applied, for example a sample size re-estimation based on an un-blinded interim analysis, addition or dropping of treatment arms or adaptive randomization, sometimes in addition to another well-understood adaptive feature. There was no prevalence in exploratory and confirmatory studies. The adaptive design feature that was applied most frequently is stopping early for futility (56% of

the reported studies), efficacy (6%) or both (21%). Blinded sample size re-estimation was also seen in 6% of the reported studies. Treatment group adaptations were mostly combined with stopping for futility, which makes sense considering the case when all of the treatment arms are stopped. Since the 2008 survey did not include the well-understood adaptive designs, no comparison was possible for these. For the less well-understood adaptive designs in both the 2008 and 2012 survey treatment group adaptations were seen as the most commonly unsed, followed by un-blinded sample size re-estimation and adaptive randomization. The barriers/obstacles reported in both the 2008 and 2012 surveys that prevented organizations from implementing adaptive design features in their clinical trials have not changed to a great extent. Most commonly reported barriers in both surveys include change management, regulatory acceptance, education and pre-planning. The most significant decrease was seen in the barriers regarding flexible randomization and drug supply management.

A literature search revealed similar outcomes: publications in both statistical and medical journals regarding adaptive design clinical trials increased since the year 2000, with stopping early for futility and/or efficacy being the most often discussed topic, followed by un-blinded sample size re-estimation and treatment group adaptations. This is also in line with the results gained in the recent survey.

The clinical trial registry review (clinicaltrials.gov was the database searched) discovered an increase in the number of studies associated with an adaptive design feature from 1996 to 2007, followed by a decrease between 2008 and 2011. The author of the publication tries to explain this decrease with a delay in the reporting. Identifying the type of adaptation used in the respective trials is not easy given the limited information available on clinicaltrials.gov. For those trials where the type of adaptive design feature was identifiable the most frequently seen adaptations were treatment adaptations (adding, dropping or selecting doses) as well as early stopping for futility. Only a small fraction of these identified trials concerned confirmatory trials.

The reviews of Scientific Advice procedures at the CHMP by the EMA as well as investigational new drug (IND) applications at the FDA by the Center for Biologics Evaluation and Research (CBER) cited in the publication does not include a comparison on the encounter of adaptive design clinical trials in certain timeframes and therefore does not allow a judgment on any increase/decrease, but rather states the numbers for a specific timeframe. The EMA counted 30 SA procedures from January 2010 to May 2012 for Phase II and III studies that involved adaptive design features. The majority was seen for oncology treatments. The features most commonly discussed were sample size re-estimation as well as treatment selection. The CBER review revealed that approximately 10% of the submissions for INDs and Investigational Device Exemptions (IDEs) for Phase I to IV studies

contained adaptive designs, with a prevalence in Phase II and III studies (44% and 46%, respectively). The identified Phase III clinical trials equally concerned well-understood and less well-understood designs.

5.2 Examples of EMA and FDA guidelines incorporating adaptive designs

In order to see to what extent and how regulatory agencies actually already encourage sponsors of clinical studies to incorporate adaptive design features in their clinical development programs, it was assessed if and how adaptive design is already mentioned/incorporated in recently released clinical guidelines. In this context clinical guidelines published either on the FDA or EMA homepage that have been released after the date of the respective main FDA and EMA guidances on adaptive design have been searched manually for any reference to adaptive design.

The tables below summarize what has been discovered amongst EMA as well as FDA guidances.

Table 3 - EMA guidelines referring to adaptive design [26 to 29]

Guideline title	Date for coming into effect	Text excerpt referring to adaptive design
Guideline on the clinical development of medicinal products intended for the treatment of chronic primary immune thrombocytopenia (EMA/CHMP/153191/2013)	01 Sep 2014	4.4.1 Dose finding studies ...To ensure an appropriate range of doses are tested an interim analysis may be planned with the possibility to broaden the study dose range.
Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 rev 2)	15 Jan 2012	4.2.1.4.3. Alternative study designs ...On occasion there may be a rationale for employing a flexible (e.g. adaptive) study design. In these cases it is essential that the study design is developed in conjunction with EU Regulators and that agreement is reached on the mode of primary analysis of outcomes, including the primary patient population

Guideline title	Date for coming into effect	Text excerpt referring to adaptive design
Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95/Rev.4)	01 Jul 2013	7.6.1. Adaptive Design If a phase II/III study is designed only to address a single and non-complex question in phase II of the trial, such as proper dose for the confirmatory stage, adaptive design might increase the efficiency of drug development (CHMP/EWP/2459/02). Whenever more complex issues are to be addressed, e.g. involving defining the proper target population, or multiple issues, e.g. sample size re-estimation and cut-offs for biomarker positive tumour samples, etc. it is questioned whether adaptive design approaches are advantageous and scientific advice should be considered.
Guideline on the investigation of medicinal products in the term and preterm neonate (EMEA/536810/2008)	01 Jan 2010	9. Special Aspects of Clinical Trial Design in Neonates ...Adaptive, sequential, Bayesian or other designs may be used to minimise the size of the clinical trial. However, a balance between the need to stop recruitment early and the need to obtain reliable safety information should be aimed at.

Table 4 - FDA guidelines referring to adaptive design [30 to 41]

Guideline title	Date for coming into effect	Text excerpt referring to adaptive design
Guidance for Industry: Analgesic Indications: Developing Drug andBiological Products	Draft guidance (published 05 Feb 2014)	6. Randomization, Stratification, and Blinding ...Stratification, adaptive allocation, or other schemes to reduce variance between arms can be used as needed. If employed, we recommend that a discussion of how the analyses will account for such schemes be included in the protocol.
Guidance for Industry: Codevelopment of Two or More New Investigational Drugs for Use in Combination	14 Jun 2013	C. Proof of Concept Studies (Phase 2) ...Scenario 1 includes a discussion of a standard factorial design as well as an adaptive factorial design that could be used if there is uncertainty about using the individual drugs as monotherapy.

Guideline title	Date for coming into effect	Text excerpt referring to adaptive design
Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products	Draft guidance (published 14 Dec 2012)	D. Adaptive Enrichment Although an enrichment characteristic should almost always be specified before a study begins, certain adaptive designs can use enrichment strategies that identify predictive markers during the course of the study...However, the issue of whether the statistical testing results obtained by such an adaptive enrichment strategy are reproducible needs to be addressed...Although there has been little practical experience with enriched study designs whose sample size changes after the start of the study, or where other changes in the design are pre-planned to be based on accrued information during a trial, a number of adaptive designs seem potentially applicable...
Guidance for Industry: Non-Inferiority Clinical Trials	Draft guidance (published 01 Mar 2010)	G. Role of Adaptive Designs in NI Studies — Sample Size Re-estimation to Increase the Size of an NI Trial Because it may be difficult to adequately plan the sample size for any study, including an NI study, especially when assumptions like the event rate may change from the planning phase to the study conduct, adaptive study designs that can allow for the prospective re-estimation of a larger sample size can be considered...If an adaptive design that allows unblinding is contemplated, then the design features and procedures for protection of the integrity of the trial need to be clearly stated in the protocolfor the trial...
Guidance for Industry: Antibacterial Therapies for Patients With Unmet Medical Need for the Treatment of Serious Bacterial Diseases	Draft guidance (published 01 Jul 2013)	a. Prospective active-controlled clinical trials in patients with serious bacterial diseases and unmet medical need ...Innovative design and analysis strategies (including randomization of clinical trial centers, adaptive design clinical trials, Bayesian design and analysis strategies, or other approaches) can be employed in prospective, active-controlled trials, with an opportunity to stop the trial early for efficacy or futility. For example, the adaptive design might result in a shorter overall duration of the trial based on modification of sample size as a result of observed rates of patients enrolled who have unmet medical need...
Guidance for Industry: Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment	Draft guidance (published 04 Jun 2013)	e. Interim analyses and data monitoring committees ...If an adaptive design such as withdrawal of a treatment arm or sample size re- estimation based on an interim analysis is applied, then the adaptive design procedures should be prospectively prespecified...

Guideline title	Date for coming into effect	Text excerpt referring to adaptive design
Guidance for Industry: Complicated Urinary Tract Infections: Developing Drugs for Treatment	Draft guidance (published 23 Feb 2012)	f. Interim analyses and data monitoring committee If interim effectiveness analyses for success or futility will be performed, they should be prespecified in the protocol and in the analysis plan along with a justification...
Guidance for Industry: Neglected Tropical Diseases of the Developing World: Developing Drugs for Treatment or Prevention	03 Jul 2014	B. Clinical Development Considerations ...Adaptive clinical trial designs may be appropriate to consider for clinical trials of some NTDs. Clinical trials can be designed with adaptive features that may enhance the efficiency of the trial. For example, the adaptive design might result in a shorter overall duration of the trial, a fewer number of patients enrolled, or a greater likelihood of showing an effect of the drug if one exists... We also encourage sponsors to discuss such clinical trial designs with the FDA before conduct of the trial to provide an opportunity for advice on trials with an adaptation...
Guidance for Industry: Acute Bacterial Exacerbations of Chronic Bronchitis in Patients With Chronic Obstructive Pulmonary Disease: Developing Antimicrobial Drugs for Treatment	28 Sep 2012	e. Interim analyses and data monitoring committee If interim (or futility) analyses will be performed, they should be specified in the analysis plan. The purpose of the interim analysis should be stated in the analysis; it is important that the interim analysis not affect trial conduct and thereby compromise trial results...
Guidance for Industry: Acute Bacterial Otitis Media: Developing Drugs for Treatment	01 Oct 2012	d. Interim analyses and data monitoring committee If interim effectiveness analyses for success or futility will be performed, they should be prespecified in the protocol and in the analysis plan along with a justification. Details on the operating procedures also should be provided before trial initiation. The purpose of the interim analysis should be stated along with the appropriate statistical adjustment to control the overall type I error rate. It is important that an appropriate firewall be in place to guarantee that the interim analysis will not affect trial conduct and thereby compromise trial results...
Guidance for Industry: Vaginal Microbicides: Development for the Prevention of HIV Infection	Draft guidance (published 21 Nov 2012)	d. Interim analysis and data monitoring committee The plan for interim analyses to assess futility and safety should be finalized before trial initiation, and included in the statistical analysis plan. Based on interim findings, a trial may be terminated early for futility if the conditional power is low. Interim findings such as rate of condom usage or specific local practices affecting HIV transmission rate should guide sample size adjustments in an ongoing trial. Such increases in sample size also should be made in accordance with accepted guidelines for adaptive trial design as documented in the published statistical literature on sample size changes...

Guideline title	Date for coming into effect	Text excerpt referring to adaptive design
Guidance for Industry: Complicated Intra Abdominal Infections: Developing Drugs forTreatment	Draft guidance (published 28 Sep 2012)	f. Interim analyses and data monitoring committee If interim effectiveness analyses for success or futility will be performed, they should be prespecified in the protocol and in the analysis plan along with a justification. Details on the operating procedures also should be provided before trial initiation. The purpose of the interim analysis should be stated along with the appropriate statistical adjustment to control the overall type I error rate. It is important that an appropriate firewall be in place to guarantee that the interim analysis will not affect trial conduct and thereby compromise trial results...

What is obvious from the tables above is that the number of FDA clinical guidances that include a reference to adaptive design is much higher than that found on the EMA homepage. However, it seems that the FDA is currently incorporating some kind of standard statement regarding interim analysis and Data Monitoring Committees in its guidelines. Common to both EMA and FDA guidelines is that both agencies encourage the use of adaptive design and refer to the advantages that adaptive design features might have on a clinical trial or the overall development program, especially for well-understood adaptive designs. But both agencies also make note of the importance to interact with the regulators as early as possible in the design of such trials.

5.3 Examples of Marketing Authorization/Variation Applications including an adaptive design clinical trial

To identify if and which applications for initial marketing authorizations as well as for extension of indications at both the EMA and the FDA already included at least one clinical trial that incorporated an adaptive design feature, a search has been performed in Cortellis™ with the search terms "adaptive" and "design". The search results were refined by region ("European Union" and "USA") as well as by document type ("Product Approval Document", "EPAR" and "Approval package"). The identified approval packages/EPARs have then been looked at individually to find out further specifics regarding the type of adaptive design as well as any additional information resulting from the agencies´ review of the application.

The table on the following pages summarizes applications at both the EMA and the FDA that included at least one clinical trial which incorporated an adaptive design feature.

Table 5- Examples of Marketing Authorization/Variation applications including an adaptive design clinical trial [42 to 55]

Tradename	INN	Applicant	Indication	Approval date EU	Approval date US	Study identifi-cation	Type of adaptive design	Additional remarks
Arcapta® (US) Onbrez® Breezhaler® (EU)	Indacaterol	Novartis	COPD	30 Nov 2009	01 Jul 2011	B2335S	Adaptive, seamless, two-stage (stage 1: dose-finding, stage 2: efficacy and safety)	Doses identified for stage 2 by DMC were not approved by FDA, but further studies investigating lower doses had to be conducted
Fulyzaq®	Crofelemer	Salix Pharma-ceuticals	Relief of non-infectious diarrhea in adult patients with HIV/AIDS on anti-retroviral therapy	Not submitted	31 Dec 2013	NP303-101 (ADVENT)	Two-stage adaptive design (stage 1: dose-finding, stage 2: efficacy and safety)	Formal SPA agreement was not reached, but numerous communications between the sponsor and the FDA occurred before the initiation of the study. Results from both stages were combined by combining p-values from each stage by a weighting procedure according to Posch et al [45]

Tradename	INN	Applicant	Indication	Approval date EU	Approval date US	Study identifi-cation	Type of adaptive design	Additional remarks
Zytiga®	Abiraterone	Janssen	1st line castration-resistant prostate cancer	25 Jan 2013 (VAR to extend the indication)	10 Dec 2012	COU-AA-302	Group-sequential design with 3 interim and 1 final analysis using the O´Brien-Fleming boundaries for OS, but only 1 analysis for co-primary endpoint rPFS	The EPAR highlights that the trial was conducted in line with a previously received Scientific Advice, but also that "the proposed trial design makes the collection of clear and unbiased data for OS difficult" [46], as cross-over of placebo-patients was allowed after unblinding. At ASCO 2012 it was argued that the trial was stopped too early to unequivocally determine efficacy in terms of OS [47].
Defitelio®	Defibrotide	Gentium S.p.A	prevention of hepatic veno-occlusive disease (VOD) also known as Sinusoidal Obstructive syndrome (SOS) in haemato-poietic stem-cell transplan-tation therapy	Received negative opinion for prevention indication on 21 Mar 2013	n.a.	EudraCT 2004-000592-33	Adaptive interim analysis to stop trial early for futility or re-calculate sample size	EPAR states that "with no effect on mortality and the fact that this was a single adaptive trial which was open label, the results are not considered robust enough"

Tradename	INN	Applicant	Indication	Approval date EU	Approval date US	Study identifi-cation	Type of adaptive design	Additional remarks
Myozyme®	Alglucosi-dasealfa	Genzyme	Addition of the following statement to section 4.1 of the Product Information: In patients with late-onset Pompe disease the evidence of efficacy is limited	28 Oct 2009 (Type II VAR)	n.a.	AGLU0274	Planned interim analysis to determine recommended date of trial termination	Duration of study was extended from 52 weeks to 78 weeks
Hemangeol® (US) Hemangiol® (EU)	Propranolol	Pierre Fabre Dermatolo-gie	treatment of proliferating infantile haeman-gioma requiring systemic therapy	23 Apr 2014 (PUMA)	14 Mar 2014	V00400 SB 201	Seamless Phase II/III design (dosage and duration selection at interim analysis after first stage)	Single, pivotal trial
Procysbi®	Mercapta-mine	Raptor Pharma-ceuticals	treatment of proven nephropa-thiccystinosis	06 Sep 2013	30 Apr 2013	RP103-03	Sample size re-estimation	Single, pivotal trial; open-labelled

Tradename	INN	Applicant	Indication	Approval date EU	Approval date US	Study identifi-cation	Type of adaptive design	Additional remarks
Zydelig®	Idelalisib	Gilead Sciences	Chronic lymphocytic leukemia, refractory follicular lymphoma, [small lymphocytic lymphoma (US only)]	19 Sep 2014	23 Jul 2014	GS-US-312-0116	Group sequential design with two pre-specified interim analysis	Trial was un-blinded early after first interim analysis for efficacy; significance of OS results (secondary endpoint) not proven, as significance level for interim analyses not pre-specified
Invokana®	Canagliflo-zin	Janssen-Cilag	Type II diabetes mellitus	15 Nov 2013	29 Mar 2013	Several Phase III trials	Sequential testing	Hypotheses of primary efficacy endpoint and major secondary efficacy endpoints tested sequentially to account for multiplicity issue and to control Type I error rate at 0.05

The table above shows that so far only a few medicinal products have been authorized for marketing by either the FDA and/or the EMA based on a submission package which included at least one adaptive design clinical trial. However, it should be noted that with the search criteria used, not all relevant approvals may have been detected. It seems that more recently, i.e. in 2013 and 2014, more applications have been approved which included adaptive design clinical trials. This is not surprising, considering that the EMA and the FDA guidances have only been released a couple of years ago. As drug development takes several years, implementation of adaptive design features will only surface in an application for marketing authorization with a delay of several years, even if a specific trial has been initiated shortly after the release of the EMA and/or FDA guidances. So it could be expected that if the EMA/FDA guidance have actually encouraged pharmaceutical industry to apply adaptive design features, further marketing authorization applications including adaptive design clinical trials will be evaluated by EMA and/or FDA in the near future.

Not surprisingly, the majority of the adaptive features that were applied in the development of the approved medicinal products relate to the well-understood adaptive designs according to the FDA guidance [4] (group-sequential designs, early termination for efficacy). What additionally seems to enhance chances to get an approval for a marketing authorization is to engage in close collaboration with the agencies in the planning phase of an adaptive design clinical trial via Scientific Advice procedures or an SPA. Furthermore using an adaptive design in a clinical trial for an extension of an indication seems to be more acceptable for agencies as extensive data in a regular Phase III trial including comprehensive safety data are already available at that point. Last but not least, adaptive design features in clinical trials seem to be more acceptable in case of a medicinal product addressing an unmet medical need, for example orphan drugs (Procysbi®, Myozyme®) or paediatric medicines (Hemangiol®). In these cases the adaptive design was even used in a single pivotal trial.

6 Discussion

6.1 Challenges and risks

Adaptive design clinical trials have not been widely used until now and first (draft) guidelines from the EMA and the FDA have only been released in 2007 and 2010, respectively [3, 4] which may suggest that both agencies and the pharmaceutical industry are still on a learning curve in the implementation of adaptive designs. In section 4 it is already mentioned that adaptive designs are not feasible for all types of clinical trials, but that the feasibility depends on multiple factors. However, even if an adaptive design is considered realizable in a clinical

trial, there are further challenges and risks associated with it, which are discussed in the following.

One of the challenges of adaptive design clinical trials is the operational implementation of the trial. Several types of adaptive design either allow that complete treatment arms/dosages are dropped, that more patients are allocated to a specific treatment arm or that the overall sample size is re-calculated after an interim analysis, which makes it hard to prospectively plan for the supply of IMP at the individual sites. Consequently Clinical Trial Supply units have to be able to react to any changes in a timely manner in order to ensure correct and in time drug supply at the sites. This challenge might be overcome by the use of computerized systems that simulate the trial and thus calculate probabilistic IMP demands. Another approach could be the engagement of an external service provider for Clinical Trial Supply, which may have broader experience in the logistical handling of adaptive design clinical trials.

A further challenge might be the acceptance of clinical trials with adaptive features by regulatory authorities. Since there is not only limited experience with these kinds of trials on the part of the pharmaceutical industry, but also on the part of the agencies, there might be some restraint by regulatory agencies to accept adaptive design clinical trials as sole proof for efficacy of a treatment and a conventional clinical trial might still be warranted. A reason could be that widely accepted statistical methods are not yet available for all types of adaptations. Therefore, clear statistical inference for a treatment effect cannot be drawn from the trial results, which makes the agency´s review hard, if not impossible. So a distinction must be made between well understood adaptations, for which statistical models are readily available, and less well understood adaptations, for which statistical models are still under development, as also suggested by the FDA in their guidance document on adaptive design clinical trials [4]. Additionally, it is important to involve the agencies as early as possible and with as much information as possible in the development of an adaptive design clinical trial (please also refer to section 4.3).

One of the major advantages of adaptive design clinical trials can also lead to a further challenge: One of the aims of implementing adaptive features into a clinical trial is to reduce time and patients needed for a trial. However, this might imply that not enough safety data can be gathered to establish a solid safety profile of the treatment tested. This might in turn decrease chances for regulatory authorities to accept the adaptive design clinical trial when submitted in support of marketing authorization applications.

One of the greatest concerns associated with adaptive design clinical trials is the possibility of introducing bias, mainly in case of un-blinded interim analysis, but possibly also in case of blinded interim analysis. ICH E9 defines bias as "*the systematic tendency of any factors associated with the design, conduct, analysis and evaluation of the results of a clinical trial to*

make the estimate of a treatment effect deviate from its true value." [9] Two different types of bias are imaginable: operational bias on the one hand and statistical bias on the other. The first one is associated with the conduct of the trial, the second one with the statistical design or analysis [56]. Both types may lead to an overestimation of a treatment effect. Sources for operational bias might be data leakage of interim results that would affect the patient´s willingness to participate in a trial or the investigator´s behavior. One example for bias is the following: under response-adaptive randomization more patients are allocated to the more effective treatment. That means that the later a patient enters a trial the greater the chance that he/she will actually receive the more effective treatment. Since patients should be informed upfront about this circumstance for ethical reasons, it might happen that patients with a poorer health condition enroll earlier, whereas healthier patients might want to delay their enrollment [57], which might influence the validity of the trial results. In order to minimize bias in adaptive design clinical trials, it is essential that the protocol is being followed strictly with little/no deviations. Furthermore, the establishment of an independent DMC and the adherence to the processes/procedures related to the handling of interim results is important (refer to section 4.4).

A further statistical challenge is the control of the Type I error rate at a pre-specified level of significance. Sources for an inflation of the Type I error rate derive from the fact that multiple statistical hypothesis are being tested, either because of performing multiple interim analyses, evaluating several endpoints (primary, secondary and/or composite endpoints), comparing multiple treatment arms or analyzing subgroups. However, as mentioned in section 3.1, there are statistical methods available to control the Type I error rate, especially for the well-understood adaptive designs.

The aforementioned challenges are applicable to all types of adaptive design, however, there are also challenges that are more specific to certain types of adaptations. The following table gives an overview of these.

Table 6 - Challenges associated with specific types of adaptation (adapted from [58])

Type of adaptive design	Challenges
Adaptive randomization	• Randomization pattern only determined after start of the study • difficult to apply in a large trial or when treatment durations is long • Statistical inference on treatment effect frequently not easy
Sample size re-assessment	• Decision needed if trial should start with a large sample size followed by a possible later reduction or with a small sample size followed by a possible increase • Will lead to undesired revelation of interim results -> operational bias
Changes to eligibility criteria	• Shift in target population • Hard to interpret results, if changed several times (i.e. estimation of treatment effect for a certain sub population, which population do the overall results apply to)
Adaptive dose-finding	• Determining the initial dose and the tested dose range • Attaining statistical significance with a desired power despite a lower number of subjects • Managing clinical trial material supply to the sites
Seamless Phase II/Phase III design	• Increased Type I error rate • Sample size estimation and allocation of subjects difficult • Combined analysis difficult in case study objectives and/or endpoints are not the same for the individual phases • Important decisions regarding the Phase III design are left to the DMC due to data confidentiality of Phase II results
Endpoint adaptation	• Risk of selecting a poor endpoint if interim data show variability regarding effect-sensitivity differences between endpoints • Importance of collecting equally good quality data on all prospectively included endpoints
Change in study objective	Switch between non-inferiority and superiority: • determination of non-inferiority margin • Sample size estimation

6.2 Advantages

Clearly, adaptive design clinical trials also have their advantages, if well-conducted. Being kicked-off as one of the items listed in the FDA´s “Critical Path Opportunities List” [2] one of the major envisaged advantages is the adaptive design clinical trials´ potential to speed up

drug development/approval. This is mainly the result of bearing the possibility of combining clinical trial stages or including experimental features into confirmatory trials. Combining clinical trials stages, as in seamless Phase II/III designs for example, not only expedites the conduct of the complete trial itself (as compared to having two distinctly operated clinical trials), but one should also consider that only one Clinical Trial Application has to be submitted to and reviewed by regulatory authorities. Although there is no break between the two phases as in a conventionally set-up drug development, in which the results of the previously completed phase are evaluated and the protocol for the upcoming trial is developed (which is sometimes called the “white space”), one has to bear in mind that the initial planning of a seamless Phase II/III design requires more extensive planning upfront.

Expediting the clinical development of a compound also entails the advantage that an effective treatment might be on the market quicker and therefore is accessible to patients earlier. For pharmaceutical companies, this means that a greater fraction of the patent for a specific compound might still be valid when the drug enters the market which enables the company to achieve a greater return on investment.

One further advantage is the flexibility that adaptive design clinical trials offer. For example, if the adaptations are prospectively pre-planned, several features of the design might be changed based on available interim results. This can possibly involve the correction of wrong assumptions made at the beginning of the trial, which could lead to the failure of a trial in case a correction is not possible due to rigid adherence to a conventional clinical trial design.

If well-conducted and valid statistical inference is ensured, adaptive design clinical trials can also be regarded as being more ethical. The aim of any adaptive design clinical trial is to accelerate clinical development which means that less patients have to be exposed to an experimental treatment, either by dropping ineffective treatment arms earlier, by changing the eligibility criteria midterm so that only patients will be enrolled that are more prone to benefit from a treatment, by reducing the sample size ad interim or by completely stopping a trial early for futility, efficacy or harm. As mentioned above this does not only mean that patients are less exposed to ineffective or unsafe treatments in clinical trial settings, but that effective and safe medicines are available to a wider audience (i.e. after marketing authorization approval) much faster.

Considering that trial teams often are faced with budget constraints, one financial aspect might also be the possibility to start the trial with a rather small budget and only request an increase of the budget after promising interim results are available. A smaller budget might be more easily approved within a pharmaceutical company, especially in the case of smaller biotech companies, whereas a project requiring a bigger budget might be considered not feasible, possibly leading to not starting a clinical trial at all.

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 section 4.3, 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. This might be achieved, for example, by seeking parallel Scientific Advice with regulatory authorities and HTA bodies.

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 [59]. 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 [60] 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.

8 Summary

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 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 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 master thesis 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. In general, adaptive design clinical trials require more extensive planning, are challenging on an operational level and are more complex to interpret from a statistical point of view, but still offer the advantage to enhance and shorten clinical development. The thesis 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. This part of the thesis is rounded out by an overview of which EMA and FDA clinical guidelines actually refer to adaptive designs. 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.

Table of figures

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Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Schriesheim, den 5. November 2014

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