

Regulations on Adaptive Design Clinical Trials

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Abstract

In recent years, adaptive designs have recaptured attentions in the clinical research society as they can improve the flexibility and efficiency of conducting a clinical trial and increase the chance of trial success. However, adaptive trials are complex to design and often accompanied with various degrees of statistical, procedural, logistic and regulatory challenges. This article provides a general overview of adaptive designs with attentions to the discussion on the basic concepts, classification, application scope and principles with current understanding of regulatory agencies throughout the article. The adaptive designs in the exploratory, seamless and confirmatory stages are separated discussed with some common types briefly described respectively in order to account for the differences in regulatory impact and concerns. The strategic regulatory, statistical and operational considerations on how to use adaptive design are presented. It is hopeful that more innovation and collaboration made by the industry, academia, and regulatory agencies could promote the application of adaptive designs and transform the drug development.

Keywords: Adaptive designs; Interim analysis; Exploratory study; Seamless phase; Adequate and well-controlled study; Group sequential

Introduction

Drug development is an expensive, low efficiency process. In the past several decades, in view of the fact that the increasing spending in biomedicine research did not bring the increasing and accelerating production of pharmaceutical development, the pharmaceutical industry and regulatory agencies are eager to find advanced drug development methods that could accelerate the pace of innovation in drug development. Starting in 2004 the Food and Drug Administration (FDA) launched a Critical Path Initiative that aimed to assist the clinical study sponsors in improving the development process and speeding up the innovative medical therapies reaching patients. In 2006, the FDA released a Critical Path opportunity report and list, in which advancing innovative trial designs was underlined as an important strategy to streamline clinical trials and the opportunity and need of using adaptive design clinical trial was particularly presented [1,2]. As the traditional structured clinical trial does not offer enough flexibility to make use of continuously accumulated knowledge that is generated as the trial progresses, the adaptive design clinical trial are recapturing much attention due to its fascinating features of flexibility and efficiency if the validity and integrity of the intended study can be preserved.

The Pharmaceutical Research and Manufacturers of America (PhRMA) established adaptive design working groups in 2005 and proposed strategies, methodologies, and implementations in its white paper to facilitate wider usage and regulatory acceptance of adaptive designs [3,4]. The European Medicines Agency (EMA) as the first major regulatory agency released an official guiding document on adaptive clinical trial in 2007 [5]. The Food and Drug Administration (FDA) subsequently published its draft guidance for the industry in 2010 [6]. These guidelines had provided industry and academia valuable insight with regard to how to perceive, plan, design, conduct, and analyze adaptive clinical trials. While increasing number of articles have been published recently to discuss a variety of topics on adaptive clinical trial, it is evident that the regulatory understanding on this theme are still evolving and at present there are a number of unanswered questions that need be addressed given the insufficient experience in the clinical research society on whether, when and how to use adaptive design.

This article is aimed to provide a general introduction of adaptive design in the clinical research and development with attentions specifically to the basic concepts, classification, principles and

regulatory current thoughts. The various definitions and classification schemes on adaptive designs are introduced and compared. Some of the commonly employed types of adaptive designs and application principles are discussed. The current regulatory and statistical perspectives and operational hurdles that associated with the use of adaptive design are presented. It is expected that some standpoints in this overview would be evolving along with the increased utilization of these designs.

What is an Adaptive Design?

When the clinical researchers design the conventional fixed sample size study, many assumptions about critical design elements may not be precisely known, such as the targeted patient subpopulation, effect size, dose response, discontinuation rates, etc. However, in adaptive designs, these elements can always be updated based on data accumulated during the study. Therefore, it is intuitively appealing that an adaptive design (AD) could increase the flexibility and efficiency of conducting a clinical trial and importantly increase the chance of trial success.

ADs are not new to clinical trials. Group sequential designs have been in use for decades. While the AD recaptured more and more research interests and application enthusiasm in the recent years, there is still no universal agreement in terms of definition, methodologies, and applications. In 2006, the PhRMA Working Group defined the AD as “a clinical study design that uses accumulated data to modify elements of the study without undermining the validity and integrity of the study” [3,4]. It also defined that the validity means “providing correct statistical inference (such as adjusted p-values, unbiased estimates and adjusted confidence intervals, etc.), assuring consistency between different stages of the study, minimizing operational bias” and integrity means “providing convincing results to a broader scientific

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community, preplanning, as much as possible, based on intended adaptations, and maintaining the blind of interim analysis results.” This definition has achieved wide acceptance. In 2007, the EMEA reflection paper defined AD as a study design if statistical methodology allows the modification of a design element (e.g. sample-size, randomisation ratio, number of treatment arms) at an interim analysis with full control of the type I error [5]. In 2010, the FDA released a draft guidance document “Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics”, in which an adaptive design clinical trial is defined as a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study [6].

The PhRMA definition fairly emphasizes the importance of preserving the validity and integrity in an adaptive study which need be at the same level of statistical inference and integrity of process as classical “fixed” designs. However, it is not specific given that during the conduct of clinical trials it is not uncommon to modify trial and/or statistical procedures. Both EMEA and FDA define the bounds of adaptive designs which is in the interim analysis and the context of their utilization, which is in pivotal confirmatory clinical trial (EMEA) or adequate and well-controlled effectiveness studies (FDA). The term “prospectively planned” is first used in the FDA draft guidance indicating that expected adaptations must be designed prospectively before the data is examined in an unblinded manner. This definition emphasizes the concept of “adaptive by design”, and implies that the only way to ensure that the validity and integrity are not compromised requires that the adaptation must be prespecified in advance.

Classification and Types of Adaptive Design

The clinical trial adaptations cover a vast range of methods and nearly address most aspects of a clinical study. An accurate classification is essential to help the clinical trial designers understand the important, subtle differences between different types of ADs and thus facilitate the more applications of ADs appropriately and efficiently. However, this presents an unexpected and unsolved challenge and a uniformly recognized classification scheme has yet to be established which confuses the clinical research society as a whole.

In PhRMA reflection paper, three particular applications were described since they are more broadly discussed and used with maximal impact. They are 1) Sample size re-estimation, 2) Adaptive dose finding, and 3) Seamless Phase II/III designs. Chow and Chang extended them and described ten different ADs based on the adaptations that are commonly employed [7]. They are 1) adaptive randomisation, 2) group sequential design, 3) sample size re-estimation, 4) drop-the-loser, 5) adaptive dose finding (e.g., dose escalation), 6) biomarker adaptive design, 7) adaptive treatment switching, 8) hypothesis adaptive design, 9) adaptive seamless phase II/III trial design, and 10) multiple adaptive design. While this classification is centered on the application frequency of adaptations, it cannot serve as a systemic taxonomy.

A “rules” based classification was presented in Dragalin’s article, in which any adaptive design would modify one of the four basic elements of the study [8]. Therefore, utilizing a matrix of rules, ADs can be classified by the number and type of rules they modify. (a) Allocation rule, which determines how new patients will be assigned to available treatments. There are two common adaptations that affect the way subjects are allocated to treatment arms. First is response-adaptive randomization, often called the “play-the-winner” model. Another one is the covariate adaptive allocation. (b) Sampling rule, which address the number of subjects (sample size) that will be included in the study.

(c) Stopping and continuing rule, refers to those adaptations that would lead to terminating the study early for reasons of efficacy, futility, safety, or continuing the study beyond its originally planned duration. (d) Decision rule, the interim decisions pertaining to design change not covered by the previous three rules, such as change of the primary endpoint, change of hypothesis from non-inferiority to superiority or vice versa, and change of the method of statistical analysis, etc. This is debatable as the involved adaptations under the decision rule may in fact be an unplanned adaptation such as any substantive protocol amendment. In general, this classification fails to provide a self-evident system.

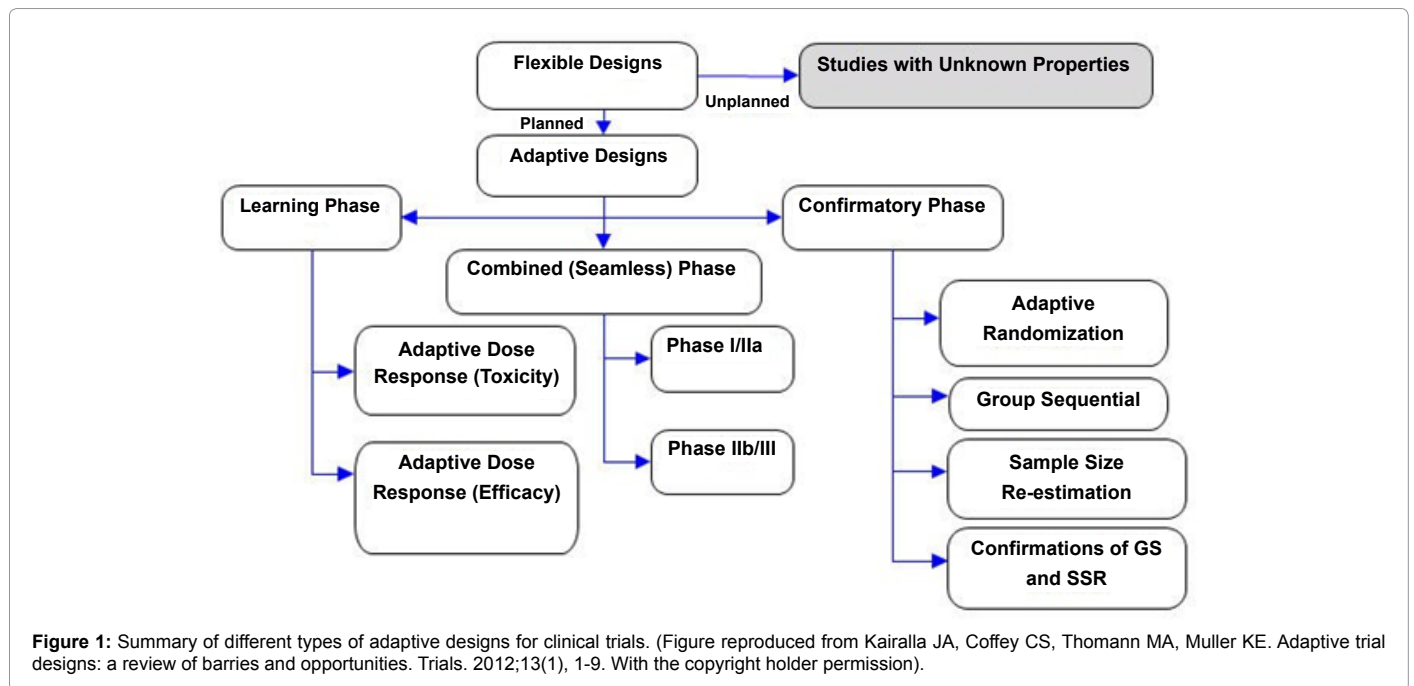
Neither EMEA nor FDA provided a clear classification scheme in their guiding documents. The reflection paper of EMEA actually did not attempt to do this. In FDA’s draft guidance, a wide range of possible adaptations has been mentioned, but they are just broadly divided into two classes according to the Type I error control rate and the regulatory experience, which are “well-understood” and “less well-understood” adaptive study designs. The distinction between them could be controversial and concerns are the difficulty to distinguish the ADs that have been classified as “well-understood” and “accepted” from those ADs that are “less well-understood” or “not accepted”. Brannath thought this classification method is subjective, unstable and misleading because it set the level of experience as the relevant criterion [9].

As Figure 1 illustrates, the structure of classification scheme developed by Kairalla et al. [10] is currently a concise and practical option. It is able to distinctly organize various adaptation types into different development phases and clarify the difference between the AD and flexible design by demonstrating that AD must be prospectively planned and adaptive by design while the latter incorporates both planned and unplanned features. Yet, more details may be further enriched in this scheme, which, for instance, may help distinguish the regulatory acceptance level and complexity regarding the design. As the regulatory impact on marketing approval varies among development stages, a brief overview of the main features of ADs in different study phases with some commonly employed types underneath respectively are described below with the emphasis on how to implement them successfully in the real settings.

Confirmatory Phase Ads in A&WC Studies

Overview

The major focus of the FDA 2010 draft guidance is adequate and well-controlled effectiveness (A&WC) studies, which aims to provide substantial evidence of effectiveness to support the efficacy claim of the drug. In order to distinguish its regulatory rigor from the exploratory studies, the term “A&WC studies” is used instead of “confirmatory studies” that defined in the ICH-E9 guidance. Unlike exploratory studies, the type I error rate must be under rigorous control and the studies must possess some prominent characteristics to be essential to make marketing approval decision by the regulatory agencies [11]. These features make the FDA classify these designs as “well-understood” and “less well-understood” [6]. The well understood ADs are those well-established clinical study designs that have planned modifications based on the results of one or more interim analyses that either needs no statistical correction or properly account for the analysis-related multiplicity of choices, such as the adaptive clinical studies that do not involve examining unblinded study outcome data, or not related to the effectiveness outcome. The less well understood ADs are typically based on unblinded interim analyses that estimate the treatment effects, in which FDA has relatively little regulatory



experience in assessing how the Type I error rate is controlled and how the impact of any adaptation-associated statistical or operational bias on the estimation of treatment effects could be minimized. It is worth reiterating that the classification of ADs based on the FDA’s understanding level is dynamic and somewhat misleading. More clarification is called for and a better structured classification system need be established in the guidance in order to facilitate the more utilization of ADs and better conform to the regulatory requirements.

Group sequential

Group Sequential (GS) designs are currently the most widely used ADs in clinical research fields. A group sequential design is a form of sequential design where interim analyses are performed after a number of subjects are enrolled in a study. Multiple groups (e.g., multiple-dose levels) are initially carried out and only one or two groups may stand out at predetermined interim points. Those groups that meet the prospective futility criterion, such as when no beneficial treatment effect or statistically demonstrated efficacy result is seen, would be terminated early before planned completion of the study. In the FDA draft guidance, the GS designs are considered “well-understood” if they are used in a prospective planned manner and Type I error rate be controlled. However, since the designs involve unblinded treatment arm comparisons, the concern of potentially introducing bias must be addressed by using independent, nonsponsor-controlled Data Monitoring Committee (DMC) to examine the interim analyses in order to protect the study integrity. Various statistical approaches to control Type I error rate can be found in the FDA draft guidance and many literatures, which are beyond the scope of this article [6,7].

Adaptive randomization

An adaptive randomization design is referred to as an adaptive design that allows modification of subject allocation to treatment groups based on accumulated study information. Common types include covariate adaptive randomization and response adaptive randomization [7,10]. As the traditional randomization with fixed allocation probabilities in advance may not ensure the covariates are balanced at all times during the study, covariate adaptive randomization could provide a

higher probability to balance the covariates among the study groups by allowing the allocation probabilities to change as a function of the current distribution of covariates. Methods and examples on covariate adaptive randomization are reported by Kairalla et al. [10] (*Trials*.2012; 13:1-9). Response adaptive randomization, often called player the winner approach, is a more common and controversial method that use observed accrual outcome responses to adjust allocation probabilities. It attractively increases the likelihood of a subject to be exposed to the best-know treatment at the time of randomization, whereas it may create ethical dilemma as well mentioned in section 5 of this article. The compromised balance of patient characteristics among the treatment groups is a major regulatory concern. Though the FDA draft guidance acknowledges the value of this method for exploratory studies, it is listed as “less well- understood” and particular attention must be paid to avoid bias and control the Type I error rate when implementing response adaptive randomization in A&WC studies.

Sample size re-estimation

A sample size re-estimation (SSR) design allows for sample size adjustment based on the observed data at interim analysis. Usually, the sample size is prospectively determined and fixed in advance according to the postulated treatment-effect size, desired power to detect a treatment effect, the targeted Type I error rate and the assumed population variance (e.g., drop-out rate). However, in case some of the factors above change at an interim stage, such as when the interim-observed treatment effect size is smaller than what is anticipated, but still clinically relevant, or when an adaptation on the study endpoint has altered the study power, SSR is warranted to allow for an increase of sample size that is initially planned. However, it is emphasized in the FDA draft guidance that this approach should only be employed for increases in the sample size, rather than decreases. The adaptation of sample size based on interim effect size estimate in an unblinded setting may cause an increase in the Type I error rate and considered “less well- understood” in the guidance.

Multiple adaptive designs

In theory, adaptive design may allow more than one design feature

to be modified during a study such as the combination of group sequential design and sample size re-estimation. However, in practice, when multiple adaptations are planned within a single study, the statistical inference will become increasingly difficult to interpret in the data analysis. In this regard, the FDA draft guidance marks this type of design “less well-understood” in an A&WC study and suggests limiting the number of adaptations and a clinical trial simulation be performed before conducting the study to evaluate the practicability of multiple adaptations in advance. The principle regarding how to apply multiple adaptations has been further elaborated in the next section of this article.

Learning Phase Ads in Exploratory Studies

Overview

Exploratory studies are defined as any studies that are not A&WC studies in FDA draft guidance. Using adaptive designs in learning or exploratory stage trials has different context than that in confirmatory or A&WC studies in therapeutic drug development. Wang [11] indicated that in exploratory trials, the role of adaptations rests with “deal better with learning and formalize the learning” [11]. Exploratory studies are intended to obtain and examine a wide range of key drug development information such as the choices of dose, regimen, population, concomitant treatments, endpoints, and such exploration should not be confused with prospectively planned adaptive A&WC studies which design to support a conclusion of drug efficacy by confirmatory evidence. The primary advantage of flexibility in the adaptive designs could be of great help in this stage to help sponsors learn and optimize based on accruing information about various aspects of dosing, exposure, differential patient response, response modifiers, or biomarker responses, and improve the planning and decision making in later A&WC studies. Utilizing adaptive design to learn the dose-response relationship, as a representative, is described below as this type is commonly used in exploratory studies. As exploratory studies have less impact on regulatory approval decisions, ADs are more encouraged in the learning stage exploratory studies by the FDA where the control of type I errors is less of an issue than the control of type II errors (avoiding false negatives). It is indicated in the draft guidance that as AD exploratory studies are usually different from A&WC studies in multiple aspects of design rigor, it is usually not appropriate to convert an exploratory study into an A&WC study while the trial is ongoing. The studies that are intended to provide substantial evidence of effectiveness should not be designed as exploratory studies, but rather as A&WC studies at initial planning. However, exploratory AD need still follow good principles of study design and circumvent the risk that unrecognized flaws may inflate type I error rate and adversely affect the development program in A&WC studies [6].

Adaptive dose response

Understanding the dose-response relationship for effectiveness and adverse effect is a primary component of drug development in the exploratory phase as this is essential to determine the dose regimen for more definitive efficacy and safety evaluation in the late phase A&WC studies. In practice, an adaptive dose response design is often used in early development phase to identify the minimum effective dose (MED) and/or the Maximum Tolerable Dose (MTD). It typically begin with multiple doses across a range and some dose groups would be terminated according to the accruing efficacy or safety data at one or more unblinded interim analyses. The response evaluated at the interim analyses could be an efficacy endpoint or a biomarker. The

optimized doses (usually 2 or 3) then can be continually evaluated in the following A&WC studies where the Type I error rate should be more carefully controlled.

Seamless phase Ads

Many authors and researchers have described the role of adaptive design in the seamless phase clinical development [5,7,10,12-14]. Multiple terms have been used to describe this particular seamless stage, such as learning/confirmatory, Phase IIB/Phase III, Phase IIa/Phase IIb, etc., and the intention is to combine learning phase exploratory study and confirmatory phase study into a single study and address objectives that are normally achieved through separate trials. A typical adaptive seamless design can be perceived as starting from a learning phase and then using the information gained from an interim analysis to extend to a confirmatory phase. The efficacy data from participants enrolled before and after the interim analysis will be evaluated in the final analysis and the valuable information at the phase II learning stage and statistical power at the phase III confirmatory phase are hopefully integrated. The desired feature of the adaptive seamless design is that other than the independent Phase II and Phase III development model, it can substantially reduce the development time between completing exploratory studies and initiating the subsequent A&WC studies by shortening the decision process. In addition, it is valuable to save the costs by eliminating ineffective treatment arms earlier and decreasing sample size in the confirmatory study. There are two seamless adaptive designs basically: inferentially seamless and operationally seamless. The inferentially seamless approach is a relatively more efficient one where the final analysis combines data from patients enrolled throughout the trial to make inferences while in the operationally seamless approach the data from two stages are analyzed separately [13]. Note that despite these advantages, the validity and efficiency of seamless ADs are challenged as some researchers think it is difficult to deal with a combined analysis if the study endpoints at two phases are different, which is quite common in practice [15,16]. Interestingly, the FDA draft guidance did not feel there is a specific need to distinguish the seamless adaptive design from others [6]. The agency is concerned that the term seamless phase II/III study can lead to confusion that whether the study was initially designed to be A&WC or not. The guidance also reminds the trial designers that seamless designs may reduce the inter-trial period of reflection and data exploration, thus limit the opportunity to reflect on data and design a thoughtful, complete late stage study. It should be noted that the concept of seamless design is not specifically for phase II/III combination, but may be extended to combine objectives from any phase of development, such as between a multiple-dose safety study and a proof-of-concept study, or a proof-of-concept study and a phase II study [13]. Overall, the FDA encourage that seamless approaches be further employed in the exploratory setting to get a better idea of their merits and drawbacks from various seamless combinations, which is certainly less risky and readily acceptable.

Scope

The adaptive designs can be applied in a wide range of aspects and virtually present protean manifestations of modifications in a clinical trial. As a matter of fact, the aforementioned common AD types described only account for a small portion of adaptations that are commonly employed in the various phases of clinical development. More diverse adaptations can be found in FDA’s draft guidance and a great number of literatures. Some are trial procedure related such as eligibility and efficacy criteria, study endpoints, dosing, treatment arms and regimens, etc. and others may associate with statistical procedure,

such as randomization, sample size, study design, study hypotheses, etc. However, there has been no such a publication that could distinctly and systemically define the scope and extent of adaptations. Further detailed appropriateness criteria should be incorporated in the final regulatory guidance for the industry in order to prevent people from abuse of this methodology. In this overview article, three application principles are underlined below, which hopefully could enlighten the scope formulation of ADs in the future.

First, ADs should not substitute poor planning. Chow and Chang [7] classified the employed adaptations in clinical trials as prospective, concurrent, and retrospective adaptations and discussed their impact, challenges and obstacles respectively [7]. Concurrent adaptations are those ad hoc modifications or changes made as the trial continues such as protocol amendment. Retrospective adaptations are referred to as modifications made to statistical analysis plan prior to database lock or unblinding of treatment codes. By contrast, prospective adaptations are usually referred to as by design adaptations, which are the ADs that discussed in this article. The strength of ADs truly relies on careful pre-planning. It is reported in the SPIRIT 2013 Explanation and Elaboration paper that “the most valid adaptive designs are those in which the opportunity to make adaptations is based on prespecified decision rules” [17]. In FDA draft guidance, the principle of careful planning, control of type I error, and ensuring the maintenance of study blinding are frequently emphasized and the role of prospective Statistical Analysis Plan (SAP) is underlined in ADs studies compared with those with conventional designs. For some complex adaptive design, more advance careful planning must be performed and the longer lead times between initiating planning and starting the study should be anticipated [6]. Adaptive designs should never be considered as a substitute for poor planning or be used to cut corner.

Second, don't be rash on multiple adaptations. The draft FDA guidance states that exploratory study design can allow multiple adaptations during the study based on interim examinations of study data, and can have multiple endpoints to be considered in the results, however, this won't be the case in confirmatory setting. Adaptation in a confirmatory trial should aim to resolve only few design uncertainties in the prespecified manner. If multiple trial aspects are subject to adaptation in the confirmatory phase, (e.g. endpoints, study groups, or data time points, etc), bias can be introduced because of the opportunity to choose the successful result from among the multiplicity of options and lead to increased Type I error rate. In addition, the multiple adaptations within a single trial may increase the complexity of the trial and make the results more difficult to interpret. As a general rule, the number of trial aspects adapted in a confirmatory study should be kept minimal, perhaps one or two. Multiple adaptations should particularly be avoided if adaptive design is used to estimate the treatment effect [6].

Third, pay attention closely to some specific applied areas. A number of authors indicated that some specific areas can potentially bring more benefits from ADs. Chow and Chang described the approach of a biomarker-adaptive design and its applicable fields [7]. Berry discussed how ADs can make oncology development more informative, accurate, and shorter by utilizing adaptation in developing post-treatment predictive biomarker in the personalized medical research [14]. As the clinical end points in oncology tend to be lengthy, the oncology researchers are leading the way to use such an adaptive approach to identify the efficient predictive biomarker and develop concurrent companion diagnostics for these biomarkers so as to inform the longer term treatment effect earlier and facilitate the

development of personalized medicine [18]. In addition, Kairalla et al. [10] believes that ADs are particularly appealing in small trials such as for rare diseases and for comparative effectiveness (CE) trials [10].

It is hopeful that these principles could enrich the understanding on ADs scope and bring practical insight on how to apply ADs to shorten the development time and importantly increase the probability of success in clinical development. More research effort is warranted to circumscribe what an AD can and cannot do especially in the A&WC setting and thus help the regulatory agencies and industry group achieve accumulated scientific evidence and experience.

During the process, some negative results should not be overlooked. For instance, Korn and Freidlin [19] compared the response adaptive randomization with designs that use fixed-ratio randomizations in both the randomized phase II and phase III settings and found that adaptive randomization did not bring additional benefits [19].

Strategic Considerations and Good Practice Standards

A number of regulatory, statistical and operational considerations must be addressed before and during the conducting ADs in order to achieve the expected development advantages. The FDA draft guidance expresses concerns that certain biases could be introduced in the ADs and undermine the validity and integrity of the study. Bias by definition is 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. During the course of the ADs clinical trials, statistical bias can be introduced by the selection of seemingly best design features such as dose, population, endpoint, treatment, or best observed interim treatment effects that are associated with the multiplicity of options and thereby increase the Type I error or make positive interim effect difficult to interpret. Operational bias is another common one that derives from the unblinding of interim analysis to the investigators. This bias may influence their opinions about the study treatments and contribute to false positive conclusions in non-inferiority trials and false negative conclusions in superiority trials [6]. The FDA draft guidance states that those prospectively planned adaptations based on trial internal interim analyses where the blinding process is well maintained could effectively reduce the risk of bias and be more readily accepted as “well-understood” ADs. Reversely, due to the limited experience, the magnitude of the risk of bias and the size of the potential bias, and how to eliminate these effects, need to be further investigated in the “less well-understood” ADs studies and the effort should be concentrating on the control of the study-wide Type I error rate, minimization of the impact of any adaptation-associated statistical or operational bias on the estimation of treatment effects, and the interpretability of trial results.

The primary statistical concern in the FDA draft guidance is to control the overall study-wide Type I error rate for all hypotheses tested in an A&WC study while the secondary concern is to avoid inflation of the Type II error rate for the important hypotheses of the study. The guidance recognizes that statistical methods for the design and analysis of ADs are technically more complex than those with conventional designs especially in the setting of less well-understood and complex ADs that involve multiple adaptations. The values of statistical simulations and Bayesian approach are described in the AD planning and evaluation. When this FDA draft guidance is compared with the EMA reflection paper and PhRMA's position paper it is evident that the agency's understanding on the statistical analysis in

ADs deepened as more practical experiences are accumulated from the pharmaceutical industry [5,6,13].

Likewise, a number of operational considerations must be taken into account during the plan and execution of ADs in order to collect the data in a timely fashion while not dilute the integrity of the study. The high level of integrated infrastructure such as efficient data capture, adaptive drug supply management, staff with sufficient training and understanding of ADs, etc. is prerequisite to ensure the successful implementation in a high complexity AD study [10]. This places substantial operational burden to the sponsor, CRO and investigative sites, which might be too demanding to those small to medium size biotech companies who may actually need ADs most [20]. In addition, there are other scientific, ethical and financial issues that need to be further addressed to ADs clinical trials. These may include how to characterize the generalizability and reproducibility of a specific AD, the costs and benefits analysis, and the approach to deal with an ethical dilemma and obtain appropriate informed consent [21]. It is recommended that before deciding on an adaptive design, a formal scenario analysis be performed to compare the scientific and operational aspects of different design options and their financial and ethical implications. The confirmatory adaptive design should be based upon the context of the overall clinical development plan and early discussions with regulatory agencies are critical to ensure the acceptance and successful implementation.

With all the strategic considerations and hurdles discussed above, a number of academic and industry groups had made their progress to develop some good practice standards with detailed guidance for the planning and implementing ADs. The PhRMA's position papers summarized the industry experience on strategic ADs considerations from the operational, regulatory, clinical, and statistical perspectives and provided some detailed recommendations such as for trial simulation, trial documentation, and data monitoring committees [13]. Detry et al. [22] further proposed eight minimum methodological standards to be applied in adaptive clinical trials based on the current guidance documents, best-practices articles, and their experience. Detailed information regarding current practice, examples of AD trials that meet the standards and the rationale for adopting the proposed standard is provided [22]. It is hopeful that the insight from these documents could be recognized in the final FDA guidance and widely applied by all the stakeholders in this field.

Concluding Remarks

The conventional clinical development model is historically rigid, time-consuming and resource-intensive. An adaptive design can take the advantage of accumulating results during the trial to modify the trial's course, therefore enhance the flexibility and efficiency of conducting a clinical trial and importantly increase the chance of trial success. The appealing characteristics embodied in ADs would inevitably impact almost all phases of clinical development and nearly all aspects of clinical trial planning, execution and statistical inference. However, the adaptive trials are complex to design and often accompanied with various degrees of statistical, procedural, logistic and regulatory challenges. The high level of understanding and infrastructure must be established before planning a successful AD and the validity and integrity of the trial must be preserved at any time.

The new century need regulatory agencies to advance regulatory science so that the new clinical trial methodologies and designs can transform the product development and speed marketing authorization. These approaches must "balance methodological rigor with the need for more rapid answers and often smaller study populations

and enable greater flexibility in response to emerging or evolving information while still addressing the fundamental, and inescapable, problems of bias and random events that make our assessments of clinical data challenging" [23]. As an important strategic priority action, FDA released draft guidance on adaptive design in 2010. This document endorsed the application of ADs and explained the level of regulatory acceptance to some common ADs in A&WC studies and advanced the regulatory position when compared with the prior EMA reflection paper. However, now that some methodological and operating characteristics of the ADs are still not well understood, more innovation and collaboration must be made jointly by the industry, academia, and regulatory agencies to accelerate experience accrual so that the scientific community as a whole can enjoy the advantages of ADs and the agile drug development can eventually benefit the patients.

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