The FDA adaptive trial design guidance in a nutshell - A review in Q&A format for decision makers

The FDA adaptive trial design guidance (1) is a thoughtful but lengthy document that explains on 50 pages wide-ranging and important topics “such as ... what aspects of adaptive design trials (i.e., clinical, statistical, regulatory) call for special consideration, ... when to interact with FDA while planning and conducting adaptive design studies, ... what information to include in the adaptive design for FDA review, and ... issues to consider in the evaluation of a completed adaptive design study.” [20-24]. **The advice in the guidance is often misinterpreted, misquoted or ignored.** This is unfortunate because an appropriate use of adaptive designs could increase the chances of success in drug development programs. Decision makers rely on the advice of regulatory affairs professionals and statisticians to interpret the guidance. Unfortunately, many clinical trial statisticians and regulatory professionals only have a rudimentary understanding of the guidance, presumably because the document is somewhat inscrutable for both audiences, too ‘regulatory’ for statisticians, too ‘statistical’ for regulatory people. **This digest was therefore written with three goals in mind:** 1) Make the content of the guidance more accessible through a question & answer format, 2) shorten the content from 50 to 10 pages by excerpting the most important dictums, and 3) keep fidelity to the original guidance by frequent use of direct quotes with reference to the respective lines in the original FDA guidance where the quote can be found in square brackets.

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The FDA Adaptive Trial Design Guidance in a Nutshell

A review in Q&A format for decision makers

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1. WHAT IS THE FOCUS OF THE GUIDANCE?

Adequate and well-controlled studies intended to provide substantial evidence of effectiveness required by law to support a marketing application [53-56, 180 - 182], abbreviated as 'A&WC studies'.

2. HOW DOES FDA DEFINE AN ADAPTIVE TRIAL DESIGN?

For the purposes of the guidance, "an *adaptive design clinical study* 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" [66-69] in a blinded or unblinded manner [70-71].

3. WHAT TYPES OF STUDIES ARE NOT CONSIDERED ADAPTIVE DESIGNS?

Revisions after unplanned findings in an interim analysis [541] and revisions based on information from a source external to the study [553], called in the guidance a 'reactive revision' [563]. However, see also Question 4.

4. WILL REACTIVE REVISIONS BASED ON EXTERNAL INFORMATION INVALIDATE MY STUDY?

Not necessarily. "In cases of serious safety concerns, and particularly in large studies, revising the study design may be critical to allowing the study to continue" [564-566]. "If the personnel who are determining the study revisions have no knowledge of any unblinded data or other information obtained during the study, then their decision-making cannot be influenced by study internal information to consciously or unconsciously introduce a study bias" [572-575]. These decisions are not to be made by a Data Monitoring Committee that has access to unblinded study results [577-579]. Interpretative problems may arise if data accumulated before and after the revision are combined [583-587].

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5. WHAT STUDIES OTHER THAN A&WC ARE CONSIDERED IN THE GUIDANCE?

The guidance does not distinguish by stages or phases of drug development and subdivides all studies into either exploratory or A&WC (187 - 188) and considers both.

6. WHAT IS MEANT BY THE TERMS 'WELL UNDERSTOOD' AND 'LESS WELL UNDERSTOOD'?

In the introduction the guidance mentions 'familiar' and 'less-familiar' adaptive design approaches, the latter "incorporate methodological features with which there is little experience in drug development at this time" [42-46]. Later the corresponding terms 'well-understood' and 'less-well understood' are used. 'Well-understood' methods' "...do not involve examining unblinded study outcome data..." [599-600], whereas "the less well-understood adaptive design methods are all based on unblinded interim analyses that estimate the treatment effect(s) [900-901]. However, the last statement cannot be taken in reverse, there are study designs that involve unblinding that are nevertheless 'well-understood', specifically, futility analysis (see below).

7. WHAT IS THE ROLE OF 'LESS-WELL UNDERSTOOD' DESIGNS IN DRUG DEVELOPMENT?

Sponsors are encouraged to use 'less-well understood' designs in the exploratory study setting [58-60], this experience, while perhaps immediately useful in designing follow-on A&WC studies, may also improve "...the understanding of circumstances where these designs are most useful and where they may pose risks to study validity..." [47-48].

8. WHAT ARE THE PRINCIPAL CONCERNS WITH ADAPTIVE TRIAL DESIGNS?

Design, analysis, or conduct flaws may "... have introduced bias that increases the chance of a false conclusion that the treatment is effective (a Type I error)" and positive study results may be "...difficult to interpret irrespective of having control of Type I error" [289-296].

9. WHY ARE CERTAIN ADAPTIVE DESIGNS 'LESS-WELL UNDERSTOOD'?

"In the case of some of the more recently developed adaptive methods, the magnitude of the risk of bias and the size of the potential bias, and how to eliminate these effects, are not yet well understood. The level of concern is greatest in an A&WC study setting but is also important in an exploratory study, where bias can adversely affect development decisions, such as choice of dose, population or study endpoints in subsequent studies" [300-304].

10. WHAT ARE THE RISKS WITH UNBLINDING OF STUDY DATA?

BIAS ASSOCIATED WITH THE MULTIPLICITY OF OPTIONS

When "... multiple sequential statistical analyses of a single primary hypothesis are conducted at successive interim stages of a clinical trial, group sequential methods ... maintain control of the Type I error rate" [319-321]. When adaptation choices are based on unblinded examination of study results multiple opportunities to succeed are created and this bias "may be readily recognized, but in complex cases may be difficult to understand and account for with statistical adjustments" [327-328].

DIFFICULTY IN INTERPRETING RESULTS WHEN A TREATMENT EFFECT IS SHOWN

"Adaptive designs that select the best observed interim treatment effect among the options ... have the potential to select the option with an interim result that is, by random chance, more favorable than the true value" [340-342]. Control of the type I error rate does control this bias of the effect estimate.

OPERATIONAL BIAS

Analysts that have access to unblinded interim analysis results "...might influence investigators in how they manage the trial, manage individual study

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patients, or make study assessments..." [372-373] and "statistical methods cannot correct or adjust for this bias" [377-378]. Even in the absence of knowledge of unblinded interim analysis results "even knowledge only of the specific adaptive choice, has the potential to introduce operational bias into the treatment-effect estimates" [382-383].

11. IS A FUTILITY ANALYSIS A 'WELL-UNDERSTOOD' DESIGN DESPITE UNBLINDING?

Yes. All less well understood adaptive designs involve unblinding, however, not all unblinded interim analyses are less well understood. The guidance states "other adaptive methods use the well-understood group sequential design ... in group sequential designs, unblinded interim analyses of accruing study data are used in a planned and confidential manner (i.e., by a DMC) that controls Type I error and maintains study integrity" [602 - 604]. A reference is made to section D, implying that this statement specifically applies to futility analysis.

The guidance elaborates on the topic of futility analysis in the following under section V. D.: "Group sequential statistical design and analysis methods have been developed that allow valid analyses of interim data and provide well-recognized alpha spending approaches to address the control of the Type I error rate (e.g., O'Brien-Fleming, Lan-DeMets, Peto methods) to enable termination of a study early when either no beneficial treatment effect is seen or a statistically robust demonstration of efficacy is observed" [772-777]. The remainder of the section discusses several well-known caveats, most of which concern protection of the study integrity.

12. ARE GROUP-SEQUENTIAL DESIGNS THAT ARE USED FOR PURPOSES OTHER THAN FUTILITY ANALYSIS 'WELL-UNDERSTOOD'? FOR EXAMPLE, CAN I USE AN ADAPTIVE GROUP SEQUENTIAL DESIGN WITH SAMPLE SIZE RE-ESTIMATION FOR AN A&WC TRIAL?

Group-sequential design, a rigorous method to control the type I error rate, is discussed in the guidance in section D "Adaptations Using Group Sequential Methods and **Unblinded** Analyses for Early Study Termination Because of Either Lack of Benefit or Demonstrated Efficacy" [769-770] where it is considered 'valid' and 'well recognized'.

Group sequential designs are otherwise mentioned only briefly and any adaptation of sample size based on interim-effect size estimates [1023] falls under section VI "Adaptive Study Designs Whose Properties Are Less Well Understood" [884-885]; see Question 18.

13. WHEN DO I HAVE TO HAVE THE INTERIM ANALYSIS PLAN FINALIZED?

If unblinding is involved the plan needs to be finalized before unblinding occurs but not necessarily before the study starts. "The term *prospective* here means that the adaptation was planned (and details specified) before data were examined in an unblinded manner by any personnel involved in planning the revision. This can include plans that are introduced or made final after the study has started if the blinded state of the personnel involved is unequivocally maintained when the modification plan is proposed" [73-77]. See also Question 29 (Statistical Analysis Plan).

14. DO ALL ADAPTATIONS NEED TO BE PLANNED?

No. If no unblinding of data is performed, "... revisions based on blinded interim evaluations of data ... do not introduce statistical bias" [90-91] and "certain blinded-analysis-based changes, such as sample size revisions based on aggregate event rates or variance of the endpoint ... can also be applied when not planned from the study outset if the study has remained unequivocally blinded" [93-96].

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15. WHAT ARE BENEFITS OF USING ADAPTIVE DESIGNS ESPECIALLY IN EXPLORATORY STUDIES?

"Compared to non-adaptive studies, adaptive design approaches may lead to a study that more efficiently provides the same information, (2) increases the likelihood of success on the study objective, or (3) yields improved understanding of the treatment's effect ..." [235-239].

"Using adaptive designs in early development studies to learn about various aspects of dosing, exposure, differential patient response, response modifiers, or biomarker responses offers sponsors opportunities that can improve later studies" [504-506]."... in some circumstances both dose-group selection and response-adaptive randomization appear to have the potential to obtain a more precise description of the dose-response relationship by starting with a broader range of doses, closer spacing of doses, or both, in a study of approximately the same sample size as is generally used in a conventional exploratory study" [510-513].

16. CAN I REVISE MY EXPLORATORY STUDY WHILE IT IS UNDERWAY SO THAT IT CAN SERVE AS AN AW&C STUDY?

Usually not. "Adaptive design exploratory studies are usually different in multiple aspects of design rigor from A&WC studies so that design revisions while the study is underway will usually not be sufficient to convert the study into an A&WC study. 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" [533-537].

17. CAN I DESIGN A SEAMLESS TRANSITION BETWEEN AN EXPLORATORY ADAPTIVE DESIGN STUDY AND A CONFIRMATORY TRIAL, A SO CALLED PHASE 2/3 STUDY, TO SAVE TIME?

Yes, but FDA is of the opinion that these terms "... provide no additional meaning beyond the term *adaptive..."* [228-229] and while acknowledging the advantage, calls out the drawbacks. "A component of the potential value of adaptive design methods relates to eliminating the time period that occurs between separate exploratory and A&WC studies in conventional drug development programs. Although the efficiency gain from this elimination of time is apparent, the approach entails risks ... and the apparent time advantage may be less valuable if a greater period of reflection and data exploration would have allowed the design of better studies" [276-281].

18. WHAT ARE TYPES OF ADAPTIVE STUDY DESIGN MENTIONED IN THE GUIDANCE WHOSE PROPERTIES ARE **LESS WELL UNDERSTOOD**?

"The less well-understood adaptive design methods are all based on unblinded interim analyses that estimate the treatment effect(s)" [900-901].

DOSE SELECTION STUDIES

"An adaptive exploratory dose-response study is intended to begin with multiple doses (sometimes many) across a range. The number of dose groups is adaptively decreased during the course of the study, using the accruing efficacy or safety data in a prospectively specified plan for design modification at one or more unblinded interim analyses" [933-936].

OUTCOME DEPENDENT RANDOMIZATION

This approach is particularly valuable in exploratory studies with the "...objective of dose-response evaluation. The method allocates fewer subjects to doses that appear to have a low probability of a treatment-related efficacy response, to have a high probability of an adverse event, or to be unlikely to contribute additional information on the shape of the dose response profile" [986-989].

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ADAPTATION OF SAMPLE SIZE

Not well understood if it involves unblinding. See Question 12.

ADAPTATION OF PATIENT POPULATION

"Adaptive design studies using unblinded interim analyses (of either clinical or biomarker data) for each subset of interest have been proposed as another method for identifying population subsets with relatively greater treatment responsiveness" [1088-1091].

"Adaptive methods that have been proposed include (1) changing only the eligibility criteria, with no change in the study overall sample size and with the final analysis including the entire study population, or (2) modifying the plan for the final analysis to include only patients with the preferred characteristic" [1100-1103].

ADAPTATION FOR ENDPOINT SELECTION

"Primary endpoint revision usually takes one of two forms, replacement of the designated primary endpoint with an entirely new endpoint, or modification of the primary endpoint by adding or removing data elements to the endpoint (e.g., the discrete event types included in a composite event endpoint" [1125 -1128].

ADAPTATION OF MULTIPLE STUDY DESIGN FEATURES IN A SINGLE STUDY

"When multiple adaptations are planned within a single study, the study will become increasingly complex and difficult to plan, with increased difficulty in interpreting the study result. In addition, if there are interactions between the changes in study features, multiple adaptations can be counterproductive and lead to failure of the study to meet its goals" [1155-1158].

19. WHAT ARE SOME SPECIAL ADAPTIVE DESIGN CONSIDERATIONS IN NON-INFERIORITY STUDIES?

According to the guidance "many design features of a non-inferiority study may not be suitable for adaptation. Chief among these features is the non-inferiority margin" [1186-1187]. However, sample size adjustment based on blinded interim analysis "...might improve the statistical power to meet the prospective non-inferiority margin, and can also increase the potential to demonstrate superiority of the test agent over the comparator in the case where this is true" [1175-1178].

"A blinded interim analysis ... can often be entirely sufficient to enable reconsideration of study sample size..., and might pose fewer difficulties and risks than methods that rely on an unblinded analysis" [1170-1173].

20. CAN I DISSEMINATE INTERIM RESULTS FROM AN EXPLORATORY OR CONFIRMATORY TRIAL?

The adaptive trial design guidance does not address this question directly, presumably because it is considered to be common knowledge. However, the FDA DMC guidance (2) states: "Unblinded interim data and the results of comparative interim analyses ... should generally not be accessible by anyone other than DMC members or the statistician(s) performing these analyses and presenting them to the DMC..." [Section 4.2. Confidentiality of Interim Data and Analyses, Guidance for Clinical Trial Sponsors. Establishment and Operation of Clinical Trial Data Monitoring Committees]. It is fair to say that FDA means by 'generally' 'almost always'. Consequences for a departure from this advice in the setting of a confirmatory trial can be serious.

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21. WHAT ARE TYPES OF ADAPTIVE STUDY DESIGN MENTIONED IN THE GUIDANCE WHOSE PROPERTIES ARE **'WELL UNDERSTOOD'**?

ADAPTATION OF STUDY ELIGIBILITY CRITERIA BASED ON ANALYSES OF PRETREATMENT (BASELINE) DATA

The guidance encourages "sample size adjustment using blinded methods to maintain desired study power" [699-671].

"Examination of baseline characteristics of the accumulating study population might show that the expected population is not being enrolled and that by modifying eligibility criteria, subsequent subject enrollment may be shifted towards a population with greater numbers of patients with the desired characteristics. Similarly, if the study enrollment rate is substantially slower than expected, the screening log can be examined for noncritical entry criteria that might be modified to allow greater numbers of screened patients to qualify" [617-623].

ADAPTATIONS TO MAINTAIN STUDY POWER BASED ON BLINDED INTERIM ANALYSES OF AGGREGATE DATA

"In studies using a discrete outcome (event) endpoint, a blinded examination of the study overall event rate can be compared to the assumptions used in planning the study" [652-653].

"For studies using a time-to-event analysis, another approach is not to plan a specific study 664 sample size in the protocol, but rather to continue patient enrollment until a prospectively 665 specified number of events has occurred (an *event-driven* study)" [663-665].

"Similarly, when a continuous outcome measure is the study endpoint, a blinded examination of the variance of the study endpoint can be made and compared to the assumption used in planning the study" [668-670].

"In some studies with continuous outcome measures the duration of patient participation and time of last evaluation may be the preferred design feature to modify" [676-677].

ADAPTATIONS BASED ON INTERIM RESULTS OF AN OUTCOME UNRELATED TO EFFICACY

The guidance mentions this example: In a dose-response study "some doses might cause an unacceptable rate of a serious adverse effect or a less serious adverse effect sufficient to make the treatment unattractive ..."[723-726]. "If the adverse effect is completely independent of the treatment's benefit, then an unblinded analysis..." [728-729] does not affect the Type I error rate and no adjustment is needed [730-731].

ADAPTATIONS USING GROUP SEQUENTIAL METHODS AND UNBLINDED ANALYSES FOR EARLY STUDY TERMINATION BECAUSE OF EITHER LACK OF BENEFIT OR DEMONSTRATED EFFICACY

FDA has concerns but they can be mitigated by a properly constituted DMC. "Implementation of group sequential design methods involves unblinded analyses of the treatment effect, thereby raising significant concerns for potentially introducing bias into the conduct of the study or into subsequent decisions regarding the conduct of the study. Protocols using group sequential designs have addressed this concern by using a committee independent of the study's conduct and sponsor to examine these analyses in a secure and confidential manner. An independent, nonsponsor-controlled Data Monitoring Committee (DMC) (see the DMC guidance) is an inherent part of the group sequential method's protection of study integrity" [817-823]. See also Question 12.

22. WHAT HELP IS AVAILABLE FROM FDA FOR ADAPTIVE DESIGNS IN **EARLY TO MIDDLE STAGE** TRIALS?

Not a whole lot. "Discussion of the plans for an adaptive design study can be the basis for requesting

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a Type C meeting. FDA's ability to address such requests for studies in early phases of drug development, however, may be limited and will depend on competing workload priorities and on the particulars of the drug and use under development. Innovative therapeutics for an area of unmet medical need are likely to garner more review attention than other products FDA believes do not fall into this category." [1602-1608].

23. WHAT HELP IS AVAILABLE FROM FDA FOR ADAPTIVE DESIGNS IN **LATE STAGE** TRIALS?

Late stage trials may need to be discussed as early as at end of phase 2a: "Depending on the preexisting breadth and depth of information regarding the drug, its specific use, and the nature of the adaptive features, an EOP2 meeting may be the appropriate place in development for initial discussion of an adaptive design A&WC study. However, if there is only limited knowledge of certain critical aspects of the drug's use before conducting the adaptive study, and the study is intended to obtain such knowledge using the study's adaptive features (particularly less well-understood methods), discussion with FDA earlier than usual is advisable (e.g., at a Type C or End-of-Phase 2A meeting). An early meeting for A&WC study protocols with complex adaptive features allows time to carefully consider the plan and to revise and reevaluate it as appropriate, without slowing the clinical development program." [1620-1628].

24. IS A SPA A GOOD IDEA?

Not really. "If there has been little or no prior discussion between FDA and the study sponsor regarding the proposed study and its adaptive design features, other information requests following initial FDA evaluation are likely and full completion of study assessment within the SPA 45-day time frame is unlikely." [1660-1663]. SPA: Special Protocol Assessment.

25. WHAT ARE CONCERNS REGARDING THE TYPE I ERROR RATE (FALSE POSITIVES)?

In addition to the well known issues with multiple hypothesis testing, adaptive designs can magnify small biases into large biases: "One type of adaptation based on an unblinded interim analysis of treatment effects is an increase in the study sample size to maintain study power when the observed effect size is smaller than that initially planned in the protocol. When a statistical bias in the estimate of treatment effect exists, an increase in the sample size does not eliminate the bias. Instead, if flaws in the design (or conduct) of a study introduce a small bias, the increase in sample size can result in the bias increasing the Type I error rate more than would occur without the sample size increase. Thus, the impact of small biases can be magnified when sample size increases are enabled." [1233-1246].

26. WHAT ARE RANDOM HIGHS AND UNSTABLE DATA?

"Estimates of the treatment effect are used to make decisions at each stage of an adaptive design study. Because these estimates can be based on a relatively small amount of data, they can be very variable or unstable. The effect estimates for the selected adaptations have the potential to overstate the true effect size because the adaptive choice is usually selected based on the largest of the observed interim treatment effects among the design choice options, which can reflect an unusual distribution of patient observations (often called random highs in group sequential designs). This could also lead to selecting a wrong adaptation choice and thus miss detecting a true treatment effect (i.e., lead to a Type II error)." [1251-1258].

27. CAN I USE SIMULATIONS TO DEMONSTRATE CONTROL OF THE TYPE I ERROR RATES?

"Using simulations to demonstrate control of the Type I error rate ...is controversial and not fully understood." [3141-1342]. However, FDA is

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otherwise supportive of modeling and simulation strategies, including those which use Bayesian approaches, because they may aid in deciding which adaptation should be selected.[1313-1322]. See Question 28.

28. WHAT ARE CONCERNS REGARDING THE TYPE II ERROR RATE (FALSE NEGATIVES)?

Adaptive design methods, while often designed to increase study power, and decrease the risk of a Type II error, may "also have the potential to inflate the Type II error rate for one or more hypotheses. An example of this is a study that begins with multiple doses (or populations or other study features) and that early in the study is adaptively modified to eliminate all but one or two doses to be continued to the study's end. This study risks failing to demonstrate treatment effects by making erroneous choices based on interim results that are very variable because of the limited amount of early study data."[1277-1287].

29. WHAT IS THE VALUE OF CLINICAL TRIAL SIMULATIONS?

The guidance first clarifies what is meant by clinical trial simulation: "In general, clinical trial simulations rely on a statistical model of recognized important design features and other factors, including the posited rate of occurrence of clinical events or endpoint distribution, the variability of these factors among patient subsets, postulated relationships between outcomes and prognostic factors, correlation among endpoints, the time course of endpoint occurrence or disease progression, and the postulated patient withdrawal or dropout patterns, among others. More complex disease models or drug models might attempt to account for changing doses, changing exposure duration, or variability in bioavailability." [1303-1311]. FDA concludes that trial simulations "can be an important planning tool in assessing the statistical properties of a trial design and the inferential statistics used in the data analysis. [1297-1299].

30. HOW LATE CAN I CHANGE MY SAP IF I PLAN AN UNBLINDED INTERIM ANALYSIS?

"In general, it is best that any SAP updates occur before any unblinded analyses are performed, and that there is unequivocal assurance that the blinding of the personnel determining the modification has not been compromised. A blinded steering committee can make such protocol and SAP changes, as suggested in the ICH E9 guidance and in the DMC guidance, but adaptive designs open the possibility of unintended sharing of unblinded data after the first interim analysis. Any design or analysis modifications made after an unblinded analysis, especially late in the study, may be problematic and should be accompanied by a clear, detailed description of the data firewall between the personnel with access to the unblinded analyses and those personnel making the SAP changes, along with documentation of adherence to these plans." [1367-1377]

31. WHAT ARE SAFETY CONCERNS THAT ARISE IN EARLY PHASE ADAPTIVE DESIGN TRIALS?

Too few patients exposed too fast. Some newer adaptive design algorithms in dose escalation studies "permit a change in dose level after each patient is treated based on the accumulated responses of previously enrolled subjects" and thus "...it is possible to reach the middle or higher end of the dose-response curve with fewer subjects at each of the prior levels." [1397-1403]. "Where there is little to no prior safety experience with a drug (or related drugs) and the known or hypothetical adverse effects can be serious, however, an adaptive study aggressively designed for most rapidly reaching a decision on the highest tolerable dose might be inappropriate." [1405-1408]. "Study simulations with multiple combinations of escalation criteria, dose-step size, and hypothetical-assumed relationships of exposure to severity and frequency of adverse events may be useful in evaluating different designs." [1413-1415]

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32. WHAT ARE SAFETY CONCERNS WITH ADAPTIVE DESIGNS IN LATE STAGE CLINICAL TRIALS?

Too few patients exposed too early. “Development programs using adaptive design methods are sometimes intended to condense the development program into fewer fully independent studies, with more rapid advancement from small early studies into the large A&WC studies" with only a "...limited amount of safety data available at the time that a large adaptive study is being planned that will entail a great increase in the number of patients exposed to the drug."[1428-1432]

"A safety concern that becomes recognized in the data of a moderate-sized study can lead to planning for better evaluation in the A&WC study designed subsequently. The more comprehensive evaluation thus obtained may be necessary to ensure an adequate safety assessment for regulatory review. An adaptive design development program that eliminates the independent mid-sized study and initiates the large adaptive A&WC study before recognizing the safety issue will not have included such additional safety assessments." [1452-1457].

33. HOW CAN FDA BE REASSURED REGARDING THE PROTECTION OF STUDY BLINDING?

"A failure either to make the appropriate decisions as directed in the prospective SAP or to maintain confidentiality of the interim results might have an adverse impact on the interpretation of the study results. The processes established, as well as how they were performed, should be well documented in the final study report. The ability for FDA to verify compliance, potentially by on-site auditing, may be critical."[1730-1734].

"This written documentation should include (1) identification of the personnel who will perform the interim analyses, and who will have access to the interim results, (2) how that access will be controlled and verified, and how the interim analyses will be performed, including how any potential irregularities in the data (e.g., withdrawals, missing values) will be managed, and (3) how adaptation decisions will be made. Other issues that should be addressed in these SOPs are (1) whether there are any foreseeable impediments to complying with the SOPs, (2) how compliance with the SOPs will be documented and monitored, and (3) what information, under what circumstances, is permitted to be passed from the DMC to the sponsor or investigators." [1690-1699].

Notes: This digest does not cover the following two sections:

XII. Evaluating and reporting a completed study

IX. Content of an adaptive design protocol

REFERENCES:

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