Adaptive Plus, LLC

Adaptive Design Consulting

VIA ELECTRONIC DELIVERY

Date: 25 May 2010

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket Number FDA-2010-D-0090
Draft Guidance for Industry on Adaptive Design Clinical Trials for Drugs and Biologics

Dear Sir or Madam,

Reference is made to the 26th February 2010 Federal Register notice (Vol. 75, No. 38) announcing the request for comments on the **Draft Guidance for Industry on Adaptive Design Clinical Trials for Drugs and Biologics**.

Adaptive Plus, LLC has reviewed this guidance, and tabulated comments are attached.

Adaptive Plus, LLC appreciates the opportunity to comment on the draft guidance. We would also be pleased to provide any further clarification of these comments if requested.

Sincerely,

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COMMENTS ON DRAFT Guidance for Industry - Adaptive Design Clinical Trials for Drugs and Biologics

Docket number: FDA-2010-D-0090

COMMENTS FROM: Jonathan R. Smith, Ph.D., Vice President, Adaptive Trial Design, Adaptive Plus, LLC

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GENERAL COMMENTS

This Adaptive Design draft guideline is well-written, very clear, and comprehensive. The authors are to be congratulated on putting together this detailed document, which in addition to providing guidance, should also serve as a very useful educational tool on Adaptive Design.

It would be difficult for the guideline to cover in detail programs with more than one adaptive design because there would be so many different combinations of design types that could be considered together. It would though seem to be helpful if a few more general statements could be made on considerations in such cases.

The guidance does already address one particular aspect of the passing of information between trials, i.e., it does already cover (lines 553-587) considerations when modifying an adaptive trial after receiving information external to the current trial (which therefore covers the case where the information is obtained from another adaptive or non-adaptive trial within the same program).

The guidance though does not cover the converse of this situation, i.e., it does not cover the impact on the sending trial when passing information from one adaptive trial to another trial (adaptive or non-adaptive) within the same program. A common example (as covered in Bretz & Wang, 2010, Drug Information Journal 44: 333, design D.1) is where one adaptive trial starts with 2 (or more) doses and placebo, then continues with 1 dose and placebo after an interim is used to select the stage 2 dose; this selected dose is then also to be used in a single two-arm (single dose arm) A&WC trial. It would be helpful if the guidance could include a few key considerations (for the sending trial) to maximize regulatory acceptability for cases such as this.

One type of adaptive design that would seem useful to cover in the guideline is where (for qualifying indications) a single design is to be used to seek Accelerated Approval (on a surrogate endpoint) at an interim analysis, and the same design is also used to obtain Full Approval (on the clinical endpoint) at a later look. Such an approach is becoming more common in certain oncology indications and of course has been used historically for many years in the HIV area. In their simplest formulation such designs could perhaps be included under "Generally Well-Understood", although certain variants (e.g., allowing an increase in numbers of events based on the interim effect size) may be of the "Less Well-Understood" type.

From reading the guidelines it may be that some sponsors will be reluctant to consider the use of "Less Well-Understood" designs in any A&WC trials, even where this would have given large gains and where it could have met all criteria/considerations covered in this document. Also, as mentioned at the March 26th conference some adaptive designs (e.g., selection of best dose in a seamless Phase II/III design, and many types of adaptations based on interim effect size) are "less far out there". In view of this, it would seem helpful if some statements could be included in the guideline which make it clear that such designs are not discouraged for A&WC trials.
At several places within the guideline the SAP is mentioned as the place to include full details on the adaptations, as well as possibly the place to include the Clinical Trial Simulation Report. As covered within the PhRMA Adaptive Design Working Group's paper on "Good Adaptive Practices" which appeared in the Drug Information Journal, the audience for the Clinical Trial Simulation Report will often be very different from the audience for the SAP, and they also recommend including full details on adaptations (particularly those that would impact trial integrity) in an IRB supplement (rather than in the protocol). Rather than mentioning "SAP" as the place to include full details on the adaptations and the Simulation Report, it would seem useful for the guidance to clarify that these details could be included in stand-alone documents that will undergo regulatory review.
The categorization of methods into "Generally Well-Understood" and "Less Well-Understood" is a reflection of the FDA's experience with the methods as of 2010. However, of course with time many methods (particularly those such as selection of best dose in a seamless Phase II/III, and many types of adaptations based on interim effect size) will become more "Well-Understood". It would therefore seem very useful if there could be a mechanism put in place to be able to promote methods from "Less Well-Understood" to "Generally Well-Understood".
For the "General References" section some readers may infer (wrongly) that methods covered in all papers cited here are acceptable, whereas the methods covered by papers not cited would not be acceptable. Also of course, new and better methods will likely be developed in the future, but are not able to be included here. One solution to avoid such problems might be to provide clarifying text at the start of the references section with these qualifiers. Another option would be to only include papers cited within the body of the guidelines.
The topic of analysis with and without over-run patients has not been covered, but this impacts designs with early stopping (including group-sequential designs) and designs with dose (or sub-population) selection. It would seem useful to provide a few statements so that any adaptive designs that would be affected by over-runs are set up in a such a way as to maximize regulatory acceptability.

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE: V. GENERALLY WELL-UNDERSTOOD ADAPTIVE DESIGNS WITH VALID APPROACHES TO IMPLEMENTATION		
Line Number	**Comment and Rationale**	**Proposed change (if applicable)**
652-666	The sentence in lines 663-665 covers studies with a time-to-event primary endpoint and describes continuing patient enrolment until a prospectively specified number of events has occurred. This may not be practical in many cases as events will often not occur early enough (relative to enrolment rate). This design may also not be preferred if the proportional hazards assumption is not satisfied, e.g., if either an early treatment effect wears off, or if treatment effect does not fully manifest itself until after the first few months. In such cases it would seem to generally be advantageous to have a higher average treatment duration than would be provided by the design described in lines 663-665. While certain sections of the preceding paragraph (lines 652-661) apply not just to binary endpoints, but also apply to time-to-event endpoints (increasing number of patients and/or increasing required number of events), this is not made explicit.	Within the paragraph covering lines 652-661, it would be very useful to explicitly cover time-to-event endpoints as well as binary endpoints, and to define the more usual approach to event-driven studies, i.e., enrol X patients then continue until Y events have occurred. For lines 663-666 it would seem advantageous in sentence 1 to delete "an event-driven study)", and to delete sentence 2, as this will have been discussed or defined in the preceding paragraph (if the suggestion given above was able to be incorporated). It would also seem advantageous to add qualifiers to the remaining part of lines 663-666, including "provided non-proportionality of hazards is not anticipated", and "when events are expected to occur very early relative to the enrolment rate".
794-797	The statement "it is important to adhere..., terminating the group if a futility criterion is met" and then "..confounding interpretation of the study results" could be argued to only apply if a binding futility rule is assumed when showing that the boundary for early demonstration of efficacy gives overall control of T1E. If instead a non-binding futility rule is assumed, then over-riding the futility boundary should not present interpretation difficulties.	After "futility criterion met" insert "(where this was assumed to be binding and so was used in Type 1 Error calculations)".

GUIDELINE SECTION TITLE: VI. ADAPTIVE STUDY DESIGNS WHOSE PROPERTIES ARE LESS WELL UNDERSTOOD		
Line Number	**Comment and Rationale**	**Proposed change (if applicable)**
Lines 905-1021, but particularly lines 934-939	In lines 934-936 it is stated that "The number of dose groups is adaptively decreased during the course of the study", but this pruning approach is not the only approach in exploratory dose-selection trials, and is likely not the preferred approach - see PhRMA Adaptive Dose-Ranging Studies Working Group's papers on this topic, i.e., Bornkamp et al (2007) (your reference on lines 1824-7) and Dragalin et al (2010) (to appear in Statistics in Biopharmaceutical Research). In practice, even though a dose has less than maximal efficacy it can still be advantageous to randomize some patients to it where this dose provides valuable information for fitting a dose-response model and for estimating quantities of interest (e.g., MED, EDγ) within model-based exploratory dose-ranging studies. In lines 937-938, the first part of this sentence ("Many adaptive study designs...uninformative doses") is also related to pruning approaches and so similar comments would apply. A further point is that it is difficult to discuss approaches for exploratory adaptive dose-ranging studies without having first discussed response-adaptive randomization. It would also seem useful to split the section "Adaptations for Dose Selection Studies" into separate sub-sections for Exploratory and AW&C trials because many of the considerations here only apply to one of these two types of trials.	Suggest re-ordering so that Section B (Adaptive Randomization, currently starting on line 975) appears before Section A (Adaptations for Dose Selection Studies, currently starting on line 905) Suggest re-ordering paragraphs in lines 933-943 and lines 945-952 so that the model-based approach is discussed first. Lines 934-5, suggest replacing "The number of dose groups is adaptively decreased during the course of the study" by "The proportion of patients randomized to individual dose groups is adaptively modified during the study so as to provide maximal information on the quantities of interest (e.g., MED, EDγ) from one or more dose-response models." Lines 937-939, suggest replacing sentence "Many adaptive...is also possible" by "Many exploratory adaptive dose-response study designs only use the doses that were considered at the start of the study, but addition of new, potentially more preferable doses is also possible." Section A (Adaptations for Dose Selection Studies, suggest splitting into separate sub-sections for Exploratory and AW&C trials.
945-952	"Five to seven" doses is mentioned on line 946, but there can be advantages to consider more than seven doses, particularly when the position of the dose-response curve is less clear. In lines 946-950 two objectives are mentioned, but it is the latter (optimizing selection of doses for evaluation in subsequent A&WC studies) that would generally be the most important, and so it would	Line 946, suggest changing "moderate number of doses (five to seven)" to "greater number of doses (five to nine) than considered in most past dose-ranging studies" Line 946, suggest changing "with the objective of identifying" to "with a secondary objective of identifying". Line 948, suggest changing "as well as optimizing the selection of two or three doses" to "and with a primary

	seem useful to stress this point. Also, such designs will often have a further primary objective of detecting a dose-response. In addition, in most cases it would seem sufficient to select "one or two" doses (rather than "two or three") in A&WC trials, particularly if the improved approaches (as described here) would now be used in Phase II.	objective of selection of one or two doses. Such designs may also have a further primary objective of detecting a dose-response."
980	Play the winner, has many known problems, and so it would seem preferable to not give this as an example of "outcome dependent randomization".	
1039-1041	The text mentions (in relation to timing of interim analysis based on the interim observed effect size) "using this approach late in the study is not advisable because a large percentage increase in sample size at that point is inefficient". However, from a statistical efficiency perspective it can be shown that it is actually preferable to carry out this interim analysis at a very late stage. If such a look is too early the estimate will be very highly variable, and when it occurs very late the chance of increasing sample size when it is not really necessary is reduced. From a logistical and timeline perspective, extra sites may need to be opened after any sample size increase to save time (rather than just continuing enrolling at the existing sites only). In practice therefore, the time of the interim would need to balance the statistical efficiency and the logistical efficiency.	Suggest replacing the sentence "In general, using this approach late in the study is not advisable because a large percentage increase in sample size at that point is inefficient" by "The interim time at which this approach is applied needs careful assessment, as it will need to balance statistical efficiency, as well as logistical considerations related to opening up new sites, etc."
1045-1047	When referring to methods for modifying the sample size of the trial it is commented that "these methods frequently are based on conditional power or predictive power". It is well known that conditional power can be highly variable, particularly at early looks, and predictive power will also be moderately variable at early looks. It would seem useful to emphasize here again this high variability, particularly for conditional power. Also, to be consistent with the later section (lines 1269-1287) on "Potential for Increased Type II	After "...conditional power or predictive power." on lines 1046-1047 suggest inserting: "The high degree of variability in conditional power, particularly at early looks, needs to be taken into consideration when developing such rules. It is also important to assess the overall impact on Power/Type II Error Rate that is obtained from such adaptation rules."

	Error Rate", it would seem useful to re-iterate here the need to also consider overall power when assessing the success of adaptations based on conditional power or predictive power.	
1054-1055	As shown by Chen, DeMets, & Lan (2004), and by Gao, Mehta, & Ware (2008) it can in certain cases be possible to test at the nominal α-level, and still control the experimentwise T1E at this desired level.	Suggest changing sentence on lines 1054-1055 from "To protect against such an increase..." to "In general to protect against such an increase..."
1058-1060	The method referred to here (combining "aspects of both alpha adjustment and weighting adjustment") is not fully clear. It appears to be referring to the Burman & Sonesson (2006) approach but it would seem useful to modify the sentence to make this explicit.	

GUIDELINE SECTION TITLE: VII. STATISTICAL CONSIDERATIONS FOR LESS WELL-UNDERSTOOD ADAPTIVE DESIGN METHODS		
Line Number	**Comment and Rationale**	**Proposed change (if applicable)**
1233-1238	This paragraph covers bias rather than Type 1 Error, and so it would seem clearer to move this to the "Bias" section starting at line 1248.	
1240-1246	This paragraph is somewhat hard to understand, and it would seem helpful to add some further clarifications. Also, as it is covering both statistical bias and operational bias it would seem useful to not use "bias" without a prefix (of "statistical" or "operational") because otherwise the meaning is not fully clear. As the focus is bias it would seem useful to move this paragraph to the "Bias" section starting at line 1248. It would also be useful to add clarifying text on exactly how the bias (whether statistical or operational) can impact the type 1 error.	

1341-1342	This sentence mentions that "Using simulations to demonstrate control of the Type 1 error rate...is controversial...", but it would seem useful to qualify this by mentioning situations where this would not be controversial. In certain situations where results cannot be obtained analytically (nor able to be obtained by numerical integration), and where the full Type 1 Error space (i.e., the global null hypothesis and all partial null hypotheses) can be defined, then simulations could be carried out to demonstrate full Type 1 error control to 3, 4, or even to 5 decimal places.	Suggest replacing sentence "Using simulations... not fully understood." by "In certain situations where Type 1 error control cannot be demonstrated analytically, but where the full Type 1 Error space (i.e., the global null hypothesis and all partial null hypotheses) can be defined, then it may be possible with simulations to demonstrate full Type 1 error control. However, in more complicated situations using simulations to demonstrate control of the Type 1 error rate, is controversial and not fully understood."

GUIDELINE SECTION TITLE: VIII. SAFETY CONSIDERATIONS IN ADAPTIVE DESIGN TRIALS		
Line Number	**Comment and Rationale**	**Proposed change (if applicable)**
1451-1459	Another important consideration related to safety for adaptive designs (including for group-sequential designs) is that with any adaptive design which may trigger a regulatory submission after stopping early, it is important to ensure that the total size of the safety database will then be sufficiently large at that stage.	

GUIDELINE SECTION TITLE: IX. CONTENT OF AN ADAPTIVE DESIGN PROTOCOL		
Line Number	**Comment and Rationale**	**Proposed change (if applicable)**
1508-1509	The sentence states that "In general, the study design should be planned in a frequentist framework to control the overall study Type I error rate." It would seem useful to clarify which parts of this sentence apply to Exploratory trials, to AW&C trials, or to both. This statement could be argued (at present) to be necessary only for AW&C trials, because it would seem acceptable for Exploratory trials to be planned in a Bayesian framework. Also, while advisable to quantify Type 1 error rate in Exploratory trials it could be argued that this is not necessary in such cases.	
1509-1512	This sentence states that "A Bayesian framework that incorporates uncertainty into planning parameters in a quantitative manner (i.e., prior distributions on parameters) can also be useful for planning purposes...". However, the incorporation of uncertainty in values of parameters may also very usefully be taken into account by measures such as Average Power (with averaging over a distribution on the effect size).	Within lines 1510-1511 suggest changing "(i.e., prior distributions on parameters)" to "(i.e., based on formal prior distributions for parameters, or by averaging power over a distribution for the parameters)"