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ADAPTIVE DESIGNS IN CLINICAL DRUG DEVELOPMENT—AN EXECUTIVE SUMMARY OF THE PhRMA WORKING GROUP

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A PhRMA Working Group on adaptive clinical trial designs has been formed to investigate and facilitate opportunities for wider acceptance and usage of adaptive designs and related methodologies. A White Paper summarizing the findings of the group is in preparation; this article is an Executive Summary for that full White Paper, and summarizes the findings and recommendations of the group. Logistic, operational, procedural, and statistical challenges associated with adaptive designs are addressed. Three particular areas where it is felt that adaptive designs can be utilized beneficially are discussed: dose finding, seamless Phase II/III trials designs, and sample size reestimation.

Key Words: Data Monitoring Committee; Dose finding; Interim analysis; Seamless Phase II/III design; Sample size reestimation.

1. BACKGROUND

A PhRMA Working Group on novel adaptive clinical trial designs was formed in the spring of 2005. The objectives of the group were to foster and facilitate wider usage and regulatory acceptance of adaptive designs to enhance clinical development, through fact-based evaluation of the benefits and

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challenges associated with these designs. An extensive White Paper presenting the investigations and findings of the group is in preparation. This manuscript is an Executive Summary for the White Paper, prepared by a writing group drawn from the full Working Group. The writing group acknowledges the contributions and participation of the following group members and consultants who have assisted in this effort: Keaven Anderson, Alun Bedding, Don Berry, Suman Bhattacharya, Sylva Collins, David DeBrota, Jeff Maca, Cyrus Mehta, Alan Pallay, Inna Perevozskaya, Judith Quinlan, Jerald Schindler, Gernot Wassmer, and Pauline Williams.

2. INTRODUCTION

By *adaptive design* we refer to a clinical study design that uses accumulating data to decide how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial. The goal of adaptive designs is to learn from the accumulating data and to apply what is learned as quickly as possible. In such trials, changes are made "by design," and not on an ad hoc basis; therefore, adaptation is a *design feature* aimed to enhance the trial, not a remedy for inadequate planning. Greater flexibility within the adaptive design framework can translate into better treatment of patients within trials (possibly including the use of fewer patients), more efficient drug development, and better use of available resources. We endorse routine consideration of adaptive designs for clinical trials and encourage critical evaluation of when and where they can be appropriately deployed.

Our objective is to facilitate wider usage of adaptive designs. Although these designs offer great opportunities, we acknowledge that challenges exist, both genuine and perceived, which must be overcome before this wider usage can become a reality. In this article, we address statistical, logistical, and procedural issues associated with adaptive designs and focus on three particular applications where we believe it is feasible to overcome the challenges and implement these approaches more broadly and with maximal impact: 1) adaptive dose finding, 2) seamless Phase II/III designs, and 3) sample size reestimation.

3. ISSUES AND RECOMMENDATIONS

3.1. Statistical Issues

Statistical issues that are generally relevant to the implementation of adaptive designs include the following:

- The statistical methodology supporting adaptive designs is highly developed (e.g., Berry, 2004; Brannath et al., 2002; Liu et al., 2002; see also *Journal of Biopharmaceutical Statistics* Special Issue on Adaptive Design in Clinical Research, 2005).
- The key statistical issue in most contexts is preservation of the Type I error rate; related issues of statistical inference have been solved broadly (Bauer and Köhne, 1994; Cui et al., 1999; Lehmacher and Wassmer, 1999; Müller and Schäfer, 2001; Proschan and Hunsberger, 1995).

- Issues of treatment effect estimation and confidence interval coverage have not been fully resolved for some adaptive designs in the frequentist paradigm. There is ongoing research in this area (e.g., Brannath et al., 2003).
- In theory, it is possible to allow for maximal flexibility in adapting aspects of the trial to incoming data (Bauer and Brannath, 2004) while controlling the Type I error. Our recommendation, however, is to specify the scope of possible adaptations and decisions prospectively. This will facilitate the interpretation of the findings and acceptance of inferences drawn from the adaptive designs.
- We support in principle the deployment of algorithms recommending adaptation treatment allocation or when to terminate a trial, as long as 1) the behavior of the algorithm is sufficiently well understood, either analytically or through simulations, and 2) its performance is monitored by a qualified monitoring committee during the course of the trial.
- We encourage the exploration of both frequentist and Bayesian approaches.

Clearly, there is no single approach for designing an adaptive trial. In all cases, the objectives of the adaptation should be clearly defined (e.g., to reduce exposure of patients to nonefficacious doses or to ensure that the sample size is sufficient to address trial objectives), and the operating characteristics of the design and methodology chosen should be well understood.

3.2. Logistical Issues

Logistical issues and challenges relevant to most effectively implementing adaptive designs include the following:

- Adaptive designs require rapid data collection to fully take advantage of the efficiencies they offer. This is best achieved if study endpoints (or other outcomes on which adaptations might be based) have short follow-up time relative to the overall duration of the trial and if data accrual can occur in real time, or at least in a timely fashion.
- We recommend electronic data capture with a goal of timely data collection and query resolution wherever possible.
- Although databases of high quality are clearly desirable, adaptations may not require fully cleaned data sets. We recommend assessing on a case-by-case basis the degree to which adaptation decisions could be suboptimal if based on data that are not fully cleaned and weighing this against the benefits of making those decisions using all available data. This will help to decide how to most efficiently make use of the information available at the time of an adaptation.
- Optimal implementation of adaptive designs will require the integration of data capture, drug supply management, and an interactive communication system between patients/investigators/study sites and the randomization center.
- Statistical methods for the design and analysis of adaptive designs are often technically and computationally more complex than those associated with conventional designs. Customized software programs may be required. The availability of additional commercial software solutions for design and analysis will reduce development and implementation times.

3.3. Procedural Issues

The procedures to be followed relating to data review, decision making, and implementation of decisions during adaptive trials while maintaining trial integrity are particularly important. We recommend the following procedural guidelines:

- Following current conventions for interim data monitoring, trial integrity and optimal interpretability of results are best ensured if interim results are reviewed by a Data Monitoring Committee (DMC), adequately "firewalled" from project personnel (sponsor, investigators) (U.S. Food and Drug Administration, 2005). Their data review is strictly confidential, and the reporting structure of the DMC to Steering Committee and sponsor is prospectively defined.
- Adaptations may involve decisions beyond the typical scope of DMC decisions, and it should be considered whether the monitoring board should be augmented with individuals with additional expertise relevant to the type of decisions to be made, including reviewing adaptation algorithms' performance and approving changes if necessary.
- Unlike most conventional monitoring of ongoing trials, in some adaptive designs, there may be a need for sponsor representation in the process due to the nature of the adaptation decisions being made, particularly when there are critical business implications. We believe that this can be accomplished without compromising the integrity of the trial, by implementing appropriate safeguards:

  1. Particular to the situation, a rationale or justification should be able to be described by which sponsor representation or sponsor ratification of a DMC recommendation is necessary because of the complex nature of the decision and/or business implications.
  2. The sponsor personnel who will have access to or knowledge of interim results are adequately distanced from all trial activities, and all involved understand the potential negative implications for the trial if information is inappropriately disseminated or acted on.
  3. Sponsor access to interim data is "minimal" to meet the needs (i.e., the smallest number of sponsor representatives needed to provide the necessary perspectives is involved, they see only the information needed for decisions, only at prespecified time points, etc.).

- Adaptations can have some potential to convey some knowledge to observers who see the actions that are taken based on the interim results. This issue is not unique to adaptive designs, as many conventionally accepted monitoring practices convey some such information (i.e., all monitoring presumably has some action thresholds, whether implicit or explicit, and lack of action can often be interpreted by observers to imply that those thresholds have not been met). Particular adaptations should be evaluated to see if they are acceptable in this regard. The standard should be the same as for conventional monitoring: is the information conveyed limited, and with minimal apparent potential for compromising the trial, so that the benefits of the adaptive design outweigh any such concerns?
- We believe that *selection* decisions (e.g., dose, patient population, etc., for continuation in a trial, as might be made in a seamless Phase II/III design) or other adaptations that may indicate a comparative direction of effect (but not specific numerical results) are generally acceptable in this regard.

- Steps should be considered in study design or protocol development to limit the amount of information that can be inferred by observers (e.g., withholding from the protocol and documenting elsewhere some statistical details governing the adaptations, "discretizing" adaptations so that they are less directly related to interim results, etc.).

4. OPPORTUNITIES AND RECOMMENDATIONS

4.1. Adaptive Dose Finding

Conventional dose-finding designs explore only a few doses of a drug in a fixed parallel group study, because of the relatively large sample sizes required to estimate pairwise differences. The doses selected for investigation may not be highly informative unless they are correctly prospectively selected in strategic locations along the true (unknown) dose-response curve. In contrast, adaptive trial designs provide opportunities to characterize the dose response more fully and efficiently. Adaptive approaches facilitate iterative learning and confirming within the trial, allowing the sponsor to optimize dose assignments of future patients to best answer the research questions of interest. Sponsors can also improve patient care within an adaptive design trial by implementing appropriate early stopping rules and adaptive treatment allocation schemes, thereby limiting patient exposure to unsafe or ineffective doses and increasing exposure to more effective doses.

The gains in efficiency make it more feasible to explore the dose response earlier in the course of clinical drug development, and this will enable better data-driven decisions. Ineffective therapies could be discontinued earlier with more confidence, and the late stage attrition rate, currently estimated at 45% in Phase III (Kola and Landis, 2004), could be reduced by facilitating the right dose or doses being taken forward in confirmatory trials. Better characterization of the dose response could also yield important dosing information to clinicians and patients at the time of launch.

To fully realize these potential gains for clinical development, we recommend the following:

- Routinely consider adaptive dose-finding designs in exploratory drug development. Evaluate whether an adaptive approach may have superior performance over a traditional fixed approach (Berry et al., 2002; Krams et al., 2003; Rosenberger and Haines, 2002; Whitehead et al., 2001). The operating characteristics of the design chosen should be well understood under a range of possible true states of nature.
- Whenever possible, use a model-based approach. Model-based approaches are typically more efficient than conventional multiple-comparison approaches and can provide more information across the full dose range.
- Consider Bayesian approaches, which are well suited for model-based adaptive designs. Bayesian models can directly incorporate historical information and auxiliary endpoints to increase efficiencies. Frequentist operating characteristics (e.g., control of the Type I error rate) can also be incorporated. Because Bayesian inferences are based on the posterior distribution of the parameter of interest and not on the frequency of certain outcomes occurring in repeated experiments, they

are ideally suited for *seamless* phase transitions (see below). In addition, Bayesian predictive probabilities directly quantify future uncertainties of interest and are, therefore, easily interpretable.
- Prospectively define the dose assignment mechanism, regardless of the methodology used. This will serve to minimize bias, enhance the integrity of the trial, and maintain the validity of inferences.
- The study must be monitored on an ongoing basis. It is not always possible to anticipate all important outcome measures prospectively when defining the dose assignment mechanism. Monitoring will ensure that the algorithm is performing as expected and that all relevant information is appropriately taken into account when assigning doses. The monitoring committee should be engaged in various scenario simulations prior to the start of the study to clarify and assist with the monitoring efforts.
- Consider extending an adaptive dose-finding trial *seamlessly* into a confirmatory phase for additional gains in efficiencies (see below).

4.2. Seamless Phase II/III Designs

By a *seamless Phase* II/III *trial design*, we refer to a program that addresses within a single trial objectives that are normally achieved through separate trials in Phases IIb and III. Specifically, the initial *learning* phase of such a trial is designed to lead to a selection decision of the type normally associated with Phase IIb; most typically, this type of design might involve a control group and some number of dose groups, and one or more of these doses (along with the control) are chosen to continue into the *confirmatory* phase. [Other types of selection can also be accommodated (e.g., a specific patient population may be selected to continue into the confirmatory phase)]. In a seamless design, the trial continues through the selection point and into the confirmatory phase for the cohorts that are chosen to continue. The statistical inference for the selected dose(s) at the end of the confirmatory phase uses all data from the relevant cohorts from both phases of the trial, with appropriate statistical methodology to avoid inflation of the Type I error rate or selection bias.

We believe that substantial benefits can be offered by such designs relative to the conventional separate-phase paradigm, including:

- Potentially substantial time savings.
- The use of fewer patients to achieve the same quality of evidence.
- An opportunity to have obtained longer-term follow-up data by the end of the confirmatory phase (from continued observation of learning phase patients).

Attributes of programs that would lend themselves to these types of designs and in which we recommend that they be strongly considered, include:

- The design of the confirmatory phase of the trial can be firmly envisioned, apart from the selection decision to be made at the end of the learning phase; this includes the appropriateness of the endpoint and determination of the final market image of the investigational product.
- Follow-up time to the endpoint (or to a good surrogate on which the selection decision can be based) is short relative to the duration of the trial.

Because these trials provide confirmatory data, it is critical that the processes for data review, decision making, and implementation be carefully specified and adhered to. In particular, to maintain the integrity of the trial results, interim results must be reviewed confidentially by a designated board without other trial responsibilities. As alluded to above, we believe that at times the nature of the trial and selection decision may justify sponsor participation in this process. We believe that with careful planning and understanding of the various roles and responsibilities involved, this can be achieved without compromising the integrity of the trial.

4.3. Sample Size Reestimation

The number of patients to be enrolled into a clinical trial [or, more generally, the planned amount of information (e.g., target number of events, follow-up period)] is generally determined in a manner that makes assumptions based on the knowledge available at the time of trial design. Ultimately, it is only within the setting of the trial itself that the correctness of those assumptions will be confirmed or refuted. In the interest of ensuring that trials are neither overly large, and thus exposing more patients than needed and wasteful of resources, nor too limited to adequately address their objectives, this leads to a motivation to allow potential revision of the amount of information collected, as long as this can be done in a manner that does not compromise the integrity of the trial or interpretability of its results. Parameters on which sample size reestimation might be considered include:

- So-called "nuisance" parameters, most commonly an estimate of variability for continuous data or an underlying event rate for binary data
- The treatment effect to be detected; however, this quantity often is not an assumption in the same sense as a nuisance parameter; it will generally have an interpretative meaning apart from any assumptions about its value (e.g., it must be clinically and commercially meaningful).

We recommend the following guidelines for sample size reestimation:

- The need for sample size reestimation should be carefully evaluated during trial planning, and the extent to which it is planned to reevaluate sample size should be described in the protocol. Sample size reestimation should never be a substitute for adequate up-front planning; rather, it is an acknowledgment of potential limitations of the information available at the time of trial design.
- These methods should generally be implemented minimally within the trial as needed to achieve a more satisfactory sample size. A single reevaluation may suffice, particularly for nuisance parameters. If a minimum sample size has been prespecified, then it will often be sensible to perform the reestimation shortly before reaching that minimum enrollment.
- Logistic concerns must be adequately planned for in advance, such as the potential need for additional drug supply if the sample size is increased.
- Where relevant, consider whether to withhold from the protocol and document elsewhere details of the reestimation procedure, to decrease the amount of information that observers can infer from any changes made to the sample size.

- We recommend that sample size reestimation based on nuisance parameters should be routinely considered, particularly when there is a good deal of uncertainty about those parameters or the sample size is very sensitive to initial assumptions. Frequently, this can be addressed sufficiently well in a blinded manner (Kieser and Friede, 2003), and this should often be the recommended approach, because reestimation can then be implemented in a manner that does not compromise the trial and which minimizes operational difficulties.
- Methods exist for sample size reestimation based on updated information on treatment effects obtained at interim analyses (e.g., Cui et al., 1999) and these can be considered.
- However, such methods must be applied cautiously. They can introduce operational biases because 1) they may provide to observers an unacceptable amount of information about the interim effects; 2) different values of the treatment effect may not be of the same level of clinical or commercial relevance; or 3) interim estimates are often too imprecise to be used efficiently in this regard (Jennison and Turnbull, 2003).
- As an alternative, it should be strongly considered whether an appropriate group sequential scheme as a method of sample size determination could better meet the study objectives, as operational concerns are minimized and statistical behavior is often superior (Tsiatis and Mehta, 2003).

5. CONCLUSION

In the discussion above, we have focused on specific types of trial designs and adaptation schemes in which we believe that the challenges to broader acceptance and implementation can be overcome, so that the advantages offered by those designs can be achieved. Assisted by experience gained in actual trials and programs, we expect that methods and procedures can continue to evolve, so that these types of designs will offer even greater ethical and efficiency benefits for clinical drug development. We encourage the relevant parties in industry, the regulatory arena, and academia to continue to engage in discussions to pave the way for increased implementation of advantageous clinical trial designs.

REFERENCES

Bauer, P., Köhne, K. (1994). Evaluation of experiments with adaptive interim analyses. *Biometrics* 50:1029–1041. Correction: *Biometrics* (1996) 52:380.

Bauer, P., Brannath, W. (2004). The advantages and disadvantages of adaptive designs for clinical trials. *Drug Discov. Today* 9:351–357.

Berry, D. A. (2004). Bayesian statistics and the efficiency and ethics of clinical trials. *Stat. Sci.* 19:175–187.

Berry, D. A., Mueller, P., Grieve, A. P., Smith, M. K., Parke, T., Krams, M. (2002). Bayesian designs for dose-ranging drug trials. In: Gatsonis, C., Kass, R. E., Carlin, B., Carriquiry, A., Gelman, A., Verdinelli, I., West, M., eds. *Case Studies in Bayesian Statistics*. Vol. 5. New York: Springer-Verlag, pp. 99–181.

Brannath, W., Posch, M., Bauer, P. (2002). Recursive combination tests. *J. Am. Stat. Assoc.* 97:236–244.

Brannath, W., König, F., Bauer, P. (2003). Improved repeated confidence bounds for one sided flexible group sequential designs. *Biom. J.* 45:311–324.

Cui, L., Hung, H. M. J., Wang, S. J. (1999). Modification of sample size in group sequential clinical trials. *Biometrics* 55:853–857.

Jennison, C., Turnbull, B. (2003). Mid-course sample size modification in clinical trials based on the observed treatment effect. *Stat. Med.* 22:971–993.

Kieser, M., Friede, T. (2003). Simple procedures for blinded sample size adjustment that do not affect the type I error rate. *Stat. Med.* 22:3571–3581.

Kola, I., Landis, J. (2004). Can the pharmaceutical industry reduce attrition rates? *Nat. Rev. Drug Discov.* 3:711–716.

Krams, M., Lees, K. R., Hacke, W., Grieve, A. P., Orgogozo, J. M., Ford, G. A. (2003). ASTIN: An adaptive dose-response study of UK-279,276 in acute ischemic stroke. *Stroke* 34:2543–2548.

Lehmacher, W., Wassmer, G. (1999). Adaptive sample size calculations in group sequential trials. *Biometrics* 55:1286–1290.

Liu, Q., Proschan, M. A., Pledger, G. W. (2002). A unified theory of two-stage adaptive designs. *J. Am. Stat. Assoc.* 97:1034–1041.

Müller, H. H., Schäfer, H. (2001). Adaptive group sequential designs for clinical trials: Combining the advantages of adaptive and of classical group sequential approaches. *Biometrics* 57:886–891.

Proschan, M. A., Hunsberger, S. A. (1995). Designed extension of studies based on conditional power. *Biometrics* 51:1315–1324.

Rosenberger, W. F., Haines, L. M. (2002). Competing designs for phase I clinical trials: a review. *Stat. Med.* 21:2757–2770.

Special Issue on Adaptive Design in Clinical Research (2005). *J. Biopharm. Stat.* 15(4).

Tsiatis, A. A., Mehta, C. (2003). On the inefficiency of the adaptive design for monitoring clinical trials. *Biometrika* 20:367–378.

U.S. Food and Drug Administration (2005). *Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees* (Draft). Rockville, MD: FDA. (Available at http://www.fda.gov/cber/gdlns/clintrialdmc.htm)

Whitehead, J., Zhou, Y., Patterson, S., Webber, D., Francis, S. (2001). Easy-to-implement Bayesian methods for dose-escalation studies in healthy volunteers. *Biostatistics* 2:47–61.