Pharmaceutical Consultant on Adaptive Clinical Trial Design in 2016

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What is an Adaptive Clinical Trial?

Clinical trial consulting and pharmaceutical consulting professionals will benefit by becoming current on adaptive trial design. Gaining in popularity since the early 1990s,[1] adaptive trials are those which observe patient outcomes after review of interim data and accommodate modifications to trial and/or statistical procedures.[2] [3] [4] Compare such trials to traditional fixed designs in which all key parameters are defined prior to patient enrollment and held constant throughout.[5] Modifications in adaptive trial parameters include such variables as dosage, sample size, drug undergoing trial, and patient selection criteria.[6] Chow & Chang describe three categories based on applied adaptations. These include prospective, concurrent (ad hoc), and retrospective designs.[7]

Current guidance (described below) addresses prospective models of adaptive clinical trials. Burnham, et. al. draw the distinction between prospective and other models by observing that prospective design does not include trials in which "ad hoc adaptations are made during the course of the trial. By contrast, these are predefined adaptations planned prior to study start." It is therefore important to note that adaptive clinical trials are not always adaptive by design.[8] The Bayesian statistical approach is commonly used in the prospective model to simulate adaptive variables during study design, based on the probability they may result in modification of trial parameters.[9] [10] [11] Regardless of the model to be employed, early stage evaluation of the appropriateness of adaptive design is a worthwhile endeavor that should include the perspective of clinical, statistical, regulatory and operational stakeholders.[12]

Adaptive Clinical Trial Advantages & Disadvantages

Adaptive clinical trials enjoy several advantages. For example, many treatment arms may be studied at the same time, whereas classical fixed trials are not often ideal for more than two or three arms.[13] There are situations in which Phase II and III may be combined into one trial.[14] Trial subjects may be studied more efficiently and in certain cases fewer will receive ineffective medications, ineffective doses or unnecessarily high doses. The flexibility to address unanticipated outcomes or events allows for changes in endpoints. Many compounds fail, and adaptive designs may also include mechanisms for earlier detection of futility. In the prospective design, the prespecified changes based on interim analysis may not require as many protocol amendments/IRB permissions as in concurrent/adaptive, retrospective/adaptive or traditional fixed designs. Adaptive trials may improve expected patient

[1] Adaptive design of confirmatory trials: Advances and challenges, Lai, et. al., Contemporary Clinical Trials 2015
[2] Effective Drug Supply for Adaptive Clinical Trials: Recommendations by the DIA Adaptive Design Scientific WorkingGroup Drug Supply Subteam, Burnham, et. al., Therapeutic Innovation & Regulatory Science 2015
[3] Clinical trialist perspectives on the ethics of adaptive clinical trials: a mixed-methods analysis, Legocki, et. al., BMC Medical Ethics 2015
[4] Draft Guidance for Industry Adaptive Design Clinical Trials for Drugs and Biologics, February 2010
[5] Ibid.@3
[6] Ibid.@1-4
[7] Adaptive design methods in clinical trials – a review, Orphanet Journal of Rare Disease, Chow and Chang 2008
[8] Ibid.@2
[9] Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials, February 2010
[10] Draft Guidance for Industry and Food and Drug Administration Staff Adaptive Designs for Medical Device Clinical Studies, May 2015
[11] Ibid.@7
[12] Good Practices for Adaptive Clinical Trials in Pharmaceutical Product Development, Biostatistics, Gaydos, et. al. 2009.
[13] Adaptive design clinical trials: Methodology, challenges and prospect, Mahajan & Gupta 2010 Indian Journal of Pharmacology
[14] Ibid.@13

outcomes, expedite completion of a trial, speed development and offer significant ethical and cost advantages over standard fixed procedures while still reaching valid statistical outcomes.[15] [16]

As one might imagine, there are also disadvantages associated with adaptive clinical trials. Prospective models reliance upon the Bayesian approach to statistical analyses can make it difficult to control type 1 error (erroneous efficacy).[17] Ad hoc changes, especially those resulting from review of un-blinded data may otherwise place the credibility of the study in jeopardy. Logistics such as drug supply become a concern when changes in treatment allocation must happen quickly without compromising the integrity of the blind.[18] Conduct of adaptive trials too early may also bring overall study findings into question.[19] FDA has encouraged the use of innovative clinical trial designs.[20] However, when presenting an adaptive design protocol to FDA for review, factors not previously accounted for will need to be described, such as certain operational logistics, simulations and comparison to other designs considered.[21]

Adaptive Trials Gaining Regulatory Acceptance

In recent years, adaptive trial designs have begun to gain more formal regulatory acceptance. In March 2004, FDA launched its Critical Path Initiative (CPI),[22] [23] describing a "widening gap between scientific discoveries that have unlocked the potential to prevent and cure some of today's biggest killers, such as diabetes, cancer, and Alzheimer's, and their translation into innovative medical treatments." The CPI proposed to address the most pressing development concerns with a focus on the "greatest opportunities for rapid improvement and public health benefits" through collaboration with the pharmaceutical industry, other government agencies and academia. Among the identified opportunities were streamlining of clinical trials including through adaptive trial designs.[24] [25]

By March 2006, FDA issued a follow-up to its 2004 report, [26] followed in December 2006 by a list of initiated critical path opportunities, including adaptive design.[27] The concept of adaptive trial design had clearly gained support among regulators and industry. Between 2005 and 2010 PhRMA facilitated a Working Group on adaptive clinical trial designs[28] that issued a "full white paper" in 2006.[29] In 2009, Gaydos, et. al. published Good Practices for Adaptive Clinical Trials in Pharmaceutical Product Development[30] and by February 2010, FDA issued Draft Guidance for Industry Adaptive Design Clinical

[15] Ibid.@ 1-3, 7, 13
[16] Speech before 2006 Conference on Adaptive Trial Design, Washington, DC Remarks by Scott Gottlieb, MD Deputy Commissioner for Medical and Scientific Affairs Food and Drug Administration July 10, 2006
[17] Ibid.@7
[18] Ibid. @ 2
[19] Ibid.@ 1-3, 7, 13
[20] Advancing Regulatory Science New Design and Analysis Tools for Randomized Trials, Michael Rosenblum Principal Investigator, Johns Hopkins Department of Biostatistics, Performer as accessed at www.fda.gov on October 13, 2015
[21] Ibid.@13
[22] Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products. FDA March 2004
[23] FDA's Critical Path Initiative as accessed at www.fda.gov on October 13, 2015
[24] Innovation/Stagnation: Critical Path Opportunities Report, FDA March 2006
[25] Critical Path Opportunities Initiated During 2006, FDA
[26] Ibid.@23
[27] Ibid.@25
[28] Viewpoints on the FDA Draft Adaptive Designs Guidance From the PhRMA Working Group, Journal of Biopharmaceutical Statistics, Gallo et. al. 2010
[29] Adaptive Designs in Clinical Drug Development – an Executive Summary of the PhRMA Working Group, Journal of Biopharmaceutical Statistics, Gallo et. al. 2006
[30] Ibid.@12

Trials for Drugs and Biologics.[31] The guidance addresses prospectively planned modifications of specified study aspects, usually based on interim data and includes topics such as:

(1) what aspects of adaptive design trials (i.e., clinical, statistical, regulatory) call for special consideration
(2) when to interact with FDA while planning and conducting adaptive design studies
(3) what information to include in the adaptive design for FDA review
(4) issues to consider in the evaluation of a completed adaptive design study

At about the same time (February 2010), FDA finalized Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials (The draft of this document was issued on 5/23/2006).[32] The Guidance notes that "the approach can accommodate adaptive trials (e.g., interim analyses, change to sample size, or change to randomization scheme) and even some unplanned, but necessary trial modifications."

This was followed in May 2015 by Draft Guidance for Industry and Food and Drug Administration Staff Adaptive Designs for Medical Device Clinical Studies.[33] Like the Drug and Biologic Guidance before it, the Device Guidance addresses prospectively planned modifications. The Guidance is applicable to PMAs, 510(k)s, de novo submissions, HDEs and IDE submissions. However, the guidance does not apply to clinical studies of combination products or development of a pharmaceutical product with an unapproved diagnostic test, although the underlying principles may be useful for such studies.

Despite the resources and attention devoted to adaptive design by FDA, and the potential cost savings to industry, adoption has not been widespread.[34] CRO adoption has been reported as "slowly shifting" [35] while "gaining acceptance."[36] In February 2013 The Tufts Center for the Study of Drug Development (CSDD) hosted a roundtable discussion comprised of opinion leaders including executives from disciplines such as clinical research and development, biostatistics, project management, and clinical operations, and received FDA and EMA perspectives as well. CSDD reported that adaptive designs were being used on approximately 20% of clinical trials and that adoption in exploratory phase trials was expected to increase significantly in coming years.[37]

Choosing the Right Adaptive Clinical Trial Expert

Adaptive clinical trial design has the potential to increase the chances of a successful drug or device development program, speed the time to market, and improve safety and efficacy for clinical trial volunteers. However, the increased complexity, required forethought and multi-disciplinary planning pose challenges not previously faced by many sponsors. Choosing the right adaptive trial consultant is a critical early consideration. Ideally, your consultant will have experience in the early-stage decision making processes involved in determining the appropriateness of adaptive design. Choose a team of scientists, regulatory professionals and statisticians with the requisite expertise who understand the increased operational demands of adaptive trial design. The team should also have experience in the design and execution of preclinical and clinical (Phases I-IV) programs, as well as proven methods to

[31] Ibid.@4
[32] Ibid.@9
[33] Ibid.@10
[34] Ibid.@1,2
[35] CROs Slowly Shifting to Adaptive Clinical Trial Designs, Zachary Brennan, June 2013, Chiltern Newsletter
[36] Implementing Adaptive Trial Design: Operational Considerations and the Role of the CRO. PPD 2012
[37] Tufts Center for the Study of Drug Development Tufts University: The Adoption and Impact of Adaptive Trial Designs, Getz & Kaitin 2013

select, validate, qualify CROs and provide oversight such that all constituencies are synchronized with regulatory and scientific strategies.

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