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Adaptive Trial Designs

*Maximizing the Use of Interim Data Analysis to
Increase Drug Development Efficiency & Safety*

SEPTEMBER 10-11, 2007, RADISSON-PLAZA WARWICK, PHILADELPHIA, PA

Featuring Case Studies and Lessons Learned from Industry Experts!

- Know when to use an adaptive vs. traditional design and address possible pitfalls for each type of design
- Understand what is necessary to obtain FDA buy-in to proposed study designs
- Know the associated costs and tackle difficulties that will be encountered with adaptive design implementation

Plus! Practical Considerations for Adaptive Trial Management & Logistics

- Assuring quality of field monitoring and availability of clinical trial supplies
- Refining operations strategy: enrollment, CRA time, site efficiency & performance

In-Depth Pre-Conference Workshop, Monday, September 10, 2007

**Lessons Learned from the Field:
Design, Planning and Implementation of over 300 Adaptive Trials**

Featuring Representation from Leading Companies:

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M.D. Anderson Cancer Center
University of Michigan
Merck Research Laboratories
Health Decisions, Inc.

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Monday, September 10, 2007

9:00

IN-DEPTH PRE-CONFERENCE WORKSHOP LESSONS LEARNED FROM THE FIELD: DESIGN, PLANNING & IMPLEMENTATION OF OVER 300 ADAPTIVE TRIALS

**Michael Rosenberg, MD, MPH, President and
CEO of Health Decisions, Inc.**

**Jim Box, Director of Information Systems,
Health Decisions**

This workshop addresses the strategic and practical aspects of conducting adaptive clinical research. Adaptive research is defined as ability to incorporate new information as it becomes available and make mid-course changes while a study is in progress.

Adaptive research has two components: strategic and tactical. Strategic aspects include elements such as sample size re-estimation, dose pruning, seamless phase II-to-phase III studies, change in allocation ratios, and similar strategies. The tactical side of adaptive involves tight study management by continuously monitoring a broad range of performance metrics as well as data in order to shorten enrollment optimally allocate resources, minimize queries, and minimize time to database lock and report production.

This session reviews experience with the design, planning, and running of more than 300 adaptive studies. Emphasis will be on:

- Incorporating strategic adaptive components in the program design
- Regulatory considerations
- Decision making
- Technology requirements
- How continuous decision making changes process
- Refining operations strategy: Enrollment, CRA time, site efficiency.

About your workshop leaders:

Michael Rosenberg, MD, MPH, has been involved with the strategic design and execution of pharmaceutical development programs for more than 25 years. He is President and CEO of Health Decisions, Inc., a leader in the application of adaptive principles to improve the efficiency of the clinical research process. Health Decisions

has won numerous awards for growth and innovative technology, including Dr. Rosenberg's selection as Ernst and Young's Entrepreneur of the Year. He has been involved with the design, conduction, and reporting of more than 300 clinical studies spanning all phases and geographical areas. He is author of the forthcoming book, Adaptive Clinical Trials.

Jim Box is the Director of the Information Systems for Health Decisions, responsible for the day-to-day operations of technical aspects of clinical studies and leader of the team that develops and supports Health Decisions' Clinical Trials Management System. Jim started with Health Decisions in 1999 and has served as Manager of Data Management and Biometrician. He has been involved many aspects of data collection and analysis, from database and CRF design, to validation programming and data guideline productions, and the production and validation of statistical tables. Jim holds Master's Degrees in Statistics from Duke University and Systems Management from the Florida Institute of Technology.

12:00

Luncheon

1:30

When Are Adaptive Designs Appropriate? Karen L. Kesler, Ph.D., Assistant Director, Biostatistics, Rho, Inc.

Adaptive designs cover a broad range of study types and can address a dizzying number of statistical and logistical challenges. However, deciding when and which of the many adaptive designs to use can be confusing. When should you use an adaptive design instead of a traditional design? Are there situations where adaptive designs are completely inappropriate? How do you determine which design is appropriate in different situations? Giving careful consideration to the above questions as early in the statistical planning provides the most benefit for the patient, client, and sponsor. This presentation will address these questions by taking into consideration several of the main types of adaptive designs and discussing what design challenges each one addresses best. In addition to some general "rules of thumb", we will discuss specific issues relating to adaptive randomization, Bayesian dose response designs, treatment pruning arm designs, sample size recalculations, and combined Phase II/III designs. In summary, this presentation will:

- Delineate what can be gained by using one of the Adaptive Designs

- Explain when not to use an Adaptive Design
- Address some possible pitfalls for each type of study design

CASE STUDY

2:15

An Adaptive Design Experience: The Planning, the Hurdles, the Outcome **Nancy.R.Burnham, Manager, Statistics, GlaxoSmithKline**

This presentation focuses on the presenter's experience of running an adaptive trial within GlaxoSmithKline. The following will be covered:

- The clinical questions leading to the choice of an adaptive approach in patients.
- Brief description of statistical methods
- Regulatory issues – Canada, US, Australia
- Agreements with the IDMC
- Communication with investigators and IRBs
- Decisions around maintaining blind, and use of internal independent statistician
- Team agreements and pre-planning during study set-up to facilitate quick data turn-around
- How drug supply was handled
- Real life interference to enrollment rate
- And ultimately, how unexpected results (good) and real life contributed to the decision to stop after the first cohort.
- Ultimate contribution to clinical development plan.

3:00

Refreshment Break

STATISTICAL CONSIDERATIONS CASE STUDY

3:15

Understanding and Responding to Statistical Challenges in Adaptive Trial Design **Pat Kelley, Director of Biostatistics, ASTRAZENECA**

Over the past several years Adaptive Trial Design has been a topic of considerable interest in the Pharmaceutical community. If you were to poll the community at large concerning these new methodologies then you would more than likely hear about the tremendous interest, the hope for increased drug development efficiency, and the promise of a decrease in the late-stage rate of development failures that has been generated.

What you usually don't hear is much discussion about the costs that will be associated or the difficulties that

will be encountered with the actual implementation of an Adaptive Design. In particular, what isn't presented is any information on the actual discussions that occur when a study team has to make a decision concerning the advisability of using an adaptive approach in study management and analysis.

This presentation will focus on such discussions as they relate to the scientific and statistical aspects of a study. Although very important in and of themselves, practical questions of trial management and logistics will not be considered.

It is hoped that those in attendance will come away with a better understanding of:

1. Different types of Adaptive Trial designs and the statistical problems that are associated with them.
2. The nature of the statistical problems and how they may affect the trial results.
3. The kind of adjustments that can be made to account for these effects.
4. The potential impact an adaptive design might have on the overall trial objective.
5. The questions one must ask in deciding for or against an adaptive design.

4:15

Adaptive in Practice: The Pragmatic Aspects **Michael Rosenberg MD, PhD, President and Chief Executive Officer, Health Decisions, Inc.**

Recent discussion about adaptive techniques has focused on strategic elements, but there is a tactical component that is at least as important in ability to reduce timelines and costs. Through experience with more than 300 adaptive studies, this session will emphasize newer systems that enable far tighter study management through the ability to provide real-time monitoring of study parameters such as enrollment, site performance, and quality of field monitoring. Application of adaptive principles through these tools and processes can dramatically reduce costs and timelines: field monitoring costs, for example, can be reduced by up to 80% through a combination of newer electronic tools and use of new data collection instruments as source data. Part of this discussion will focus on technology and limitations of web-based EDC. These powerful benefits can be realized immediately, since they are internal issues.

5:00

Close of Day One

Tuesday, September 11, 2007

8:45 *Statistical Issues in Adaptive Trial Designs*
Shein-Chung Chow, Ph.D., Department of Biostatistics and Bioinformatics, Duke University School of Medicine

In recent years, the use of adaptive design methods in clinical research and development based on accrued data has become very popular due to its efficiency and flexibility in modifying trial and/or statistical procedures of on-going clinical trials. Commonly considered adaptive designs in clinical trials include adaptive group sequential design and adaptive seamless trial design. As indicated by the United States Food and Drug Administration (FDA), the use of adaptive design methods in clinical trial may not be feasible if it is unable to avoid/eliminate/control operational bias and/or it is unable to preserve the overall type I error rate. In this presentation, some statistical issues that are commonly encountered when implementing an adaptive design in clinical trials are discussed. The issues include, but are not limited to, (i) the shift in target patient population, (ii) the need for flexible sample size re-estimation, and (iii) statistical analysis and sample size calculation for an adaptive seamless trial design with different study endpoints.

DOSE-SCHEDULE FINDING STRATEGIES

9:30 *Dose-Schedule Finding in Phase I/II Clinical Trials Using a Bayesian Isotonic Transformation*
Yisheng Li, Ph.D. Assistant Professor, Department of Biostatistics, University of Texas M. D. Anderson Cancer Center

A dose-schedule-finding trial is a new type of oncology trial in which investigators aim to find a combination of dose and treatment schedule that has a large probability of efficacy yet a relatively small probability of toxicity. We demonstrate that a major difference between traditional dose-finding and dose-schedule-finding trials is that while the toxicity probabilities follow a simple non-decreasing order in dose-finding trials, those of dose-schedule-finding trials adhere to a partial order. We show that the success of a dose-schedule-finding method requires careful statistical modeling and a sensible dose-schedule allocation scheme. We propose a Bayesian hierarchical model that jointly models the unordered probabilities of toxicity and efficacy, and apply a Bayesian isotonic

transformation to the posterior samples of the toxicity probabilities, so that the transformed posterior samples adhere to the partial order constraints. Based on the joint posterior distribution of the order-constrained toxicity probabilities and the unordered efficacy probabilities, we develop a dose-schedule-finding algorithm that sequentially allocates patients to the best dose-schedule combination under certain criteria. We illustrate our methodology through its application to a clinical trial in leukemia, and compare its performance to that of an existing approach in the literature.

10:15 *Refreshment break*

10:30 *Adaptive Designs for Dose-Ranging Phase I/II Trials*
Naum Khutoryansky, Ph.D., D.Sc., Statistician-Fellow, Biostatistics, NOVO Nordisk

Adaptive designs are described for phase I/II clinical trials with objectives either to target the minimum effective dose, or maximum tolerated dose, or to find the dose-response curve and therapeutic range. The following adaptations are under consideration: sample size re-estimation, early stopping due to efficacy or futility, and dropping inferior treatment groups. An adaptive design can also involve any combination of these adaptations. Different types of dose increments are discussed including dose escalation and dose reduction, and their combinations. Some statistical methods to control type I error will be presented including Fisher's combination of independent p-values and hierarchical testing.

- Different types of adaptive design to determine the minimum effective dose and to find the dose-response curve
- Fisher's combination of independent p-values based on sub samples from different stages
- Using futility and efficacy stopping rules in multiple stage designs with flexible sample sizes
- Controlling type I error in multiple stage adaptive designs
- Controlling type I error in the hierarchical dose reduction design
- A combination of the dose escalation and dose reduction designs

FUTILITY ANALYSIS

11:15 *Futility Analysis*
A. Lawrence Gould, Senior Director, Scientific Affairs, Merck Research Laboratories

The predictive probability of not rejecting a null hypothesis on completion of a trial measures the futility of

continuing the trial past an interim stage. This presentation focuses on two issues: when the interim analysis should be carried out, and how pre-trial information can be incorporated into the design of the trial.

- Need to wait until accumulating at least 40% of the planned observations before considering futility termination if interim observed difference is not negative
- Could terminate after observing 30% of planned obsns if interim difference is fairly strongly in the wrong direction and if there is a lot of uncertainty about the true treatment effect
- Conclusion does not appear to be very sensitive to sample size (intended power)
- Can terminate earlier when some variability of the true treatment effect is permitted but at the cost of a larger sample size or lesser power

i.e., based on the effect size at an interim analysis the final size of the trial is determined. Details will be given on: (i) how the adaptive design development was able to be carried out without delaying the start of the trial; (ii) optimal timing for this interim analysis; (iii) what was necessary to obtain FDA buy-in to the proposed design; (iv) gains versus standard group sequential designs; and (v) processes that were put in place to protect the integrity of the trial.

This is one of the few Adaptive Phase III Designs incorporating adaptive re-sizing that have been conducted and discussed extensively with regulators. Therefore, in the absence of FDA guidelines for adaptive designs the process used here to obtain FDA buy-in to the design should provide insight to others on how to set up such trials in a way that would be acceptable to regulators, while obtaining large savings in the expected duration of the trial.

12:00 Luncheon

SAMPLE SIZE RE-ESTIMATION

1:30 *Treatment Effect Sensitivities: Sequential Trial Designs and Adaptive Sample Size Re-estimation*
Michael O'Connell, Director, Life Science Solutions, Insightful

Specifying the treatment effect size up front is often challenging for new therapeutics; and it is difficult to power and design a study in such a setting. Indeed, this has been a key factor in the evolution of adaptive clinical trial design and sample size re-estimation methods. This presentation examines the specification of the treatment effect size and considers sequential and adaptive designs in this context. Attendees will learn:

- How to design clinical trials when effect size is uncertain
- Adaptive / sequential trial design approaches with a range of effect sizes
- Situations where adaptive / sequential designs work better

“Adaptive procedures can offer significant ethical and cost advantages over standard fixed procedures...”

— Scott Gottlieb, M.D., Deputy Commissioner, Medical and Scientific Affairs, US Food and Drug Administration

REGULATORY CONSIDERATIONS CASE STUDY

2:15 *Adaptive Trial Re-Sizing With Emphasis on Regulatory Interactions*
Jonathan Smith, Ph.D., Vice President, Strategic Development, Biostatistics, Quintiles, Inc.

This presentation will describe a recently started Phase III adaptive design that incorporates adaptive re-sizing,

3:00

Innovative Approaches for Designing and Analyzing Adaptive Dose-Ranging Trials
Amit Roy, Associate Director, Bristol-Myers Squibb Company

Suboptimal dose selection has been highlighted by the FDA as a key factor influencing the decline in successful NDA filings, and adverse post-approval findings. One of the initiatives sponsored by PhRMA to address this issue is the Adaptive Dose-Ranging Studies (ADRS) Working Group, which has evaluated several innovative adaptive dose-ranging designs and methods, with the goal of providing recommendations on their use in clinical drug development. This presentation describes the results of a comprehensive comparison of a conventional dose-ranging design, and six innovative methods of designing

and implementing ADRS. The statistical operating characteristics of these designs and methods for establishing proof-of-concept and dose-response were evaluated by simulation, under a variety of trial scenarios and dose-response functions.

Learning Objectives:

- Why should adaptive designs be considered for dose-ranging studies?
- What are the issues that need to be addressed in designing an adaptive clinical trial?
- How should the data from dose-ranging studies be analyzed?
- How can the potential advantages of adaptive designs over conventional designs be quantified?
- What are the recommendations of the PhRMA ADRS Working Group?

ADAPTIVE TRIAL OPERATIONS

3:45

Technology Solutions for the Implementation of Adaptive Trials

Graham Nicholls, Product Manager, Randomization and Trial Supply Management, ClinPhone

Adaptive trials promise to bring enormous gains to drug development, not least in enhancing optimal dose selection, and in reducing the time between Phases II and III. Implementing such designs, however, brings new challenges. This presentation explores the practical considerations of running adaptive trials and explains how current technology can be applied and developed to implement these effectively. This will include randomization and trial supply management applications, trial supply simulation and forecasting solutions, fully integrated EDC, ePRO and IVR/IWR solutions, and how clinical data can be accessed in a timely manner for decision making when paper data collection processes are in use.

OPTIMALITY CURVE DEVELOPMENT

4:30

Response Adaptive Designs for Balancing Complex Objectives

Janis Hardwick, Professor, University of Michigan

In most experimental situations, there are many desirable but conflicting design considerations. Often, however, designs are either optimized with respect to a single objective or arbitrary tradeoffs among objectives are built in.

In this talk we consider formally balancing two important experimental criteria in an effort to find designs that come close to optimizing performance on both objectives. This is done by generating the "optimal trade-off curve" for the objectives and then assessing a number of popular adaptive designs in relationship to the optimality curve. We also examine the pointwise behavior of the designs discussed, considering in particular the variability of results. Here, we use as examples specific objectives related to making correct terminal decisions and improving the well being of trial patients. However, the approach presented, and programs used to achieve it, can be applied to nearly any trial objectives.

1. We present a specific design that performs very nearly optimally on both criteria considered.
2. We show that it can be worthwhile to trade away complete optimality for better intuition, design simplicity and near optimality on multiple criteria.
3. The programs discussed can be used to determine any experimental design characteristics such as entire distributions of the various objectives rather than simply presenting mean results.
4. The techniques used here to optimize tradeoffs are quite general, in that one can combine several objectives into a single function or evaluate combinations of more than two objectives.

5: 15

Seamless Phase 2B/3 Trials and Sample Size Re-Estimation: Case Studies

Yannis Jemai, Ph.D. Sr. Biostatistician, and Misha Salganik, Senior Biostatistician, Cytel, Inc.

It is now widely accepted that adaptive trial designs can reduce the cost and time needed for drug development while increasing the chances of success. Using case studies of actual adaptive studies from our biopharmaceutical consulting, we will examine the statistical and practical aspects of applying adaptive methodologies in late stage trials.

Statistical issues include preserving the type 1 error of the trial, handling multiple testing of hypotheses, and conducting inference. Practical issues involve preserving the integrity and interpretability of the study, as well as planning for the logistics will be addressed. Given the increased complexity of adaptive designs we'll also examine the crucial role modeling and simulation plays during trial planning.

6:00

Close of Conference



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