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Adaptive Clinical Trials:

Innovations in Trial Design, Management, and Analysis

Herman A.M. Mucke, PhD

A comprehensive assessment of a vital new approach to clinical trial design

The pharma industry is gradually coming to realize that the classically structured clinical trial does not offer enough flexibility to make use of continuously emerging knowledge that is generated as the trial progresses. This report is a comprehensive assessment of the benefits, challenges, and accumulated industry experience with regard to adaptive clinical trials. It includes:

- **A critique of the structural, conceptual, and ethical issues inherent in the traditional clinical trial**
- **An in-depth review, based on actual case studies (e.g., Napo, Genaera, Pfizer, Lilly, Millennium, and various academic institutions), of the use of adaptive and Bayesian approaches in Phases I, II, and III**
- **An assessment of various hybrid and seamless designs in which the line between trial stages is blurred**
- **Evolving regulatory positions of FDA, EMEA, and ICH on adaptive designs; industry response and initiatives**

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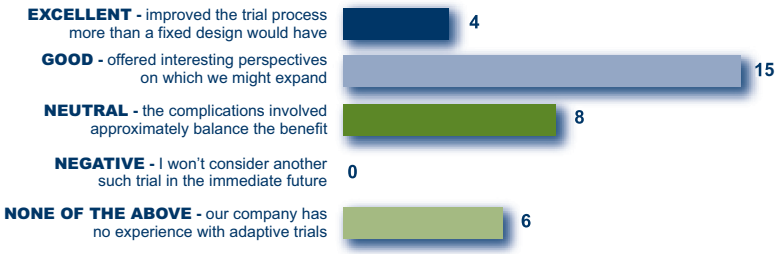
Overview

- A review of specialized software vendors (e.g., Cytel, Tourtellotte, Pharsight, CTriSoft) and their applications that have emerged to support adaptive designs
- A CHI Insight Pharma survey of the views and experiences of individuals involved with adaptive designs
- Three future scenarios for the integration of adaptive designs in clinical trials by 2015: (1) United States Leads the Way, (2) Globally Integrated Midphase Revamping, and (3) the Late Phoenix Scenario
- Roundtable interviews with senior executives in industry and consulting who bring decades of combined experience in adaptive and Bayesian clinical trial designs

Describe Your Experience with Flexible or Adaptive Trial Designs



Source: CHI Insight Pharma Reports, Adaptive Trials Survey, Q207 (N=33)

Unacceptable levels of attrition in the clinical stage of development are driving profound changes in the architecture, design, and analysis of clinical trials. The majority of respondents to our survey said that reduction in patient numbers, less exposure to study drug, and drops in overall trial duration were key points in favor of adaptive designs; however, a majority also had specific concerns with adaptive trials that involved methodological, logistical, and regulatory uncertainties:

Methodological: Will adaptive and/or "seamless" designs lead the sponsor to erroneous conclusions if used in Phase II and (in particular) in pivotal trials?

Logistical: Can such trials be fully kept under control without major organizational change/expansion and/or increased dependency on outside statistical and monitoring advice?

Regulatory: Will regulatory authorities (FDA, EMEA) accept adaptive designs and—more importantly—will they accept the trial sponsor's interpretation of the results of such trials?

Adaptive Clinical Trials: Innovations in Trial Design, Management, and Analysis examines the key challenges involved in adaptive trials, such as:

- Staff training requirements
- EDC to enable near-real-time capture, validation, and analysis of trial-emergent data
- Working with Data Monitoring Committees (DMC)
- Ways in which adaptive modifications, e.g., dropping and replacing a dosage arm, can have ripple effects on a project's critical path
- The challenges of prognosis, analysis, and interpretation

Adaptive trials are emerging as a solution to lengthening development timelines, runaway costs, and overall lack of predictivity in the drug development process. Drug companies, regulators, and academic investigators have shown a willingness to explore adaptive and Bayesian options as part of a general revamping of the drug development process. We predict that increasing guidance and endorsement from regulatory bodies will lead the industry to fully embrace adaptive trials by 2015.

About the Author: *Hermann A.M. Mucke, PhD,* spent 17 years in academia and industry before he founded H.M. Pharma Consultancy (www.hmpharmacon.com) in 2000 to become an independent pharmaceutical consultant, analyst, and science author. His last industry position was Vice President R&D in a European pharmaceutical company that he helped to take public on the Frankfurt Stock Exchange in 1999. Since then, Dr. Mucke, who holds a PhD in biochemistry from the University of Vienna (Austria), became a consultant and advisory board member for several European and US pharmaceutical companies and a regular reviewer of drugs and patents for Thomson Current Drugs and Ashley Publications. He has served as an outside expert author for CHI since 2004. Dr. Mucke is based in Vienna and can be reached at office@hmpharmacon.com or by fax at +43 1 494 9989.

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- Redirect capital and human resources to development programs with the greatest likelihood of success
- Expose clinical trial subjects to fewer unsafe or ineffective drugs
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- Increase industry's and society's confidence in including pediatric subjects in clinical trials

Biostatisticians and decision analysts, portfolio managers, market forecasters, business development managers, and decision makers throughout the R&D organization will benefit from this report

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