

The Future Outlook of Adaptive Clinical Trials: An Industry Perspective

Keaven M. Anderson, Ph.D.

May 19, 2010

Merck Research Laboratories
Keaven_Anderson@merck.com

Bayesian and Adaptive Trial Methods Meets the Pragmatic Clinical Trial and Comparative Effectiveness Research

Acknowledgements

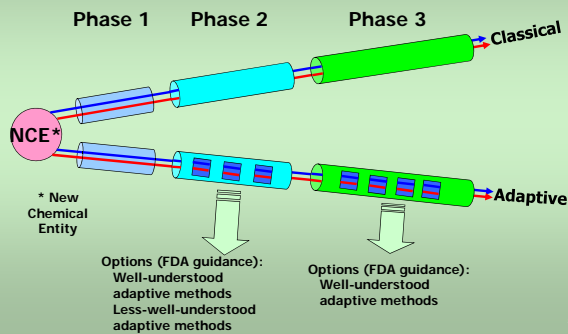
- PhRMA Adaptive Design Working Group (ADWG) and Adaptive Design Limited Duration Key Issue Team (LDKIT)
 - Particular thanks to Brenda Gaydos
- Merck ADAPT initiative team members
 - Jerry Schindler, Nicole Dossin, Darcy Hille, Jim Bolognese, Weili He and many others
- Berry Consultants
 - Don Berry, Jason Connor

Overview

- Definitions
- Benefits: Merck results
- Very basic Bayes (vs frequentist)
- Bayesian examples for individualized medicine
- FDA guidance for drugs and biologics
- Conclusions

Definitions

Adaptive and Conventional Clinical Development Processes

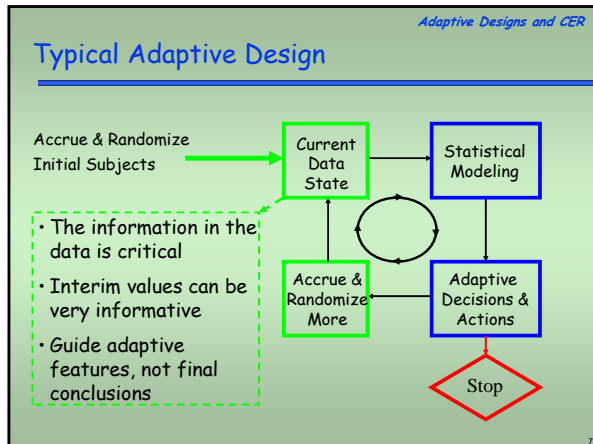


Adaptive Design Definition

Adaptive design refers to a clinical study design that uses accumulating data to decide on how to modify aspects of the study as it continues, without undermining the *validity* and *integrity* of the trial

Definition: (from An Executive Summary of PhRMA Working Group): (Reference: Adaptive Design: Classification and Terminology, Vladimir Dragalin, DIJ, Nov. 2006, 40(4):425-435)

- Essential components:
 - changes are made by pre-specified algorithm(s) and not on an ad hoc basis
 - adaptation is a design feature and not a remedy for poor planning



- Adaptive Designs and CER
- ### Adaptive Clinical Trial Goals
- Exploratory trials
 - ♦ Combined Proof-of-Concept/Dose Findings Studies
 - ♦ Adaptively allocate to best of many doses for better estimation at the 'steep' part of the curve
 - ♦ Adaptively stop trial early for futility
 - ♦ **Adaptively allocate subsets of patients to best treatments**
 - Confirmatory trials
 - ♦ Adaptively allocate to 'best' subset of doses
 - ♦ **Adaptively select appropriate population**
 - ♦ Adaptively increase/decrease sample size to efficiently accomplish objectives
 - ♦ Adaptively stop trial early for success or futility

Adaptive Designs and CER

From Sunitinib® U.S. Prescribing Information

Efficacy Parameter	SUTENT (n=207)	Placebo (n=105)	P-value
Time to Progression ^a (months)	6.0 (4.4, 9.9)	5.0 (4.4, 9.9)	<0.0001*
Overall Response Rate (ORR) (%) (95% CI)	6.8 (3.7, 11.1)	0 (3.7, 11.1)	0.006 ^c

CI=Confidence interval, HR=Hazard ratio, PR=Partial response
 * A comparison is considered statistically significant if the p-value is < 0.0042 (O'Brien Fleming stopping boundary)
^a Time from randomization to progression; deaths prior to documented progression were censored at time of last radiographic evaluation
^b Time from randomization to progression or death due to any cause
^c Pearson chi-square test

Regulatory acceptance

From April 24, 2010 google search of "clinical trial interim efficacy statistically significant" HIGHLIGHTING ADDED

- Adaptive Designs and CER
- ### Range of Possible Adaptation (FDA draft guidance)
- study eligibility criteria
 - ♦ either for subsequent study enrollment or subset analysis
 - randomization procedure
 - treatment regimen
 - ♦ e.g., dose level, schedule
 - total sample size (including early termination)
 - concomitant treatments
 - schedule of patient evaluations
 - primary endpoint
 - selection and/or order of secondary endpoints
 - analytic methods
- IF-focus during study*

- Adaptive Designs and CER
- ### Why Do Adaptive Trials in CER?
- Smaller trials ... usually
 - More accurate conclusions
 - Faster, better, less expensive drug development
 - Better treatment of patients in trials
 - More flexible post-market trials
 - Compare real-world outcomes in real-time
 - Better, more cost-effective treatment of patients in & out of trials

Adaptive Designs and CER

Benefits: Merck Results

2009 Business Benefits

Development Costs Savings

- Average per trial benefit for 2009:
 - ◆ \$2.3 MM grant cost savings
 - ◆ ~10 month cycle time reduction
 - ◆ ~25% reduction in patient sample
- 2009 \$30 MM CSE benefits (surpassed the \$18.2 MM CSE goal for 2009)

Revenue Enhancement

- Per program increase in product revenue NPV due to cycle time reduction

Size of Product (Peak annual sales):	Incremental Benefit in NPV resulting from Advancing Launch by:		
	1 Year	6 Months	3 Months
≥2.5 Billion	509MM	153MM	51MM
>1 Billion but less than 2.5 billion	177MM	53MM	18MM
<1 Billion	147MM	44MM	15MM

13

ADAPT Business Case* Summary: Status of Adaptive Design Studies, April 2010

Category	n
Stopped for futility	9
Completed as written	5
Ended early, no IA	2
Cancelled	2
In progress	5
Total	23

*Represents a sample of adaptive design studies started between 2004-2008 for which the ADAPT team is tracking information/outcome

14

NCI Cancer Bulletin, April 6, 2010*

- "Phase III Lung and Pancreatic Cancer Trials Stopped"

◆ <http://www.cancer.gov/ncicancerbulletin/0406>

"The ATTRACT-1 trial was stopped after a planned interim analysis showed that continuation of the trial would be of no prospective benefit of demonstrating a statistically significant difference in overall survival compared with placebo."

"Also last week, the decision of its phase III PACT trial, which compared the combination of gemtuzumab with locally advanced pancreatic cancer, was stopped. An interim data analysis showed that the trial would not meet the goal of demonstrating persuasive evidence of clinical effectiveness ..."

*From April 24, 2010 google news search of "clinical trial interim futility"

15

2010 Focus Areas at Merck

- 4 major areas for enrollment & training
 1. Resource & management support
 2. Broad-based education & training
 3. Clinical-Program-specific training
 4. Logistical support for AD
- Target
 - ◆ 40% adaptive trials in Phases II and higher

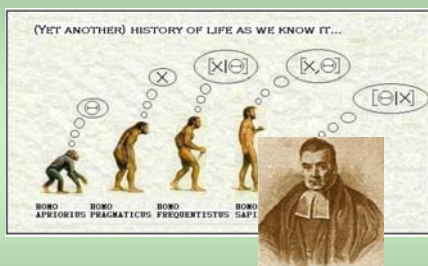
16

Basic Bayes

What is Bayesian Statistics?

- The Bayesian approach learns as evidence accumulates
 - ◆ Formally combines prior with current information
- Bayesians consider the prior information and the trial results as part of a continual data stream
 - ◆ Inferences updated with each new data accrual
- While not confined to be adaptive, Bayesian statistics provide a natural fit with adaptive design

18



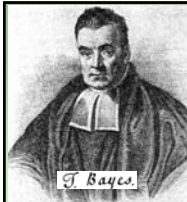
$X = \text{data}, \Theta = \text{parameter}$

Mike West, Duke U.,

http://www.isis.duke.edu/~mw/ABS04/Lecture_Slides/4_Stats_Regression.pdf

19

Reverend Thomas Bayes, FRS



c 1702 - 1761

- English mathematician and Presbyterian minister
- Bayes theorem published posthumously
- Buried in Bunhill Fields Cemetery in London where many Nonconformists are buried

20

Very basic Bayes...

■ Bayes theorem

- ♦ $\Theta = \text{parameter}, X = \text{data}$

$$P\{\Theta | X\} = \frac{P\{X | \Theta\}P\{\Theta\}}{P\{X\}}$$

■ Prediction based on Bayesian analysis

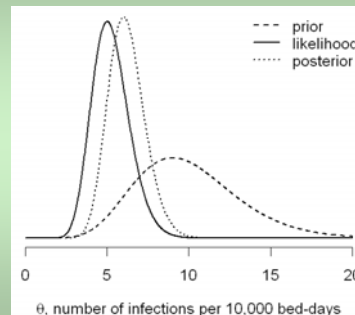
- ♦ $Z = \text{future data}$

$$P\{Z | X\} = \int P\{Z | \Theta\}P\{\Theta | X\}d\Theta$$

- ♦ Is this what CER wants?

21

Bayesian Analysis Example



David Spiegelhalter and Kenneth Rice (2009), Scholarpedia, 4(8):5230.
http://www.scholarpedia.org/article/Bayesian_statistics

22

Bayesians vs. Frequentists

- Bayesians: relative evidence for parameter values given a dataset
- Frequentists: relative chance of datasets given a parameter value.
- Little agreement over which is 'right', most 'appropriate' or 'useful'.
- In many cases, estimates, intervals, and other decisions will be extremely similar
 - ♦ Exception: in hypothesis testing Bayesian and frequentist methods can give strongly discordant conclusions.
- Many Bayesian procedures can be calibrated to have desired frequentist properties
 - ♦ E.g., intervals with 95% coverage
 - ♦ This can be useful when justifying Bayesian methods to regulators

David Spiegelhalter and Kenneth Rice (2009), Scholarpedia, 4(8):5230.
http://www.scholarpedia.org/article/Bayesian_statistics

23

Bayesian Methods in CER

Why Do Adaptive Trials in CER?

- Smaller trials ... usually
- More accurate conclusions
- Faster, better, less expensive drug development
- Better treatment of patients in trials
- More flexible post-market trials
- Compare real-world outcomes in real-time
- Better, more cost-effective treatment of patients in & out of trials

25

What Does Bayes Add to CER?

- Synthesis
 - ◆ Bayes is ideal for combining information
 - ◆ Meta-analysis or combining past studies with new data
- Prediction
 - ◆ Longitudinal data models within trials
 - ◆ Predictive probabilities of trial success
 - ◆ Predict individual patient result on different treatments
- Personalized medicine:
 - ◆ Bayes conditions on all known data
 - ◆ Combines patient information & historical data
 - ◆ Probabilities average over uncertainty in historical estimates

26

Some Current Areas of Application

- | | |
|-----------------------|----------------------|
| ■ Alzheimer's Disease | ■ Lung Cancer |
| ■ Aneurysm | ■ Lupus |
| ■ Atrial Fibrillation | ■ Migraines |
| ■ Crohn's Disease | ■ Obesity |
| ■ Diabetes | ■ Pre-term labor |
| ■ Emphysema | ■ Spinal Cord Injury |
| ■ Heart Valves | ■ Spinal Implants |
| ■ HIV | ■ Stroke |
| ■ Libido | ■ Uterine Cancer |
| ■ Lymphoma | ■ Vaccines |

27

Adaptive Processes for CER

- Comparative effectiveness is more a process
 - ◆ RCTs have a start & a finish, CER does not
 - ◆ Products enter and leave market
 - ◆ Practice/guidelines change as products proven more effective, less safe, less tolerable
- Goal: Produce an adaptive infrastructure for comparing approved products in post-market setting

28

Bayesian Approach to Individualized Medicine: Merck Oncology

Challenges to Oncology Drug Development: Problem Statements

- Cancer is an incredibly complex set of diseases**
- Cancer is hundreds of different diseases
 - Redundant pathways / mechanisms
 - Animal models insufficient
- Biomarker-focused strategies**
- Current methods for identifying compounds with their potential to predict clinical outcomes/biomarkers
 - Insufficiently correlating clinical outcomes/biomarkers
- Interference**
- Over 1000 oncology compounds are in development, leading to intense competition for sites and patients
 - Many competitors working on the same known cancer targets
- Difficulty optimizing portfolio value**
- Even large oncology players have finite resources
 - Each compound has many development options

30

Adaptive Designs and CER

Well-understood vs Less-well understood adaptive designs

- Well-understood adaptive clinical study designs
 - ♦ A considerable experience in modern drug development provides confidence that these design features and procedures will enhance efficiency while limiting risk of introducing bias or impairing interpretability
 - ♦ Many of these designs based on blinded review of data
- This guidance encourages sponsors to gain experience with the less well-understood methods in the exploratory study setting (see section IV.D).
 - ♦ The less well-understood adaptive design methods are all based on unblinded interim analyses that estimate the treatment effect(s).
 - ♦ *Bayesian designs would generally fall here!*

37

Adaptive Designs and CER

Blinded vs Unblinded Adaptation

- Unblinded adaptation
 - ♦ Revisions not previously planned and made or proposed after an unblinded interim analysis raise major concerns
 - ♦ Revisions after any unblinded analysis should be prospectively defined and carefully implemented
- Blinded adaptation
 - ♦ Revisions based on blinded interim evaluations of data do not introduce statistical bias to the study or into subsequent study revisions
 - ♦ Certain blinded-analysis-based changes, such as sample size revisions ... can also be applied when not planned from the study outset if the study has remained unequivocally blinded

38

Adaptive Designs and CER

PhRMA Executive Summary of Key Issues

- *Less "well understood" designs that are A&WC should be explicitly encouraged*
- *Process and type of information needed to reach agreement/commitment on Type I error rate control needs to be defined*
- *Guidance should define general approach to documentation of operating procedures*
 - Study level versus Corporate level
 - Linked to inspection risk

39 39

Adaptive Designs and CER

Industry Concerns/Initiatives Going Forward

- AD in early stage and much education still needed
- Possible constraints on FDA resourcing for early discussion about innovative designs
- Share/discuss examples with FDA to move approaches to "well-understood"

40 40

Adaptive Designs and CER

FDA/DIA Symposium

Adaptive Design for Clinical Trials:
FDA Draft Guidance Symposium
March 26, 2010

41

Adaptive Designs and CER

FDA Draft Guidance Workshop 2010

- Guidance encourages AD in exploratory and confirmatory settings
- AD need to be done well to be accepted
- In absence of verbal clarifications from FDA, guidance may appear discouraging to some
- Agency will consider adaptive designs in "confirmatory settings"
- Cautions not meant to discourage applications of AD
- Control of operational bias essential, including documentation

42 42

Drug Information Journal
2009;43:539-556

BIOSTATISTICS 539

Brenda Gaudin
Eli Lilly

Keaven M. Anderson
Merck

Daniel Berry
MD Anderson Cancer Center

Nancy Burkhon
GSK

Cheryl Chesney-Dale
Pfizer

Joseph DeBorja
Roche

Parvati Faridpour
Novartis

Paul Galle
Novartis

Sam Givens
Roche

Roger Lewis
Harbor UCLH Medical Center

Jill Marx
Novartis

José Pinheiro
Novartis

YR Pritchatt
Abbott

Michael Ryan
Wyeth

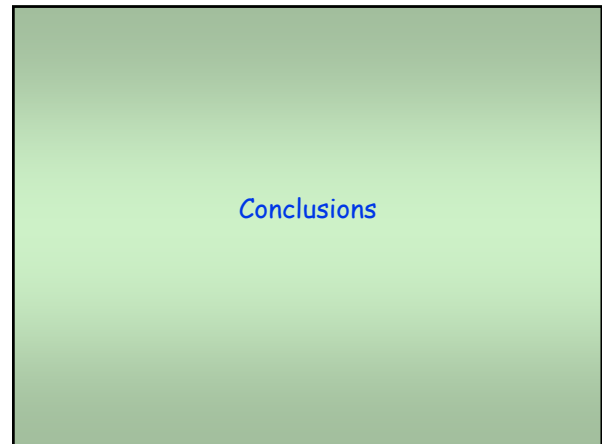
Good Practices for Adaptive Clinical Trials in Pharmaceutical Product Development

This article is a summary of good adaptive practices for the planning and implementation of adaptive designs compiled from experiences gained in the pharmaceutical industry. The target audience is anyone involved in the planning and execution of clinical trials. The first step prior to planning an adaptive design is to assess the appropriateness of its use. Hence, strategic points to consider when assessing if an adaptive design is the right choice for a trial are discussed. In addition, strategic points for consideration at the design and implementation stage are included from operational, regulatory, clinical, and statistical perspectives. Good practices for trial simulation, trial documentation, and data monitoring committees are provided.

INTRODUCTION
Callo et al. (1) define an adaptive design as one that uses accumulating data from the ongoing trial to modify certain aspects of the study without undermining the validity and integrity of the trial. The flexibility of adaptive designs has the potential to translate into more ethical treatment of patients within a trial (eg, response-adaptive), increased likelihood of taking the right doses into phase 3 (eg, model-based

proprate estimation of treatment effect at the end of the trial. Statistical methods for the design and analysis of adaptive designs are often technically and computationally more complex than those associated with conventional designs. As a result, customized software programs are frequently required.

Operational issues relate to the logistical and procedural implementation of adaptive designs. Many of the operational issues also apply to more traditional group sequential designs. But



Adaptive Designs and CER

What do we need going forward?

- Continued dialog between regulators and developers
- Continued methods research/software development
- Execution process/software
- Documentation and auditing capabilities that are well-understood to assure regulatory acceptance
- **Education**
- For CER
 - ◆ Continued focus on individualized medicine
 - ◆ Combining information across trials

 **ISPOR** **Speaker**

Third Plenary Session
Bayesian and Adaptive Trial Methods Meet the Pragmatic Clinical Trial and Comparative Effectiveness Research



Keaven M. Anderson PhD
Executive Director
Clinical Biostatistics and Research Decision Sciences
Merck Research Laboratories
North Wales, PA, USA