Brief Overview of Adaptive Designs

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More Information and Readings at:
http://people.csail.mit.edu/mrosenblum/Teaching/adaptive_designs_2010.html

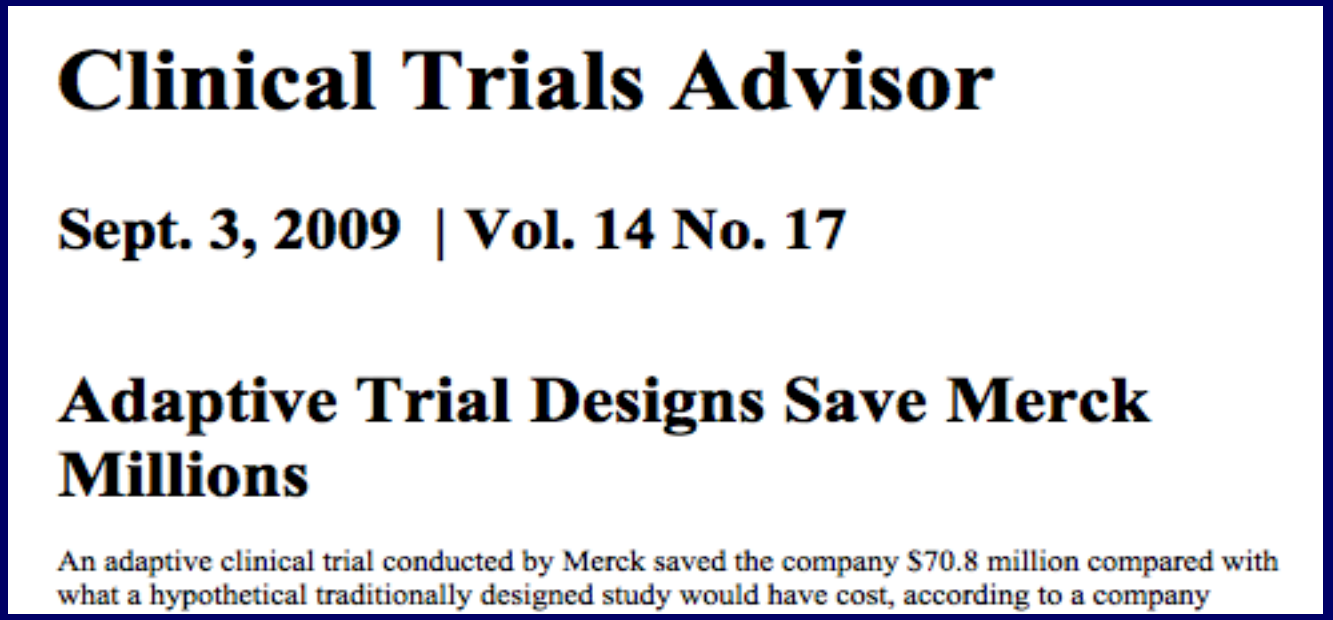
Adaptive Clinical Trial Designs

FDA is Interested:

"A large effort has been under way at FDA during the past several years to encourage the development and use of new trial designs..."

Adaptive Clinical Trial Designs

- Pharmaceutical Companies are Interested:



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Adaptive Trial Designs Save Merck Millions

An adaptive clinical trial conducted by Merck saved the company $70.8 million compared with what a hypothetical traditionally designed study would have cost, according to a company

"An adaptive clinical trial conducted by Merck saved the company $70.8 million compared with what a hypothetical traditionally designed study would have cost…"

Why Use Adaptive Designs?

Potential Benefits:

- Can Reduce Cost, Duration, and Number of Subjects of Trials
- Can Give More Power to Confirm Effective Drugs and Determine Subpopulations who Benefit Most

Care Must Be Taken to:

- Guarantee Correct Probability of False Positive Results (e.g. 0.05)
- Minimize Bias
- Lead to Interpretable Results

Group Sequential Randomized Trial Designs

- Participants Enrolled over Time
- At Interim Points, Can Change Sampling in Response to Accrued Data:
  - Can Stop Trial Early (e.g. for Efficacy, Futility, or Safety)
  - Can Change Probability of Assignment to Different Arms (e.g. to Maximize Number of Patients Assigned to Best Arm)
  - Can Recruit from Subpopulation in which Treatment Effect is Strongest (“Enrichment”)

FDA Draft Guidance on Adaptive Designs

Focus is AW&C (adequate and well-controlled) trials.

Distinguishes well understood vs. less well understood adaptations.

Explains chief concerns: Type I error, bias, interpretability.

FDA Draft Guidance on Adaptive Designs

Well Understood Adaptations:

- **Adapt Study Eligibility Criteria Using Only Pre-randomization data.**
- **Adapt to Maintain Study Power Based on Blinded Interim Analyses of Aggregate Data (or Based on Data Unrelated to Outcome).**
- **Adaptations Not Dependent on Within Study, Between-Group Outcome Differences**

FDA Draft Guidance on Adaptive Designs

Well Understood Adaptations:

- **Group Sequential Methods (i.e. Early Stopping)**

FDA Draft Guidance on Adaptive Designs

Less-Well Understood Adaptations:

- **Adaptive Dose Selection**
- **Response-Adaptive Randomization**
- **Sample Size Adaptation Based on Interim-Effect Size Estimates**
- **Adaptation of Patient Population Based on Treatment-Effect Estimates**
- **Adaptive Endpoint Selection**

Hypothetical Example Based on AIDS Clinical Trials Group Study A5175

Prospective Evaluation of Antiretrovirals in Resource Limited Settings (PEARLS)

The following slides are modified from slides generously shared by Thomas Campbell and ACTG (previously presented at 2008 World AIDS Conference).

Study Design

- 1:1:1 randomization of ARV naïve subjects:
  - Arm 1A: ZDV/3TC BID + EFV QD
  - Arm 1B: ddI-EC QD + FTC QD + ATV QD
  - Arm 1C: TDF/FTC QD + EFV QD

- Primary Endpoint is time from randomization to the first of: virologic failure, AIDS progression, death due to any cause.

During Planned DSMB Review May 2008

- Found conclusive evidence that Arm 1B (ddI-EC+FTC+ATV) is inferior to control Arm 1A (ZDV/3TC+EFV) for the primary efficacy endpoint.
- Participants in inferior arm were switched to an NNRTI-based study-provided regimen.
- However, there was strong effect modification by sex, baseline CD4 count, and TB history.

What if Adaptive Design Had Been Used?

- Could an adaptive design have provided more information?
- For example, could we have pre-planned analyses and decision rules to allow subpopulations for which there is no evidence of Arm 1B inferiority to continue in that arm?
- How would that affect power, bias, interpretability, expected number of subjects assigned to an inferior arm?