# On Superiority of Adaptive Sequential Designs

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**FDA/Industry Statistics Workshop**

**September 18-19, 2003**

# Prelude

## Statistical Inference

- a game with two players
  - one player is *nature*
  - the other player is *the statistician*
- unknown true state of nature
- experiments
- random chance

## Two Strategies

- static designs
  - correct assumption or loss of power
- adaptive designs
  - best assumption with the flexibility to modify

## Intuition

Adaptive designs are superior

# Motivation

## Group Sequential Designs

- Armitage, McPherson and Rowe (1969)
- large body of literature

## Unavoidable Difficulty

- low conditional power

## Sample Size Adjustment

- the observed effect

## Lack of Efficiency

- Tsiatis and Mehta (2002)
- Jennison and Turnbull (2003)

## Better Efficiency and Effectiveness

- a minimum effect size (Liu and Chi, 2001)

# Two-Stage Designs

## Hypothesis

$H_0 : \delta \leq 0$ in favor of $H_1 : \delta > 0$ with a minimum effect size $\delta_{\text{min}}$

## Procedure

Assume observations from two distinct stages are independent, for which $p_1$ and $p_2$ are the 1st and 2nd stage $p$-values against $H_0$

- specify $\alpha_1 < \alpha < \alpha_1^*$, $\beta_1^* < \beta$, and a conditional error function $A(p_1)$ such that
  - $P_{\delta_{\text{min}}}\{p_1 \leq \alpha_1^*\} = 1 - \beta_1^*$
  - $\alpha_1 + \int_{\alpha_1}^{\alpha_1^*} A(p_1)dp_1 = \alpha$
- reject $H_0$ if $p_1 \leq \alpha_1$; accept $H_0$ if $p_1 > \alpha_1^*$; continue, otherwise
- reject $H_0$ if $p_2 \leq A(p_1)$

## Validity

Type I error rate is controlled if $p_1$ and $p_2$ are independent

# Two-Stage Designs

## Example 1

Two-stage group sequential designs

- fixed second stage sample size $n_2$
- $p_1$ and $p_2$ are independent
- $A(p_1) = 1 - \Phi\{\mu - \gamma\Phi^{-1}(1 - p_1)\}$
  - $\Phi(\cdot)$ is the cdf of the standard normal distribution
  - $\gamma = \{w/(1-w)\}^{1/2}$ where $w$ is the information fraction
  - $\mu$ is calculated to satisfy

$$\alpha_1 + \int_{\alpha_1}^{\alpha_1^*} A(p_1)dp_1 = \alpha$$

## Example 2

Two-stage adaptive designs where

$$n_2 = n_2(p_1)$$

# Two-Stage Adaptive Designs

## Notion of Adaptation

Formalization of the process for

- interim analysis
- decision making on modifications
- assessing the final trial outcomes

## Three basic components

- interim data
- adaptation rule
- final trial outcome

## Notations

- interim data $X_*$ and full data $X$
- a countable set $M$ of modifications
- adaptation rule $g : X_* \longrightarrow M$
- a procedure $p_m(X)$ for each $m \in M$
- the adaptive procedure $p_g = p_{g(X_*)}(X)$

# Two-Stage Adaptive Designs

## Stochastic Independence

Let $X = (X_*, X^*)$ where $X_*$ and $X^*$ are independent. Consider

- $g = g(X_*)$
- $p_1 = p_1(X_*)$
- $p_{2m} = p_{2m}(X^*)$ for each $m \in M$
- $p_2 = p_{2g}$

i) $(g, p_2)$ is independent of $p_1$ iff $g$ and $p_1$ are independent, or

ii) $(g, p_1)$ is independent of $p_2$ iff $p_{2m}$ follow the same distribution for all $m \in M$

## Application

Sample size adjustment (Liu and Chi, 2001)

$$g = n_2(p_1) = \{z_{A(p_1)} + z_{\beta_2}\}^2 / \delta^2_{\text{min}}$$

where

- $\beta_2 = (\beta - \beta_1^*)/(\beta_1 - \beta_1^*)$
- $\beta_1 = P_{\delta_{\text{min}}}\{p_1 > \alpha_1\}$

# Efficiency

## Assumptions

- same $n_1$ and $\alpha_1$, and therefore, $1 - \beta_1$
- same $1 - \beta$

## Notations

- $d$ for design
- $N_d(\delta)$ for average sample size
- Thall, Simon and Ellenberg (1988)
  - $\pi$ for probability that $\delta = \delta_m$
  - $1 - \pi$ for probability that $\delta = 0$
- $\mathcal{N}_d(\pi) = \pi N_d(\delta_m) + (1 - \pi) N_d(0)$

## Definition

Design $d_2$ is more efficient than design $d_1$ if and only if $\mathcal{N}_{d_2}(\pi) \leq \mathcal{N}_{d_1}(\pi)$

# Effectiveness

## Notations

- $C(n)$ for cost of experimentation, increasing in $n$
- $S(n)$ for payoff in future for rejecting $H_0$, decreasing in $n$

## Benefit

$$\begin{aligned} & B_d(\delta) \\ = \; & [\{S(n_1) - C(n_1)\}P_1 - C(n_1)Q_1] \\ & + \int_{\alpha_1}^{\alpha_1^*} \{S(n_1+n_2)P_2 - C(n_1+n_2)\} f_\delta(p_1)dp_1 \end{aligned}$$

where

- $P_1 = P_\delta\{p_1 \le \alpha_1\}$
- $Q_1 = P_\delta\{p_1 > \alpha_1^*\}$
- $n_2 = n_2(p_1)$
- $P_2 = P_\delta\{p_2 \le A(p_1) \,|\, p_1\}$
- $f_\delta(p_1)$ for density of $p_1$

## Risk

$$R_d(\delta) = C(n_1) + \int_{\alpha_1}^{\alpha_1^*} C(n_1+n_2) f_\delta(p_1)dp_1$$

# Effectiveness

## Definition

Design $d_2$ is more effective than design $d_1$ if and only if

i) $R_{d_2}(\delta) \leq R_{d_1}(\delta)$ for $\delta \geq \delta_{\text{min}}$, and

ii) $B_{d_2}(\delta) \geq B_{d_1}(\delta)$ for $\delta \geq \delta_{\text{min}}$

## Incremental Risk Benefit Ratio

$$\begin{aligned} & IRBR(\delta) \\ = \; & \{R_{d_2}(\delta) - R_{d_1}(\delta)\}/\{B_{d_2}(\delta) - B_{d_1}(\delta)\} \end{aligned}$$

## Alternative Formulations

- $B_d(\delta)$ in health outcomes, and $R_d(\delta)$ in monetary cost
- $B_d(\delta)$ and $R_d(\delta)$ both in health outcomes
- $B_d(\delta)$ and $R_d(\delta)$ in personal benefit and loss

# Numerical Example

## Clinical Trial

- double-blind parallel study to compare an experimental drug to a placebo
- response to treatment, success or failure
- response rate of the drug $r_2 = 0.5$
- response rate of the placebo $r_1 = 0.35$ but higher rate $r_1 = 0.4$ possible
- $\pi = 0.5$

## Benefit-Risk Considerations

- $C(n) = 2 + 0.05n$
- $S(n) = 10(120 - 12 - n/30)$

## Test Statistic and Effect Size

- $T = (2n)^{1/2}\{arcsin(\hat{r}_2^{1/2}) - arcsin(\hat{r}_1^{1/2})\}$
- $\delta = (2)^{1/2}\{arcsin(r_2^{1/2}) - arcsin(r_1^{1/2})\}$
- $\delta_{\text{min}} = 0.1424$

# Numerical Example

## Common Design Features

- $\alpha = 0.025$, $\beta = 0.05$
- $w = 0.5$
- $\alpha_1 = 0.00153$ by O'Brien-Fleming $\alpha$-spending function
- $n_1 = 338$ per group
- $1 - \beta_1 = 0.3648$

## Comparison of Designs

| | $d_{gs}$ | $d_{a_1}$ | $d_{a_2}$ |
|---|---|---|---|
| $\beta_1^*$ | 0.02159 | 0.02946 | 0.02938 |
| $\alpha_1^*$ | 0.27595 | 0.23329 | 0.23365 |
| $\mathcal{N}_d(\pi)$ | 487.81 | 491.70 | 470.76 |
| $B_d(\delta_{\min})$ | 823.87 | 831.07 | 836.40 |
| $R_d(\delta_{\min})$ | 29.26 | 28.17 | 27.46 |

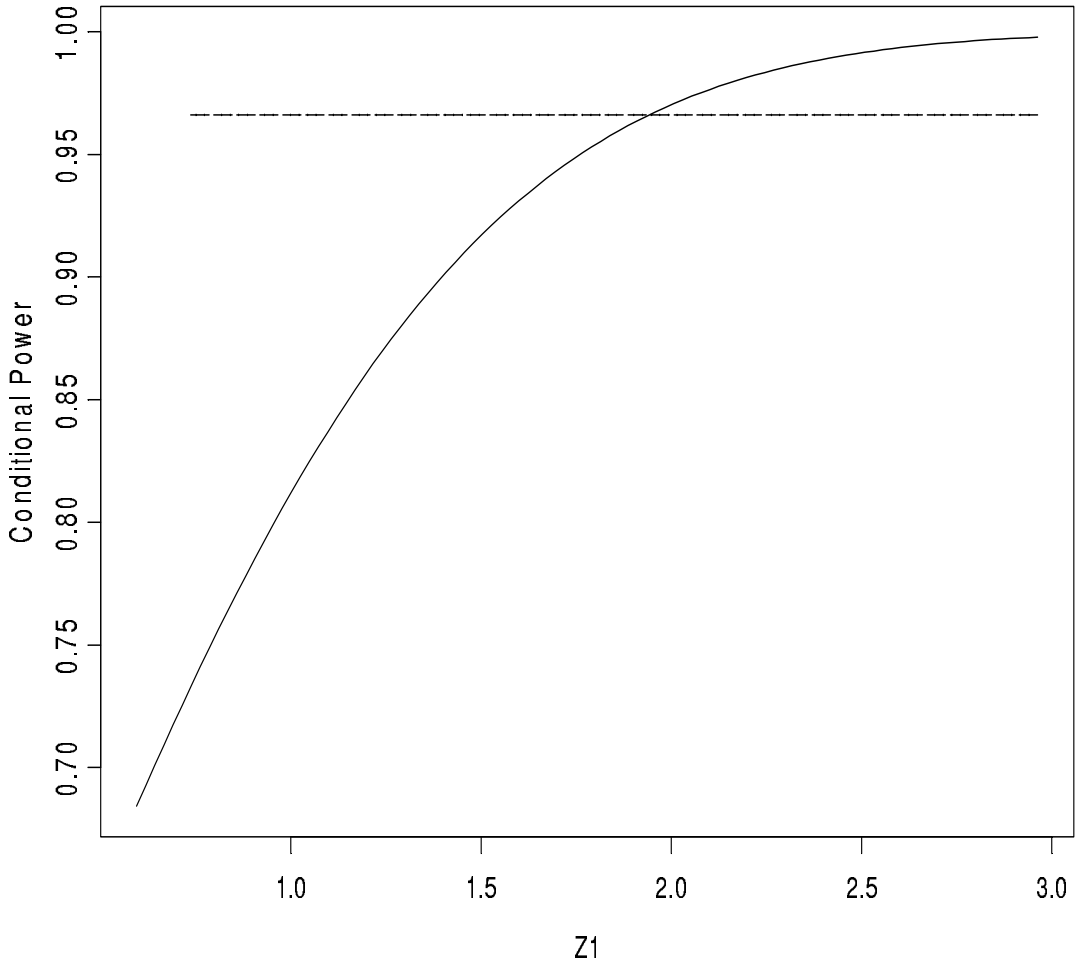
$d_{gs}$ — two-stage group sequential design

$d_{a_1}$ — two-stage adaptive design

$d_{a_2}$ — adaptive design with upto three stages

# Numerical Example

## Conditional Power

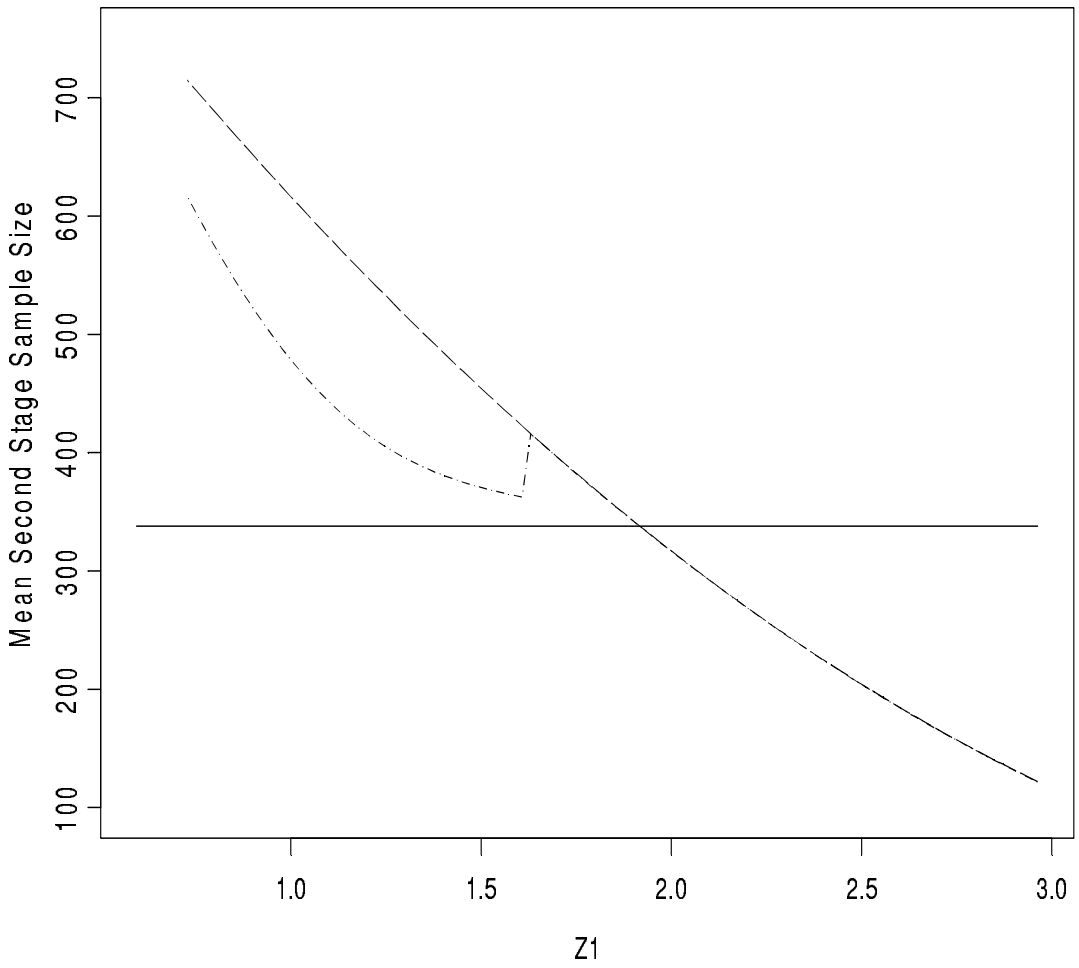



solid — $d_{gs}$

dash — $d_{a_1}$ and $d_{a_2}$

# Numerical Example

## Mean Second Stage Sample Size



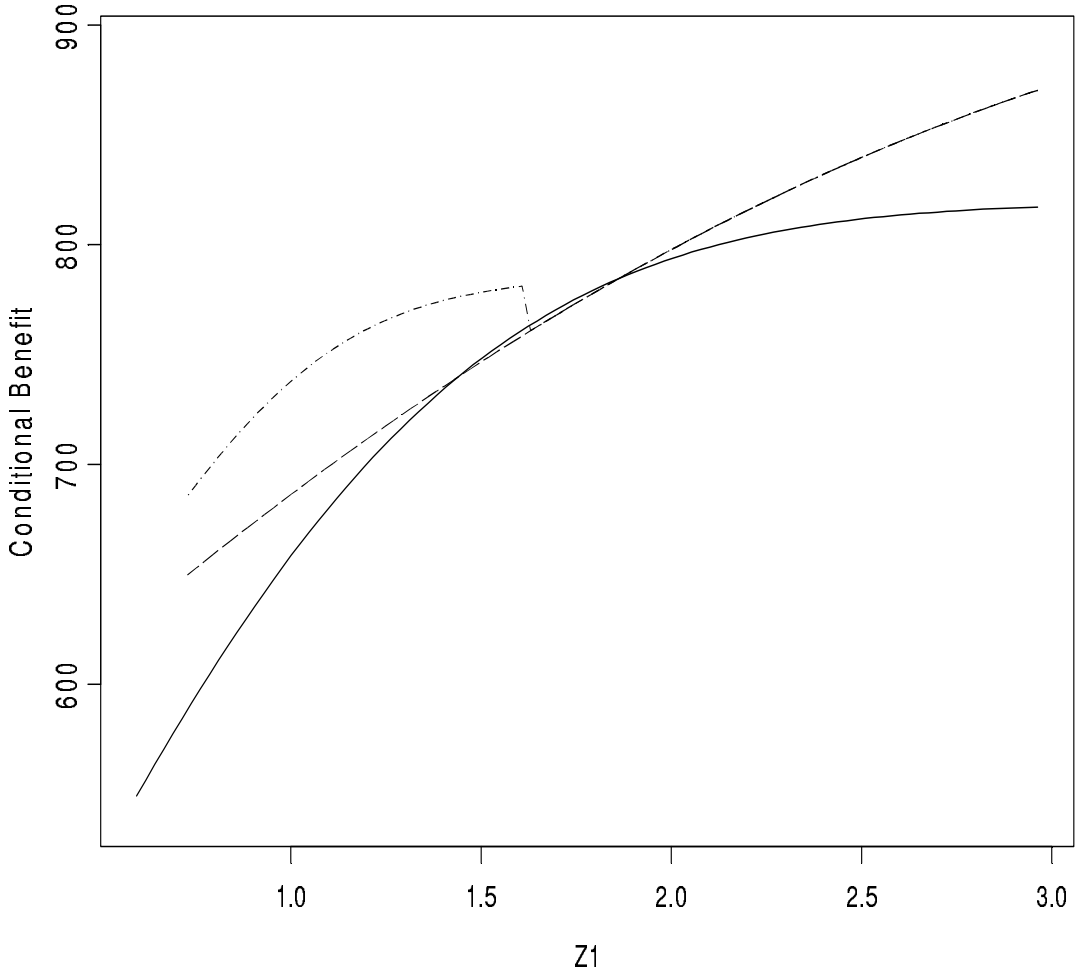

solid — $d_{gs}$

dash — $d_{a_1}$

dot-dash — $d_{a_2}$

# Numerical Example

## Conditional Benefit



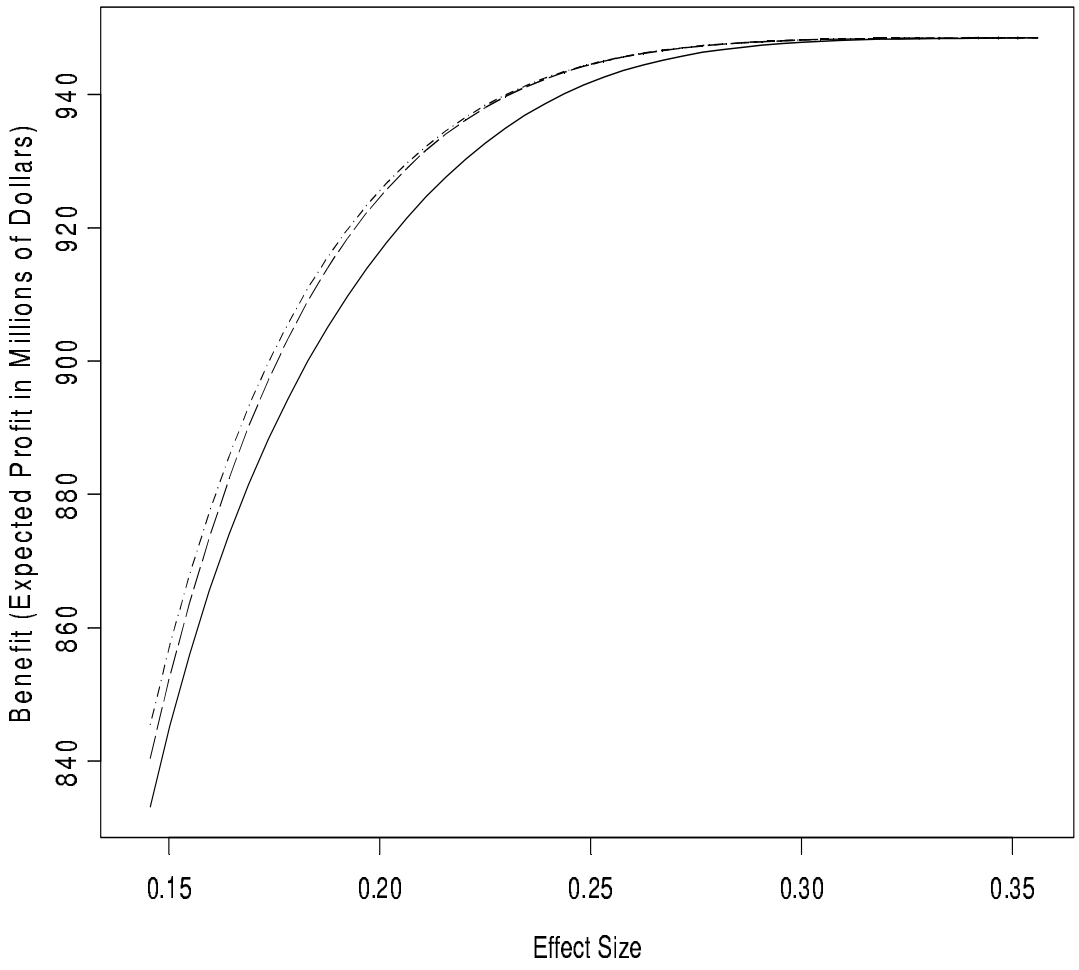

solid — $d_{gs}$

dash — $d_{a_1}$

dot-dash — $d_{a_2}$

# Numerical Example

## Benefit Function



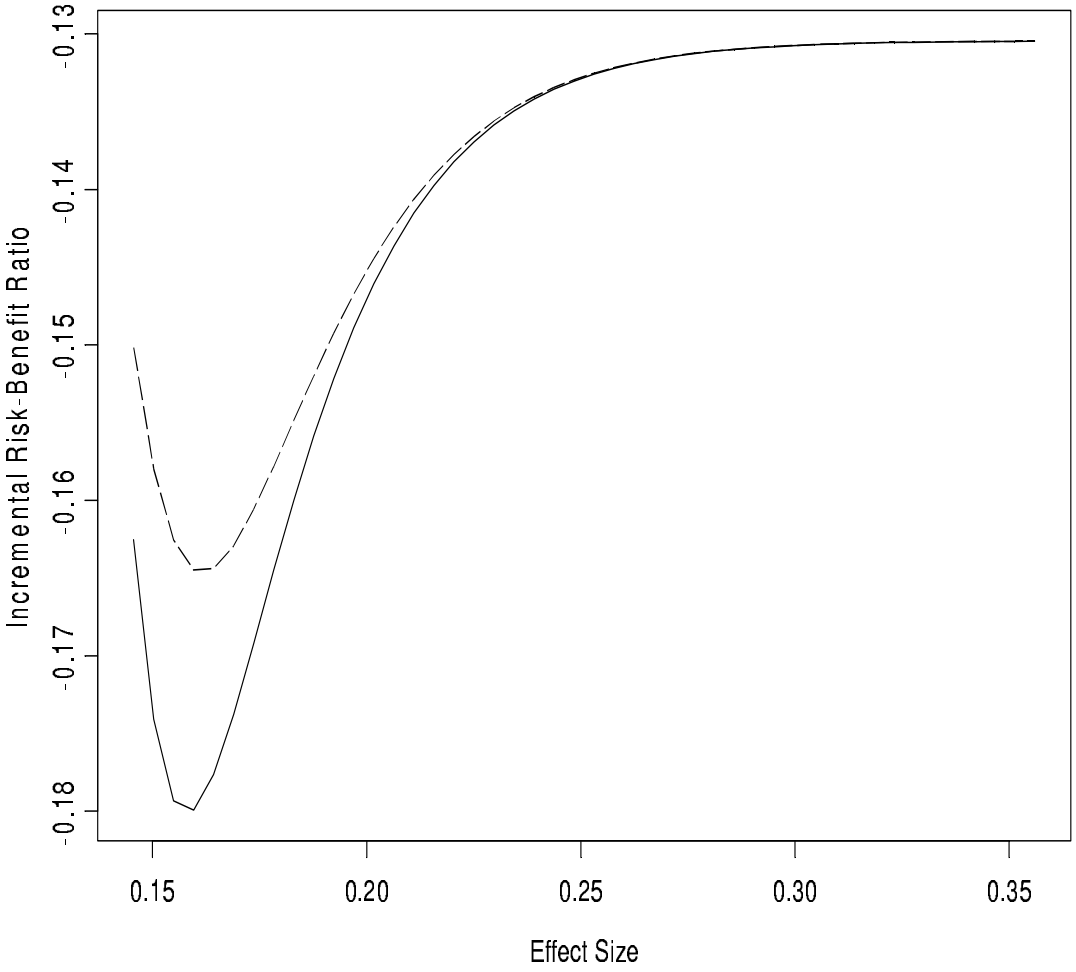

solid — $d_{gs}$

dash — $d_{a_1}$

dot-dash — $d_{a_2}$

# Numerical Example

## IRBR




solid — $d_{a_1}$ against $d_{gs}$

dash — $d_{a_2}$ against $d_{gs}$

# Discussion

## Sample Size Adjustment

- adaptive designs can be more efficient and effective by allowing sample size increase
- adaptive designs can be more efficient and effective without sample size increase
- extended UMP criteria of Tsiatis and Mehta (2002) are problematic
- sufficiency is no guarantee of optimality

## Other Adaptations

- dose or regimen selection
- change or selection of endpoints
- improvement of statistical analysis

## New Clinical Development Paradigm

- phase 2/3 combination designs
- accelerated approval of life-saving drugs