Effectiveness of Clinical Trials Designs for Drug Development

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J&J Pharmaceutical Research and Development

BASS XI

November 1-3, 2004

Sample Size Calculation

- **Who's done it?**
- **What's involved?**

  Effect size

  Variance, control rate, etc.

  Power

- **How large should the power be?**

  80% or 90%

  Higher power is better

  Smaller sample size is more efficient

Success Rates in Drug Development

Stage	PWC	DiMasi et al*
Preclinical	60%	
Phase I	64%	71%
Phase II	39%	44%
Phase III	62%	68%
Regulatory	82%	

*DiMasi et al. J of Health Economics, 22, 151-185

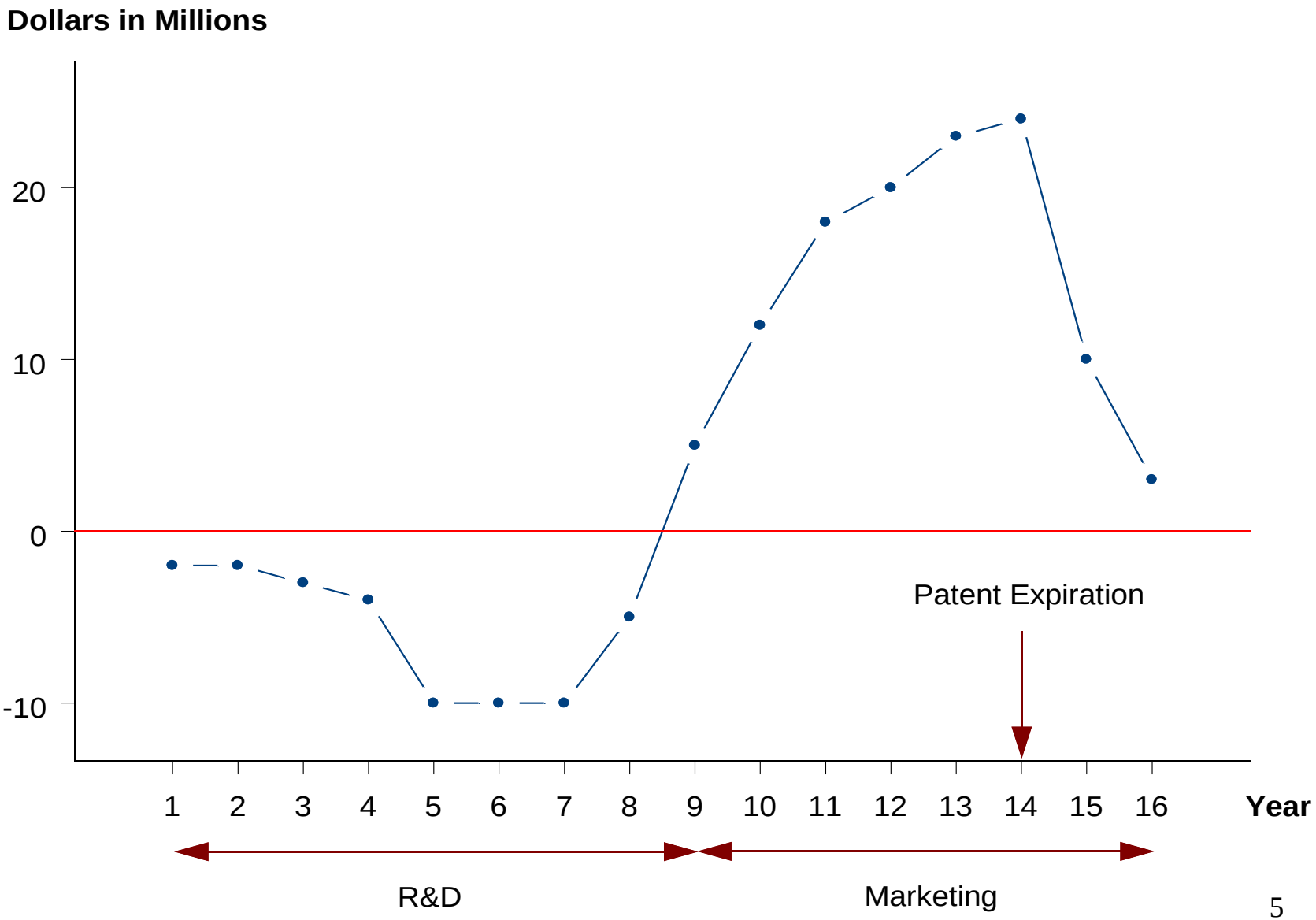
Choice of Power

- **Combined phase 2 and 3 success rate**

  40% x 60% or about 25%

- **What's the optimal power when the drug is not effective?**
- **Would nearly 100% power be optimal if the drug is effective?**
- **Should the power be different depending on stage of development or prior success rate?**
- **What design should be employed?**

Cash Flow of a Single Pharmaceutical Product



Asset Valuation

- **Basic architecture**
  1. Probability of success
  2. Expected return if successful
  3. Cost of development
  4. Time to market
- **Reference**

1. **Senn S.** (1996). Some statistical issues in project prioritization in the pharmaceutical industry. *Statistics in Medicine* **15**, 2689-2702.
2. **Senn S.** (1998). Further statistical issues … *Drug Information Journal* **32,** 253-259.
3. **Burman, C. F. and Senn S.** (2003). Examples of option values in drug development. *Pharmaceutical Statistics* **2**, 113-125.

Asset Valuation

- **Probability of success**

$$p(n) = p_1\, p_2(n)\, p_3\, p_4$$

1. p_1 – probability that drug is efficacious
2. $p_2(n)$ – power, increasing with sample size n
3. p_3 – probability that drug is safe
4. p_4 – probability of regulatory success

- **Cost of development**

  $C(n)$ – cost of development in present value, increasing in sample size

Asset Valuation

- **Expected return if successful**
  1. $t_1(n)$ – time of entry to market
  2. t_2 – time of patent expiration
  3. r_t – expected return at time t in present value, estimated based on information available at time zero
  4. $S(n)$ – total expected return, sum of s_t over the period between $t_1(n)$ and t_2
- **Expected net present value (NPV)**

  $\mathrm{NPV}(n) = S(n)\, p(n) - C(n)$
- **Pearson Index**

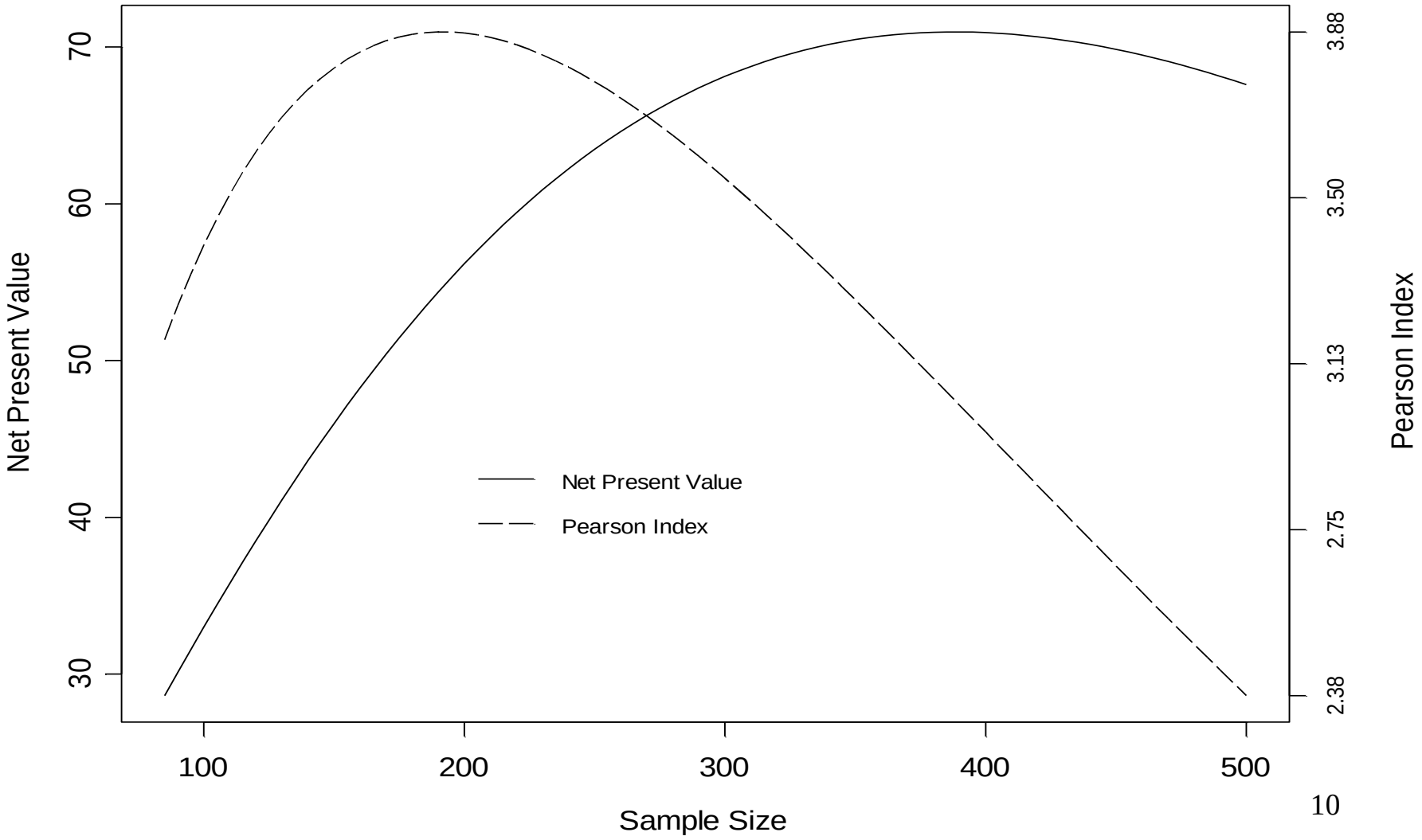
  $\mathrm{PI}(n) = \mathrm{NPV}(n) \,/\, C(n)$

Difficulties With the Pearson Index

- Example
  - $\delta = 0.3$, $\sigma = 1$, $\alpha = 0.025$, $p_1 = 0.5$, $p_3 = p_4 = 1$

	Standard	Max. PI
Power	0.90	0.55
Sample Size	468	192
PI	2.56	3.88
NPV (mil.)	69.16	54.74
Cost (mil.)	26.97	14.12

Pearson Index for Single-stage Designs With Prior = 0.50



Benefit-risk Evaluation

- **Value-at-Risk (VaR)**

  $C(0)$ – Prior cost incurred

  $C(n)$ – Cost to be incurred

  $\text{VaR}(n) = C(0) + C(n)$

- **Gain**

  $G(n) = \max\{0, S(n) - \text{VaR}(n)\} I \text{ or } 0$

- **Loss**

  $L(n) = \max\{0, \text{VaR}(n) - S(n)\} I + \text{VaR}(n)(1-I)$ *or* $\text{VaR}(n)$

Benefit-risk Evaluation

- **Benefit**

$$B(n) = \max\{0,\ S(n) - \mathrm{VaR}(n)\}p(n)$$

- **Risk**

$$R(n) = \max\{0,\ \mathrm{VaR}(n) - S(n)\}p(n) + \mathrm{VaR}(n)\{1 - p(n)\}$$

- **Expected Cash Flow**

$$\mathrm{CF}(n) = B(n) - R(n) = S(n)p(n) - \mathrm{VaR}(n)$$

- **Benefit-Risk Ratio**

$$\mathrm{BR}(n) = B(n) / R(n)$$

Benefit-risk Evaluation

- **Comparing Two Designs d_1 and d_2**

  Let $\mathrm{CF}(d_1) \leq \mathrm{CF}(d_2)$. *$d_1$ is more effective than d_2 iff*

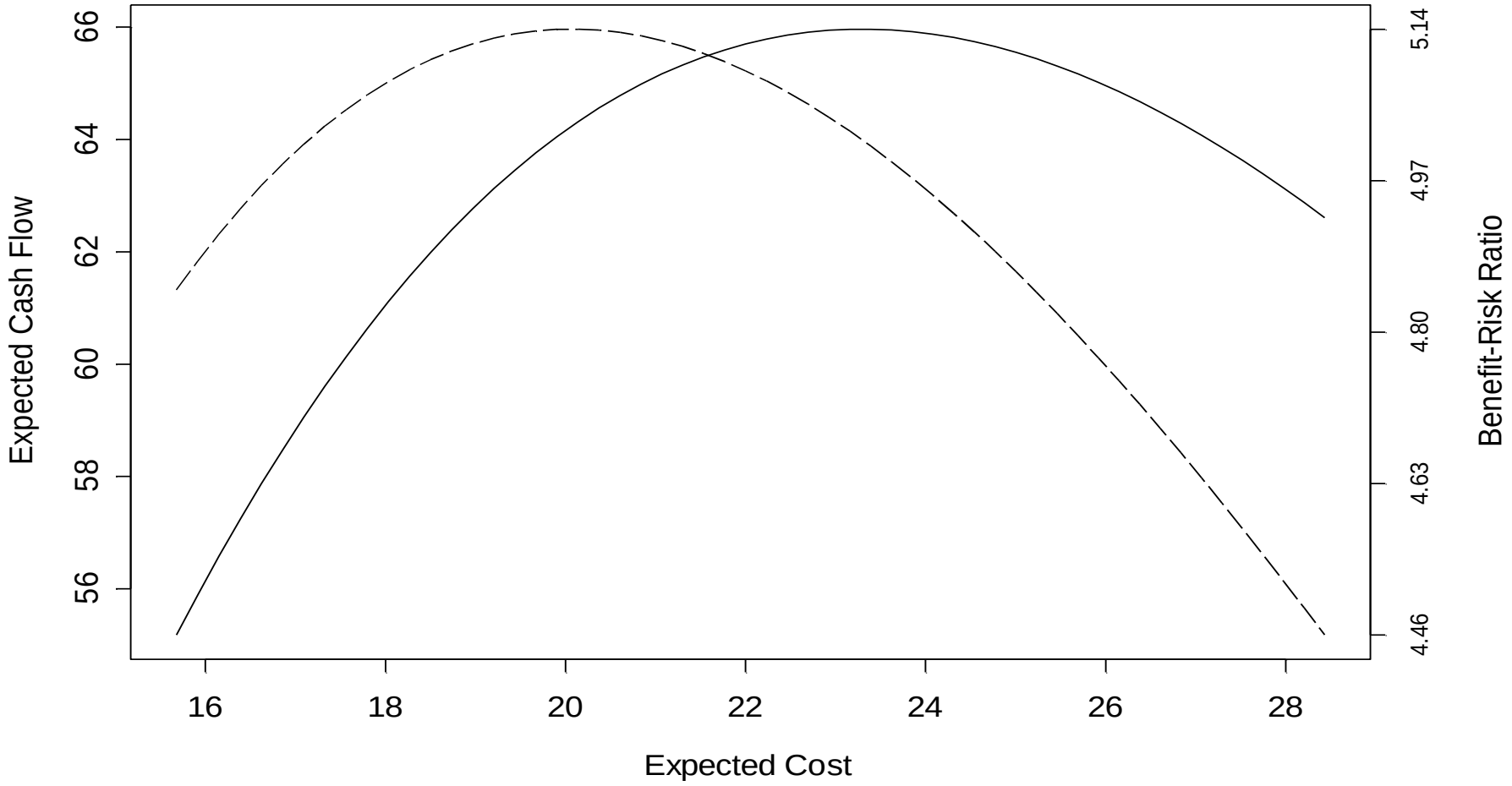
  - $\mathrm{BR}(d_1) \geq \mathrm{BR}(d_2)$ *and*
  - $C(d_1) < C(d_2)$.

  Otherwise, d_2 is more effective than d_1

- **Most Effective Design for a Class *D***

  Design d in D is most effective iff it is more effective than any other design in D*

Most Effective Single-stage Design



Most Effective Single-stage Design

	Standard	Max. PI	Max. BR	Max. CF
Power	0.90	0.55	0.76	0.84
N	468	192	319	389
PI	2.56	3.88	3.45	3.04
NPV	69.16	54.74	69.27	70.96
Cost	26.97	14.12	20.09	23.34
Benefit	81.74	63.63	79.77	82.34
Risk	17.56	13.87	15.51	16.43
Cash Flow	64.16	49.74	64.27	65.86
BR	4.65	4.58	5.14	5.02

Two-stage Design With Futility

- **Futility Criteria**
  - $\beta^* = 0.05$ and given n_1
  - Futility level $1 - \alpha^*$ with $P_\delta\{ Z_1 \geq z_{\alpha^*}\} = 1 - \beta^*$
  - Stop for futility if $Z_1 < z_{\alpha^*}$
- **Test Procedure**
  - Test Statistic $Z = \lambda^{1/2} Z_1 + (1 - \lambda)^{1/2} Z_2$
  - Reject the null if $Z \geq z_\alpha$
- **Choice of n_2**
  - Most effective n_2 given $Z_1 \geq z_{\alpha^*}$
  - Stop with n_{20}, number of patients already entered

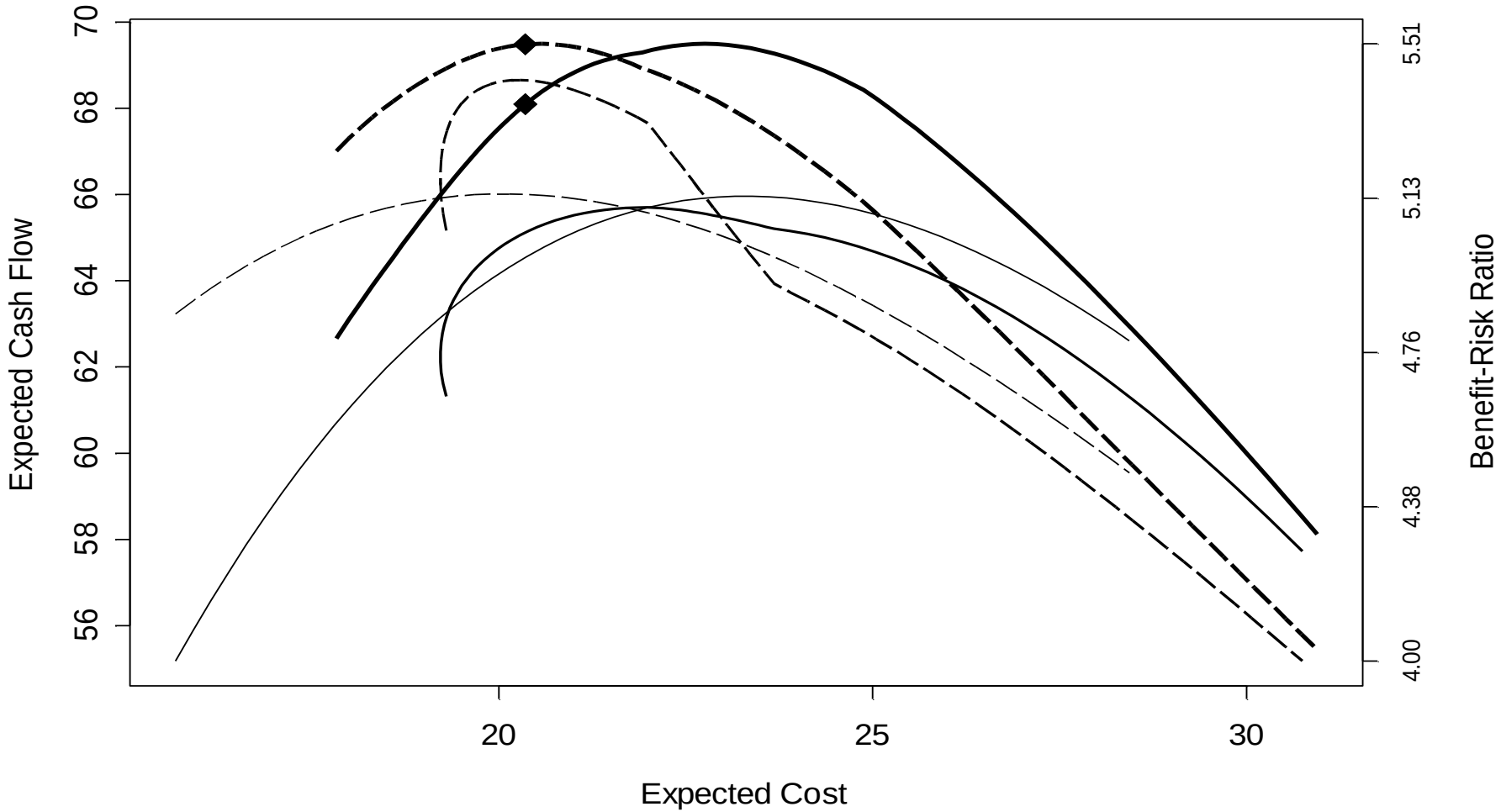
Two-stage Adaptive Design

- **Conditional Critical Value and Error**
  - $z(z_1) = (z_\alpha - \lambda^{1/2} z_1) / (1 - \lambda)^{1/2}$
  - $A(z_1) = 1 - \Phi\{z(z_1)\}$
- **Conditional Test**

  $Z_2 \geq z(z_1)$
- **Conditional Single-stage Design**

  Conditional on $Z_1 = z_1$ the second stage can be treated as a single-stage design with type I error rate $A(z_1)$
- **Choice of n_2**
  - Most effective n_2 given $Z_1 = z_1$ for $z_1 \geq z_{\alpha^*}$
  - Stop with n_{20}

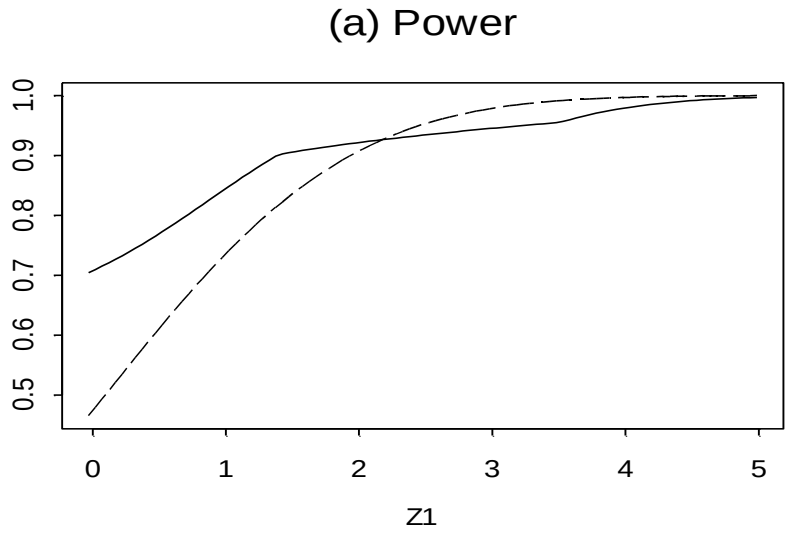
Most Effective Design

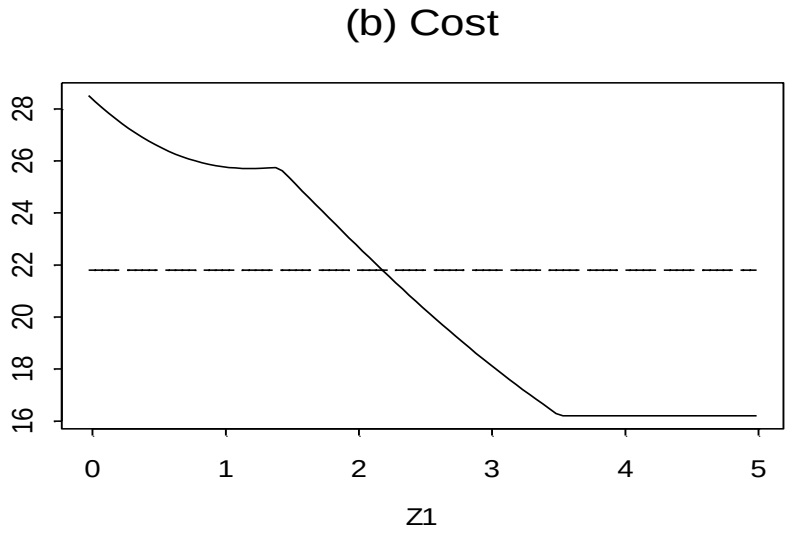


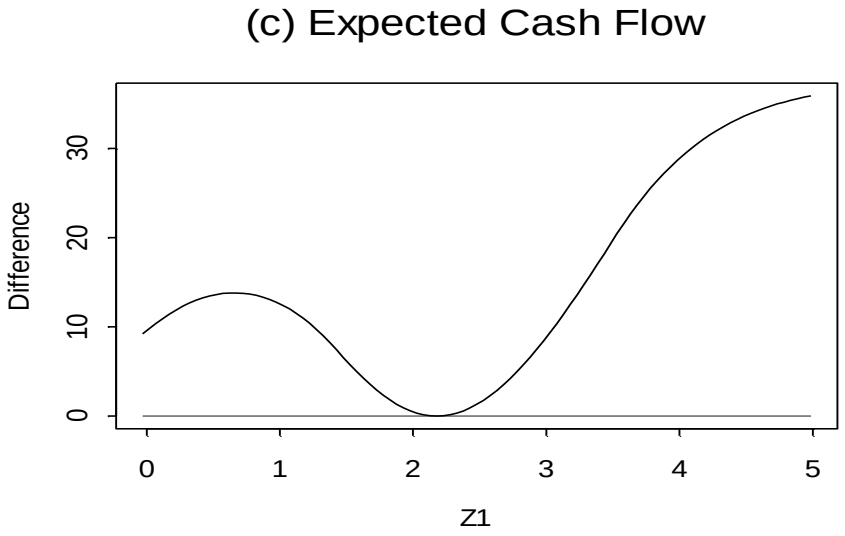
Comparison of Designs

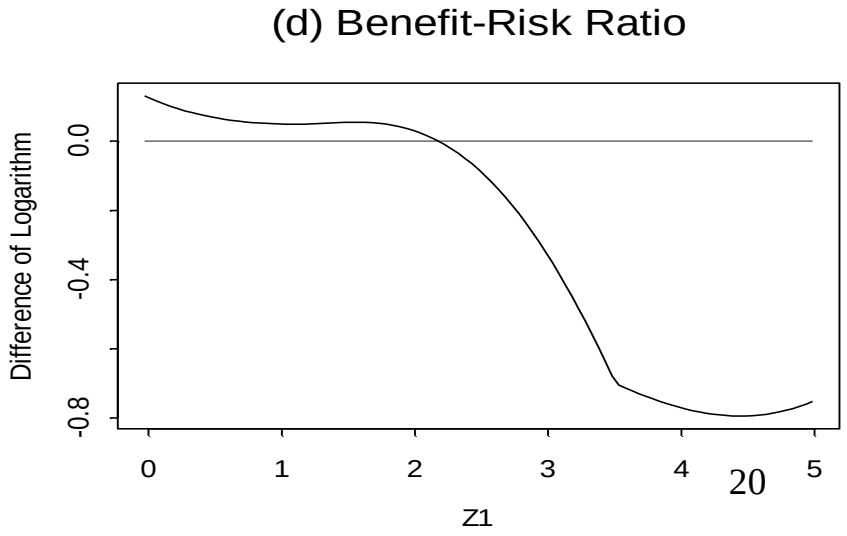
	Opt SSD	Opt TSD	AD*	Opt AD
Power	0.76	0.79	0.78	0.79
N	319	323.4	325.29	329.5
PI	3.45	3.45	3.59	3.57
NPV	69.27	70.06	73.10	73.36
Cost	20.09	20.29	20.36	20.55
Benefit	79.77	79.77	83.20	83.51
Risk	15.51	14.71	15.10	16.15
Cash Flow	64.27	65.06	68.10	68.35
BR	5.14	5.42	5.5097	5.5112

Conditional Measures of Adapted Two-stage Design



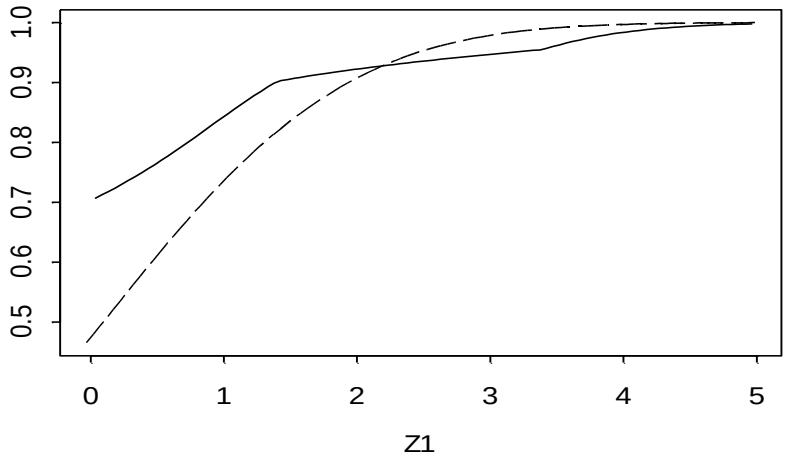




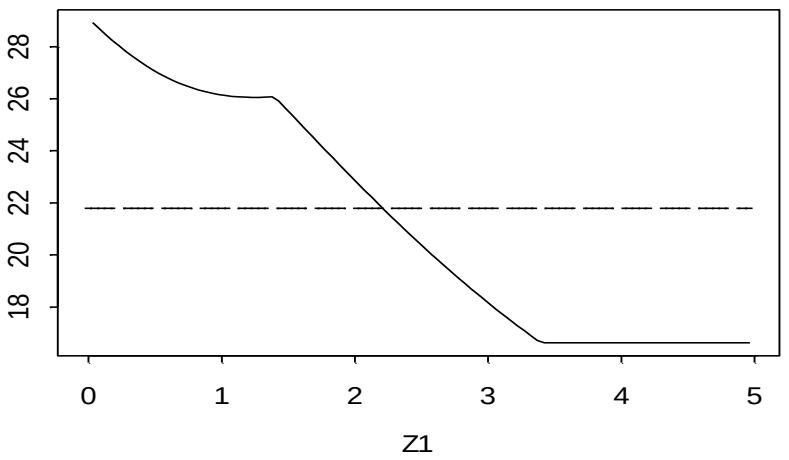


Conditional Measures of Most Effective Two-stage Adaptive Design

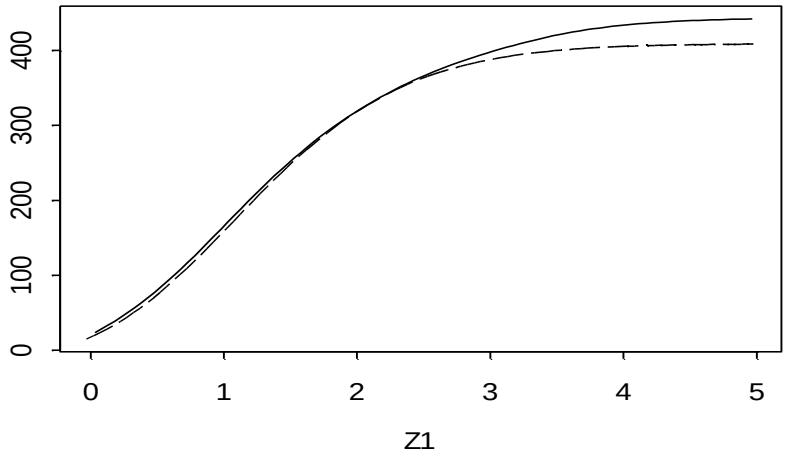
(a) Power



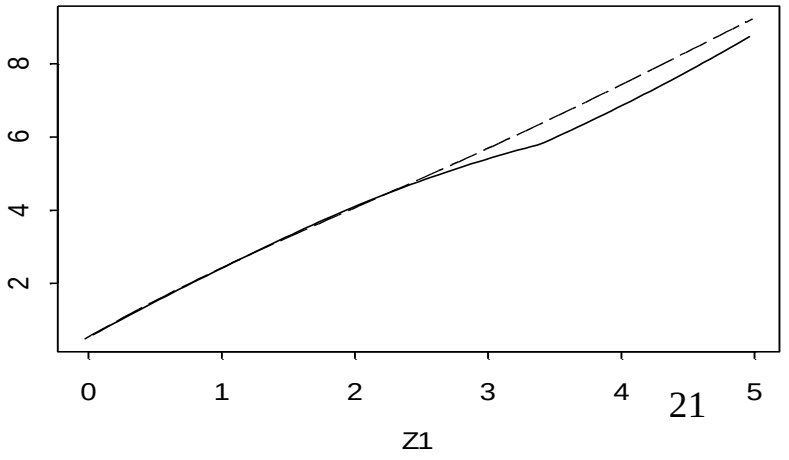
(b) Cost



(c) Expected Cash Flow



(d) Benefit-Risk Ratio



Extensions

- **Monetary model**
  1. Monetary benefit and risk
  2. Pharmaceutical industry for portfolio management
- **Health-economic model**
  1. Monetary cost and health related benefit
  2. CMS or NIH
- **Ethical Model**

  Health related cost and benefit
- **Personal Model**

Conclusion

- Neyman-Pearson theory not suitable for project evaluation
- Adaptive designs can be more effective
- Static designs should always include the option to adapt
- Adaptive designs are broader, including phase 2/3 combination designs, which are less costly and time-consuming to traditional clinical development paradigm