The Use of Decreasingly Informative Priors in Adaptive Clinical Trial Designs

Roy T. Sabo

Department of Biostatistics
School of Medicine
Virginia Commonwealth University

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- Two Sample Optimal Design (Rosenberger *et al.*, 2001):
  - Minimizes treatment failures $(n_1(1-p_1)+n_2(1-p_2))$.
  - Assumes fixed variance for each success rate.
  - Allocation weights:

$$\begin{aligned} w_1 &= \frac{\sqrt{p_1}}{\sqrt{p_1}+\sqrt{p_2}} \\ w_2 &= 1-w_1 \end{aligned}$$

  - In actual trials, p_j is replaced with sample proportion $\hat{p}_j$.

- Three Sample Optimal Design (Tymofyeyev *et al.*, 2007; Jeon and Hu, 2010):
  - Assuming fixed variances, minimizes treatment failures $(n_1(1-p_1)+n_2(1-p_2)+n_3(1-p_3))$.
  - Let $\mathbf{w}^* = (w_1^*, w_2^*, w_3^*)^T$ denote optimal proportions.
  - $B \in (0, 1/3)$ represents minimum allocation proportion.
  - Then for $p_1 > p_2 > p_3$, allocation weights are:

$$\begin{aligned} w_1^* &= l_2^{-1}(l_1 + l_3 B) \\ w_2^* &= B \\ w_3^* &= 1 - B - w_1^*, \end{aligned}$$

- Three Sample Optimal Design, continued:
  - where

$$
\begin{aligned}
l_1 &= (a(p_1 - p_3) + b(p_2 - p_3) + d)/p_3 q_3 \\
l_2 &= (b(p_1 - p_2) + c(p_1 - p_3) - d)/p_1 q_1 + l_1 \\
l_3 &= (a(p_1 - p_2) - c(p_2 - p_3) + d)p_2 q_2 - l_1 \\
a &= -(Bq_2 - (B-1)q_3)/p_1 q_1 \\
b &= -(B(q_3 - q_1))/p_2 q_2 \\
c &= (Bq_2 - (B-1)q_1)/p_3 q_3 \\
d &= \sqrt{-ab(p_1 - p_2)^2 - ac(p_1 - p_3)^2 - bc(p_2 - p_3)^2}
\end{aligned}
$$

- If $w_1^* \leq B$, the solution is $\mathbf{w}^* = (B, B, 1-2B)^T$.
- If $w_3^* \leq B$, the solution is $\mathbf{w}^* = (1-2B, B, B)^T$.

- Three Sample Optimal Design, continued:
  - When $p_1 = p_2 > p_3$, if

$$B \leq min\left[\frac{\sqrt{p_1}}{2(\sqrt{p_1}+\sqrt{p_3})}, \frac{\sqrt{p_3}}{\sqrt{p_1}+\sqrt{p_3}}, 1/3\right],$$

    the solution is:

$$\begin{aligned} w_1^* &= w_2^* = \frac{\sqrt{p_1}}{2(\sqrt{p_1}+\sqrt{p_3})} \\ w_3^* &= \frac{\sqrt{p_3}}{\sqrt{p_1}+\sqrt{p_3}} \end{aligned}$$

  - If $B > \frac{\sqrt{p_1}}{2(\sqrt{p_1}+\sqrt{p_3})}$, the solution is $\mathbf{w}^* = (B, B, 1-2B)^T$.
  - If $B > \frac{\sqrt{p_3}}{\sqrt{p_1}+\sqrt{p_3}}$, the solution is $\mathbf{w}^* = ((1-B)/2, (1-B)/2, B)^T$.

- Three Sample Optimal Design, continued:
  - When $p_1 > p_2 = p_3$, if

$$B \leq min\left[\frac{\sqrt{p_3}}{2(\sqrt{p_1}+\sqrt{p_3})}, 1/3\right],$$

    the solution is:

$$\begin{aligned} w_1^* &= \frac{\sqrt{p_1}}{\sqrt{p_1}+\sqrt{p_3}} \\ w_2^* &= w_3^* = \frac{\sqrt{p_3}}{2(\sqrt{p_1}+\sqrt{p_3})} \end{aligned}$$

  - If $B > \frac{\sqrt{p_3}}{2(\sqrt{p_1}+\sqrt{p_3})}$, the solution is $\mathbf{w}^* = (1-2B, B, B)^T$.
- In actual trials, p_j is replaced with sample proportion $\hat{p}_j$.

- Problems with optimal design:
  - Allocation weights not defined when $y_j = 0$ or $y_j = n_j$.
  - Allocation weights more variable when n_j are small.
- Possible Solutions:
  - *Hard* Lead-In: fix allocation proportions for certain number of subjects.
  - Conditional Hard Lead-In: fix allocation proportions until at least one success observed in each arm.
- Natural lead-in:
  - Restricts allocation proportions in early phases of trial.
  - Ability to adapt increases as trial continues.
  - Often use Bayes estimators.

- Two Sample Natural Lead-In (Thall and Wathen, 2007):
  - Allocation weights:

$$
\begin{aligned}
w_1 &= \frac{p_1^{c(n,N)}}{p_1^{c(n,N)} + p_2^{c(n,N)}} \\
w_2 &= 1 - w_1 \\
c(n,N) &= n/2N
\end{aligned}
$$

  - In actual trials, p_1 and p_2 replaced with posterior probabilities $P(p_1 > p_2)$ and $P(p_2 > p_1)$ (Thompson, 1933).
  - Allocation proportions begin at equal allocation.
  - Allocation allowed to increase as trial continues.

- Three Sample Natural Lead-In (Bello and Sabo, submitted):
  - Allocation weights (based off Hu and Zhang (2004)):

$$
\begin{aligned}
w_j &= \frac{w_j^* \left((w_j^* \sum_{i=1}^{3} n_i)/n_j \right)^{\gamma(n,N)}}{\sum_{k=1}^{3} w_k^* \left((w_k^* \sum_{i=1}^{3} n_i)/n_k \right)^{\gamma(n,N)}} \\
j &= 1, 2, 3, \\
\gamma(n,N) &= (N - (n+1))/n
\end{aligned}
$$

  - In actual trials, p_1 replaced with posterior probability $P\left[(p_1 > p_2) \bigcap (p_1 > p_3)\right]$, etc.
  - Allocation proportions begin at equal allocation.
  - Allocation allowed to increase as trial continues.

- Problems with Natural Lead-In Methods:
  - *Ad hoc*: not designed to optimize anything.
  - If estimators of p_j not used, then allocation proportions *DO NOT* converge to optimality.
- Alternative Solutions:
  - Use posterior to estimate mean or mode instead of efficacy probabilities
  - Use posterior estimators that do not change much when n is small.
  - Use optimal designs in two- and three-group cases.

- Decreasingly Informative Priors:
  - Mass or density functions.
  - Parameters are functions of observed (n) and planned (N) sample sizes.
  - Skeptical priors: centered around some value θ_0.
- In Bayes set-up:
  - Identical priors for all groups (e.g. treatment groups).
  - When n is small, more information in prior than likelihood.
  - As n increases, information incrementally transferred to likelihood.

- General Set-Up:

$$\theta \sim P(\theta|y) = \frac{f(y|\theta)\pi(\theta|\theta_0, n, N)g(\theta_0|\lambda)}{\int f(y|\theta)\pi(\theta|\theta_0, n, N)g(\theta_0|\lambda)}$$

  - $y \rightarrow$ observed data
  - $\theta \rightarrow$ parameter of interest
  - $f(.) \rightarrow$ likelihood
  - $\pi(.|\theta_0, n, N) \rightarrow$ DIP
  - $g(.) \rightarrow$ hyperprior on θ_0 with hyperparameter λ

- Say we have binary outcomes in K groups.
- Model: beta-binomial conjugate pair.
- Point Mass DIP centered at p_0.
  - $f(.) \rightarrow y_k \sim \text{binomial}(n_k, p_k)$
  - DIP:
    $\pi(.|\theta_0, n, N) \rightarrow p_k \sim \text{beta}\left[1 + p_0(N-n), 1 + (1-p_0)(N-n)\right]$
  - $g(.) \rightarrow p_0 = p_0$ with probability 1
  - $\theta \rightarrow p_k \sim$
    $\text{beta}\left[1 + y_k + p_0(N-n), 1 + (n_k - y_k) + (1-p_0)(N-n)\right]$

- Say we have binary outcomes in K groups.
- Model: beta-binomial conjugate pair.
- DIP centered at p_0 with hyperprior.
  - $f(.) \rightarrow y_k \sim \text{binomial}(n_k, p_k)$
  - DIP:
    $\pi(.|\theta_0, n, N) \rightarrow p_k \sim \text{beta}\left[1 + p_0(N-n), 1 + (1-p_0)(N-n)\right]$
  - $g(.) \rightarrow p_0\ \text{beta}\left[1+\delta_1, 1+\delta_2\right]$
  - $\theta \rightarrow p_k \sim f(p_k|y_k, n, N, p_0, \delta_1, \delta_2)$

- Say we have continuous outcomes in K groups.
- Model: normal-normal conjugate pair.
- DIP centered at μ_0 with hyperprior and fixed variance ϕ_0.
  - $f(.) \rightarrow y_k \sim \text{normal}(\mu_k, \phi_k)$
  - DIP: $\pi(.|\theta_0, n, N) \rightarrow \mu_k|\phi_k \sim \text{normal}(\mu_0, \phi_0(n, N))$, where $\phi_0(n, N)$ is some increasing function of n.
  - $g(.) \rightarrow \mu_0$ normal$(0, \phi_A)$, where ϕ_A is large
  - $\theta \rightarrow \mu_k \sim f(\mu_k|y_k, n, N, \theta_0, \phi_0, \phi_A)$

- Say we have count outcomes in K groups.
- Model: gamma-Poisson conjugate pair.
- DIP centered at λ_0 with hyperprior.
  - $f(.) \rightarrow y_k \sim \text{Poisson}(\lambda_k)$
  - DIP: $\pi(.|\theta_0, n, N) \rightarrow \lambda_k \sim \text{gamma}(\alpha_0(n,N), \beta_0(n,N))$, where $\alpha_0(n,N) \rightarrow 1$ and $\beta_0(n,N) \rightarrow 0$ as $n \rightarrow N$.
  - $g(.) \rightarrow \alpha_0 \sim \text{gamma}(\alpha_1, \beta_1)$ and $beta_0 \sim \text{gamma}(\alpha_2, \beta_2)$ are both difuse.
  - $\theta \rightarrow \lambda_k \sim f(\lambda_k|y_k, n, N, \alpha_0(n,N), \beta_0(n,N), \alpha_1, \alpha_2, \beta_1, \beta_2)$

- Calculating $P(p_1 > p_2)$ or $P\left[(p_1 > p_2) \bigcap (p_1 > p_3)\right]$:
  - Integration
  - Direct Sampling (conjugate pairs, DIP with point mass, NLI)
  - MCMC.
- Posterior Mean or Mode:
  - Can be calculated directly (conjugate pairs, DIP with point mass, NLI).
  - Integration, Direct Sampling, MCMC

- Two Group Case (DIP with Point Mass)
- True Efficacy: $p_1 = 0.5$ and $p_2 = 0.3$, $N = 200$

		DIP		
	TW	$p_0 = 0.2$	$p_0 = 0.3^*$	$p_0 = 0.4$
$\%(n_1 > n_2)$	99.7%	98.4%	99.4%	99.6%
Power	80.9%	71.8%	78.6%	79.7%
$\hat{n}_1$	144.7	153.8	148.3	143.0
$\hat{n}_2$	55.3	46.2	51.7	57.0
(SD)	(16.37)	(20.07)	(16.60)	(14.16)

$*$ indicates correct choice of prior.

- Two Group Case (DIP with Point Mass)
- True Efficacy: $p_1 = 0.7$ and $p_2 = 0.5$, $N = 200$

		DIP		
	TW	$p_0 = 0.4$	$p_0 = 0.5^*$	$p_0 = 0.6$
$\%(n_1 > n_2)$	98.9%	98.2%	98.5%	98.6%
Power	79.1%	75.8%	79.8%	77.5%
$\hat{n}_1$	143.6	150.0	146.8	142.9
$\hat{n}_2$	56.4	50.0	53.2	57.1
(SD)	(17.80)	(19.08)	(17.14)	(15.32)

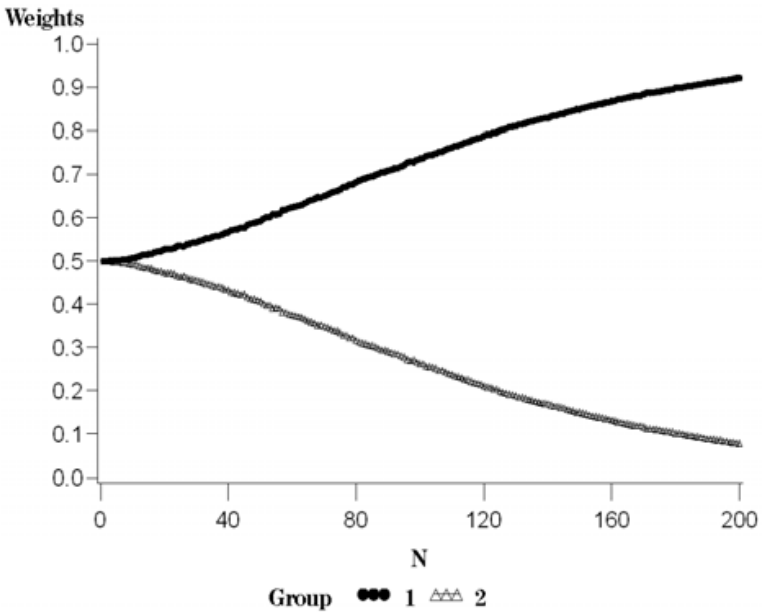
$*$ indicates correct choice of prior.

- Two Group Case (DIP with Point Mass)
- True Efficacy: $p_1 = 0.9$ and $p_2 = 0.7$, $N = 200$

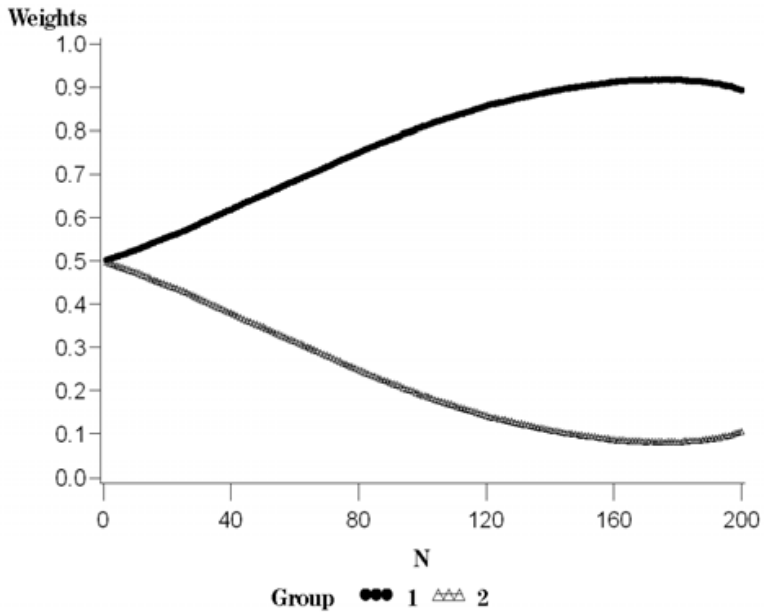
		DIP		
	TW	$p_0 = 0.6$	$p_0 = 0.7^*$	$p_0 = 0.8$
$\%(n_1 > n_2)$	99.9%	99.3%	99.8%	99.9%
Power	95.3%	92.2%	94.7%	93.8%
$\hat{n}_1$	153.0	154.0	153.0	151.5
$\hat{n}_2$	47.0	46.0	47.0	48.5
(SD)	(15.76)	(15.70)	(14.09)	(13.34)

$*$ indicates correct choice of prior.

- Two Group Case (DIP with Point Mass)
- True Efficacy: $p_1 = 0.5$ $p_2 = 0.3$, $N = 200$

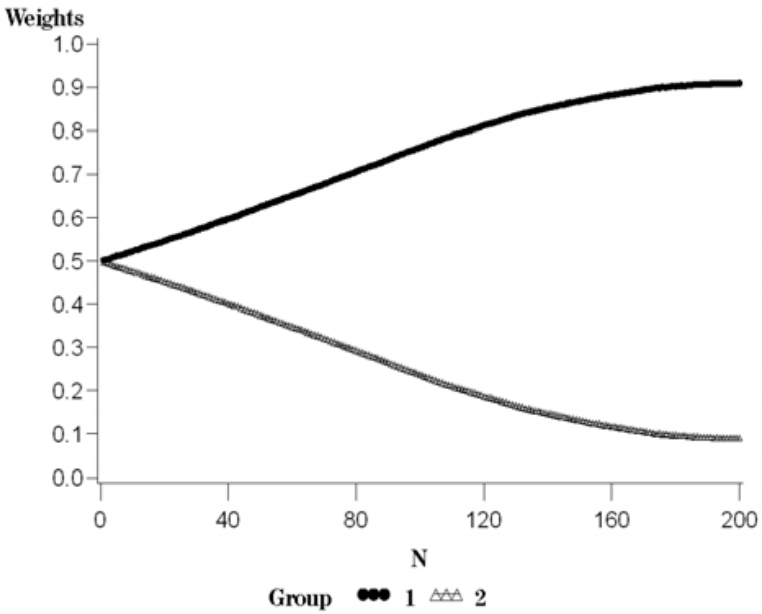


(a) TW

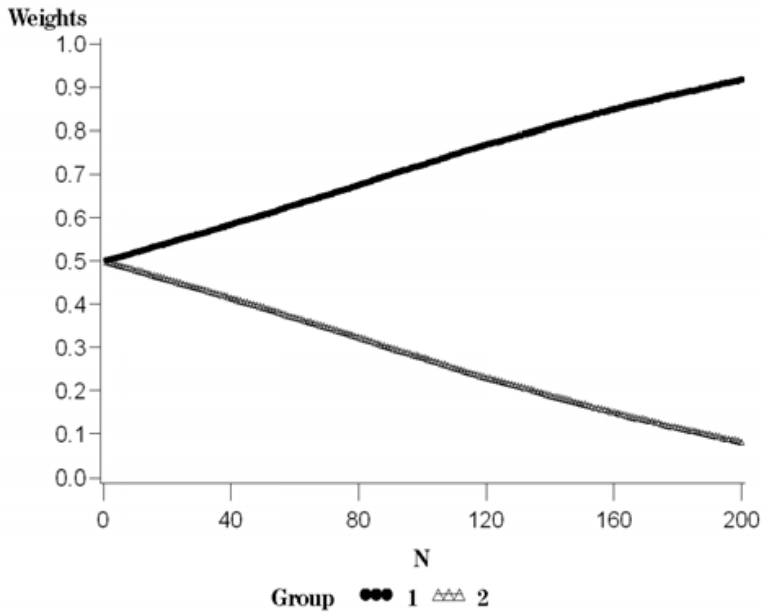


(b) DIP $p_0 = 0.2$

- Two Group Case (DIP with Point Mass)
- True Efficacy: $p_1 = 0.5$ $p_2 = 0.3$, $N = 200$



(c) DIP $p_0 = 0.3$



(d) DIP $p_0 = 0.4$

- Two Group Case (DIP with Hyperprior; posterior mean)
- True Efficacy: $p_1 = 0.25$ and $p_2 = 0.1$, $N = 200$

	Bal.	TW	DIP
Exp. Succ.	35.1 (3.85)	36.5 (4.28)	36.1 (4.00)
$\hat{n}_1$	100.2 (7.13)	110.6 (7.81)	105.3 (6.89)
$\hat{n}_2$	99.8 (7.13)	89.4 (7.81)	94.7 (6.89)
Power	80.0%	81.2%	80.3%
Error	0.0%	0.0%	0.0%
R_{50}	–	1.24 (0.15)	1.06 (0.04)
R_{75}	–	1.40 (0.22)	1.14 (0.07)
R_{100}	–	1.58 (0.30)	1.53 (0.25)

- Two Group Case (DIP with Hyperprior; posterior mean)
- True Efficacy: $p_1 = 0.55$ and $p_2 = 0.4$, $N = 352$

	Bal.	TW	DIP
Exp. Succ.	167.2 (7.86)	167.9 (8.92)	167.8 (8.57)
$\hat{n}_1$	175.7 (9.47)	183.1 (10.23)	181.4 (9.65)
$\hat{n}_2$	176.3 (9.47)	168.9 (10.23)	170.6 (9.65)
Power	80.0%	81.3%	80.1%
Error	0.0%	0.0%	0.0%
R_{50}	–	1.08 (0.04)	1.05 (0.03)
R_{75}	–	1.13 (0.06)	1.10 (0.04)
R_{100}	–	1.17 (0.07)	1.17 (0.07)

- Two Group Case (DIP with Hyperprior; posterior efficacy)
- True Efficacy: $p_1 = 0.25$ and $p_2 = 0.1$, $N = 200$

	Bal.	TW	DIP
Exp. Succ.	35.1 (3.85)	40.6 (5.12)	38.5 (4.56)
$\hat{n}_1$	100.2 (7.13)	138.6 (12.85)	122.7 (7.60)
$\hat{n}_2$	99.8 (7.13)	61.4 (12.85)	77.3 (7.60)
Power	80.0%	77.8%	83.1%
Error	0.0%	0.0%	0.0%
R_{50}	–	2.56 (1.11)	1.44 (0.29)
R_{75}	–	5.51 (3.12)	2.24 (0.73)
R_{100}	–	12.2 (8.22)	12.3 (7.78)

- Two Group Case (DIP with Hyperprior; posterior efficacy)
- True Efficacy: $p_1 = 0.55$ and $p_2 = 0.4$, $N = 352$

	Bal.	TW	DIP
Exp. Succ.	167.2 (7.86)	178.0 (15.11)	175.1 (12.79)
$\hat{n}_1$	175.7 (9.47)	244.1 (22.60)	226.9 (17.08)
$\hat{n}_2$	176.3 (9.47)	107.9 (22.60)	125.1 (17.08)
Power	80.0%	76.5%	81.5%
Error	0.0%	0.0%	0.0%
R_{50}	–	2.63 (1.12)	1.69 (0.46)
R_{75}	–	5.55 (3.14)	3.24 (1.57)
R_{100}	–	12.3 (8.44)	12.4 (8.13)

- Three Group Case (DIP with Hyperprior; posterior mean)
- True Efficacy: $p_1 = 0.25$, $p_2 = 0.15$ and $p_3 = 0.1$, $B = 0.2$, $N = 345$

	Bal.	BS		DIP	
E(S)	57.2 (4.2)	62.6 (6.1)		59.0 (4.6)	
Power	79.5%	81.1%		78.5%	
Error	0.0%	1.1%		1.3%	
R_{50}	–	2.93 (2.17)	2.36 (1.79)	1.39 (0.75)	1.29 (0.69)
R_{75}	–	2.30 (1.05)	1.96 (0.98)	1.53 (0.77)	1.32 (0.70)
R_{100}	–	2.18 (0.75)	1.87 (0.73)	2.18 (0.74)	1.83 (0.72)

- Three Group Case (DIP with Hyperprior; posterior mean)
- True Efficacy: $p_1 = 0.55$, $p_2 = 0.45$ and $p_3 = 0.4$, $B = 0.2$, $N = 618$

	Bal.	BS		DIP	
E(S)	288.4 (8.9)	294.4 (14.9)		290.2 (11.6)	
Power	78.8%	81.3%		80.1%	
Error	0.0%	0.7%		1.3%	
R_{50}	–	2.34 (1.50)	2.00 (1.58)	1.44 (0.70)	1.31 (0.67)
R_{75}	–	2.00 (0.84)	1.61 (0.87)	1.66 (0.67)	1.36 (0.65)
R_{100}	–	1.89 (0.61)	1.50 (0.63)	1.90 (0.58)	1.46 (0.61)

- Three Group Case (DIP with Hyperprior; posterior efficacy)
- True Efficacy: $p_1 = 0.25$, $p_2 = 0.15$ and $p_3 = 0.1$, $B = 0.2$, $N = 345$

	Bal.	BS		DIP	
E(S)	57.2 (4.2)	67.2 (6.5)		62.5 (5.6)	
Power	79.5%	77.0%		76.9%	
Error	0.0%	0.7%		0.9%	
R_{50}	–	3.68 (2.46)	3.32 (1.44)	1.88 (0.89)	1.81 (0.79)
R_{75}	–	3.07 (0.82)	2.99 (0.61)	2.43 (0.79)	2.37 (0.73)
R_{100}	–	2.93 (0.40)	2.94 (0.32)	2.91 (0.44)	2.93 (0.35)

- Three Group Case (DIP with Hyperprior; posterior efficacy)
- True Efficacy: $p_1 = 0.55$, $p_2 = 0.45$ and $p_3 = 0.4$, $B = 0.2$, $N = 618$

	Bal.	BS		DIP	
E(S)	288.4 (8.9)	305.6 (21.0)		302.4 (19.3)	
Power	78.8%	80.2%		80.3%	
Error	0.0%	0.5%		0.8%	
R_{50}	–	3.54 (2.26)	3.20 (1.39)	2.57 (0.76)	2.52 (0.72)
R_{75}	–	3.03 (0.68)	2.99 (0.51)	2.85 (0.52)	2.84 (0.47)
R_{100}	–	2.93 (0.38)	2.95 (0.29)	2.93 (0.40)	2.94 (0.32)

- Stem cell transplant patients treated at VCU Medical Center $(2003 - 2010)$.
- Mobilization groups:
  - Chemotherapy (Chemo)
  - Granulocyte-colony stimulating factor (GCSF).
- Efficacy: patients produce $\geq 5 \times 10^6/kg$ total CD34+ cells.
  - Chemo: $n = 96, \hat{p}_e = 0.78$
  - GCSF: $n = 222, \hat{p}_e = 0.64$
- Patient data simulate a prospectively planned clinical trial.
  - Patients accrued in chronological order *per treatment*.
  - Outcomes available in order of mobilization (takes only a few days).

- Data Example: Stem Cell Mobilization
- Simulated trial after $N = 150$ patients accrued.

Method	Successes	n_1	n_2	p-value
Balanced	91	74	76	0.1698
TW (Mean)	94	79	71	0.1287
TW (Prob)	93	81	69	0.1067
DIP (Point)	92	77	73	0.1093
DIP (Mean)	94	86	64	0.1204
DIP (Prob)	95	87	63	0.0925

Summary

- The DIP Methodology:
  - Identical skeptical priors across groups.
  - Priors become decreasingly informative as observations become available.
  - "Tempers" extreme outcomes in early stages of trials.
- In Outcome-Adaptive Allocation:
  - Modest improvement in successes vs. balanced case.
  - Less adaptation vs. Natural Lead-In method.
  - Less variability vs. Natural Lead-In.
- Other Applications:
  - Continual Reassessment Method (CRM).
  - Interim Analyses, Early Trial Termination.

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Thank You

Questions?