Utility-Based Optimization of Combination Therapy Using Ordinal Toxicity and Efficacy in Phase I/II Clinical Trials

Peter F. Thall
Department of Biostatistics
University of Texas, M.D. Anderson Cancer Center

Memorial Sloan Kettering Cancer Center

October 2, 2009

Collaborators

Hoang Nguyen – Biostatistics Dept, M.D. Anderson, Texas
Computer Programming, Prior Calibration, Model Refinements, Graphics

Collaborators

Hoang Nguyen – Biostatistics Dept, M.D. Anderson, Texas
Computer Programming, Prior Calibration, Model Refinements, Graphics

Nadine Houede – Institut Bergonie, Bordeaux, France
Medical Application, Utility Elicitation and Restaurant Selection

Collaborators

Hoang Nguyen – Biostatistics Dept, M.D. Anderson, Texas
Computer Programming, Prior Calibration, Model Refinements, Graphics

Nadine Houede – Institut Bergonie, Bordeaux, France
Medical Application, Utility Elicitation and Restaurant Selection

Xavier Paoletti – Institut Curie, Paris, France
Gaussian Copula Formulas and Wine Selection

Collaborators

Hoang Nguyen – Biostatistics Dept, M.D. Anderson, Texas
Computer Programming, Prior Calibration, Model Refinements, Graphics

Nadine Houede – Institut Bergonie, Bordeaux, France
Medical Application, Utility Elicitation and Restaurant Selection

Xavier Paoletti – Institut Curie, Paris, France
Gaussian Copula Formulas and Wine Selection

Andrew Kramar – Parc Euromedecine, Montpellier, France
Detailed Editing and La Joie de Vivre

OUTLINE

OUTLINE

1. Combination Bio-Chemotherapy for Bladder Cancer

OUTLINE

1. Combination Bio-Chemotherapy for Bladder Cancer

2. Data Structure and Probability Models

OUTLINE

1. Combination Bio-Chemotherapy for Bladder Cancer
2. Data Structure and Probability Models
   - Bivariate Almost Ordinal (Toxicity, Efficacy)

OUTLINE

1. Combination Bio-Chemotherapy for Bladder Cancer

2. Data Structure and Probability Models

   - Bivariate Almost Ordinal (Toxicity, Efficacy)
   - A Flexible Parametric Model

OUTLINE

1. Combination Bio-Chemotherapy for Bladder Cancer

2. Data Structure and Probability Models

   - Bivariate Almost Ordinal (Toxicity, Efficacy)
   - A Flexible Parametric Model
   - Establishing Priors

OUTLINE

1. Combination Bio-Chemotherapy for Bladder Cancer

2. Data Structure and Probability Models

   - Bivariate Almost Ordinal (Toxicity, Efficacy)
   - A Flexible Parametric Model
   - Establishing Priors

3. Trial Design and Conduct

OUTLINE

1. Combination Bio-Chemotherapy for Bladder Cancer

2. Data Structure and Probability Models

   - Bivariate Almost Ordinal (Toxicity, Efficacy)
   - A Flexible Parametric Model
   - Establishing Priors

3. Trial Design and Conduct

   - Utilities

OUTLINE

1. Combination Bio-Chemotherapy for Bladder Cancer

2. Data Structure and Probability Models

   - Bivariate Almost Ordinal (Toxicity, Efficacy)
   - A Flexible Parametric Model
   - Establishing Priors

3. Trial Design and Conduct

   - Utilities
   - Safety Rules

OUTLINE

1. Combination Bio-Chemotherapy for Bladder Cancer

2. Data Structure and Probability Models
   - Bivariate Almost Ordinal (Toxicity, Efficacy)
   - A Flexible Parametric Model
   - Establishing Priors

3. Trial Design and Conduct
   - Utilities
   - Safety Rules

4. Computer Simulations

OUTLINE

1. Combination Bio-Chemotherapy for Bladder Cancer

2. Data Structure and Probability Models
   - Bivariate Almost Ordinal (Toxicity, Efficacy)
   - A Flexible Parametric Model
   - Establishing Priors

3. Trial Design and Conduct
   - Utilities
   - Safety Rules

4. Computer Simulations

Dose-Finding for Combination Therapy of Bladder Cancer

Dose-Finding for Combination Therapy of Bladder Cancer

Goals: Find an optimal dose pair of combination therapy = chemotherapeutic (chemo) agents gemcitabine + cisplatin + biological agent for untreated advanced bladder cancer, based on **Toxicity** and **Efficacy** (a "phase I/II" trial)

Dose-Finding for Combination Therapy of Bladder Cancer

Goals: Find an optimal dose pair of combination therapy = chemotherapeutic (chemo) agents gemcitabine + cisplatin + biological agent for untreated advanced bladder cancer, based on **Toxicity** and **Efficacy** (a "phase I/II" trial)

Treatment Regime: In each 28-day cycle, the patient receives

1. biological agent orally each day at dose levels d_1 = 1, 2, 3 or 4
2. gemcitabine on days (1, 8, 15) at dose levels d_2 = 1, 2 or 3 (750, 1000 or 1250 mg/m^2/day)
3. a fixed dose of 70 mg/m^2 cisplatinum on day 2

$$\Longrightarrow \boldsymbol{d} = (d_1, d_2) \in \{1, 2, 3, 4\} \times \{1, 2, 3\}$$

The Dose Pair Domain $\mathcal{D}$

The Dose Pair Domain $\mathcal{D}$

	(1, 3)	(2, 3)	(3, 3)	(4, 3)
$\uparrow$	(1, 2)	(2, 2)	(3, 2)	(4, 2)
d_2	(1, 1)	(2, 1)	(3, 1)	(4, 1)

$d_1 \longrightarrow$

d_1 = dose of biological agent

d_2 = dose of chemo agent gemcitabine

Clinical Outcomes (evaluated over two 28-day cycles)

Clinical Outcomes (evaluated over two 28-day cycles)

Toxicity includes AEs (fatigue, diarrhea, mucositis) related to the biological agent and chemo-related AEs (renal tox, neurotoxicity)

Y_1 = 0 if no grade 3,4 (severe) TOX
Y_1 = 1 if grade 3,4 TOX occurs, but **resolved within 2 weeks**
Y_1 = 2 if grade 3,4 TOX occurs, & **not resolved within 2 weeks**

Clinical Outcomes (evaluated over two 28-day cycles)

Toxicity includes AEs (fatigue, diarrhea, mucositis) related to the biological agent and chemo-related AEs (renal tox, neurotoxicity)

Y_1 = 0 if no grade 3,4 (severe) TOX
Y_1 = 1 if grade 3,4 TOX occurs, but **resolved within 2 weeks**
Y_1 = 2 if grade 3,4 TOX occurs, & **not resolved within 2 weeks**

Efficacy is evaluated by the end of two cycles (day 56)

Y_2 = 0 if progressive disease (**PD**) at any time in the first 2 cycles
Y_2 = 1 if stable disease (**SD**) at day 56
Y_2 = 2 if complete or partial remission (**CR/PR**) at day 56

Interim Within-Patient Treatment Modifications

Interim Within-Patient Treatment Modifications

1. If grade 1 or 2 non-haematologic TOX in cycle 1, the dose of the biological agent is reduced

2. If the patient does not recover from a grade 3, 4 non-haematologoc TOX in two weeks, the bio agent is stopped, but the patient may continue to receive the chemo agents (physician decision)

3. If $Y_1 = 2$ (unresolved gr. 3,4 TOX) or $Y_2 = 2$ (PD) then treatment is stopped

Interim Within-Patient Treatment Modifications

1. If grade 1 or 2 non-haematologic TOX in cycle 1, the dose of the biological agent is reduced

2. If the patient does not recover from a grade 3, 4 non-haematologoc TOX in two weeks, the bio agent is stopped, but the patient may continue to receive the chemo agents (physician decision)

3. If Y_1 = 2 (unresolved gr. 3,4 TOX) or Y_2 = 2 (PD) then treatment is stopped

4. Y_1 = 2 and no PD before day 56 $\Longrightarrow$ Y_2 is *inevaluable*

The Outcome Domain

Y_2

		0 = **PD**	1 = **SD**	2 = **CR/PR**	
	0	(0, 0)	(0, 1)	(0, 2)	–
Y_1	1	(1, 0)	(1, 1)	(1, 2)	–
	2	(2, 0)	(2, 1)	(2, 2)	**(2, Ineval)**

10 elementary outcomes, including $\{Y_1 = 2$ and Y_2 inevaluable$\}$

A General Probability Model

A General Probability Model

Outcomes

$\mathbf{Y} = (Y_1, Y_2)$ where ordinal $Y_j \in \{1, ..., m_j\}$

where m_j = # levels of outcome $j = 1, 2$

A General Probability Model

Outcomes $\mathbf{Y} = (Y_1, Y_2)$ where ordinal $Y_j \in \{1, ..., m_j\}$

where m_j = # levels of outcome $j = 1, 2$

Doses $\boldsymbol{d} = (d_1, d_2)$

A General Probability Model

Outcomes $\mathbf{Y} = (Y_1, Y_2)$ where ordinal $Y_j \in \{1, ..., m_j\}$

where m_j = # levels of outcome $j = 1, 2$

Doses $\boldsymbol{d} = (d_1,\ d_2)$

Marginals $\pi_{k,y}(\boldsymbol{d}, \boldsymbol{\theta}) = \Pr(Y_k = y \mid \boldsymbol{d}, \boldsymbol{\theta})$

A General Probability Model

Outcomes $\mathbf{Y} = (Y_1, Y_2)$ where ordinal $Y_j \in \{1, ..., m_j\}$

where m_j = # levels of outcome $j = 1, 2$

Doses $\boldsymbol{d} = (d_1,\ d_2)$

Marginals $\pi_{k,y}(\boldsymbol{d}, \boldsymbol{\theta}) = \Pr(Y_k = y \mid \boldsymbol{d}, \boldsymbol{\theta})$

Joint pmf $\boldsymbol{\pi}(\boldsymbol{y}|\ \boldsymbol{d}, \boldsymbol{\theta}) \ = \ \Pr(\mathbf{Y} = \boldsymbol{y} \mid Z = 1, \boldsymbol{d}, \boldsymbol{\theta})$

where $\boldsymbol{y} = (y_1, y_2)$ is observed if $Z = 1$

Likelihood

$Z = I(Y_2 \text{ is evaluable}), \qquad \zeta = \Pr(Z = 1)$

$\delta(\boldsymbol{y}) = I(\mathbf{Y} = \boldsymbol{y}, Z = 1)$

$\delta_1(y_1) = I(Y_1 = y_1)$

$$\mathcal{L}(\mathbf{Y}, Z \mid \boldsymbol{d}, \boldsymbol{\theta}) =$$

$$\prod_{Z=0}^{1} \left[\zeta \prod_{\boldsymbol{y}} \left\{ \boldsymbol{\pi}(\boldsymbol{y} \mid \boldsymbol{d}, \boldsymbol{\theta}) \right\}^{\delta(\boldsymbol{y})} \right]^{Z} \left[(1-\zeta) \prod_{y_1=0}^{2} \left\{ \pi_{1,y_1}(\boldsymbol{d}, \boldsymbol{\theta}) \right\}^{\delta_1(y_1)} \right]^{1-Z}$$

The Aranda-Ordaz (AO) Model (1983)

The Aranda-Ordaz (AO) Model (1983)

Given linear term $\eta(d, \boldsymbol{\alpha})$ the AO model is

$$\Pr(Y = 1|d, \boldsymbol{\alpha}) = \xi\{\eta(d, \boldsymbol{\alpha}), \lambda\} = 1 - (1 + \lambda e^{\eta(d, \boldsymbol{\alpha})})^{-1/\lambda}, \quad \lambda > 0$$

1. For $\eta(d, \boldsymbol{\alpha}) = \alpha_0 + \alpha_1 log(d)$, $d = 0 \Longrightarrow \xi = 0 \Longrightarrow$ The outcome is impossible if no treatment is given

The Aranda-Ordaz (AO) Model (1983)

Given linear term $\eta(d, \boldsymbol{\alpha})$ the AO model is

$$\Pr(Y = 1|d, \boldsymbol{\alpha}) = \xi\{\eta(d, \boldsymbol{\alpha}), \lambda\} = 1 - (1 + \lambda e^{\eta(d, \boldsymbol{\alpha})})^{-1/\lambda}, \quad \lambda > 0$$

1. For $\eta(d, \boldsymbol{\alpha}) = \alpha_0 + \alpha_1 log(d)$, $d = 0 \Longrightarrow \xi = 0 \Longrightarrow$ The outcome is impossible if no treatment is given

2. For $\eta(d, \boldsymbol{\alpha}) = \alpha_0 + \alpha_1 d$, $d = 0 \Longrightarrow \xi = 1 - (1 + \lambda e^{\alpha_0})^{-1/\lambda} =$ baseline Pr(Y=1) without treatment

The Aranda-Ordaz (AO) Model (1983)

Given linear term $\eta(d, \boldsymbol{\alpha})$ the AO model is

$$\Pr(Y = 1|d, \boldsymbol{\alpha}) = \xi\{\eta(d, \boldsymbol{\alpha}), \lambda\} = 1 - (1 + \lambda e^{\eta(d, \boldsymbol{\alpha})})^{-1/\lambda}, \quad \lambda > 0$$

1. For $\eta(d, \boldsymbol{\alpha}) = \alpha_0 + \alpha_1 log(d)$, $d = 0 \Longrightarrow \xi = 0 \Longrightarrow$ The outcome is impossible if no treatment is given

2. For $\eta(d, \boldsymbol{\alpha}) = \alpha_0 + \alpha_1 d$, $d = 0 \Longrightarrow \xi = 1 - (1 + \lambda e^{\alpha_0})^{-1/\lambda} =$ baseline Pr(Y=1) without treatment

3. λ=1 $\Longrightarrow \xi\{\eta(d, \boldsymbol{\alpha}), 1\} = \frac{e^{\eta(d,\alpha)}}{1+e^{\eta(d,\alpha)}}$ (logistic)

The Aranda-Ordaz (AO) Model (1983)

Given linear term $\eta(d, \boldsymbol{\alpha})$ the AO model is

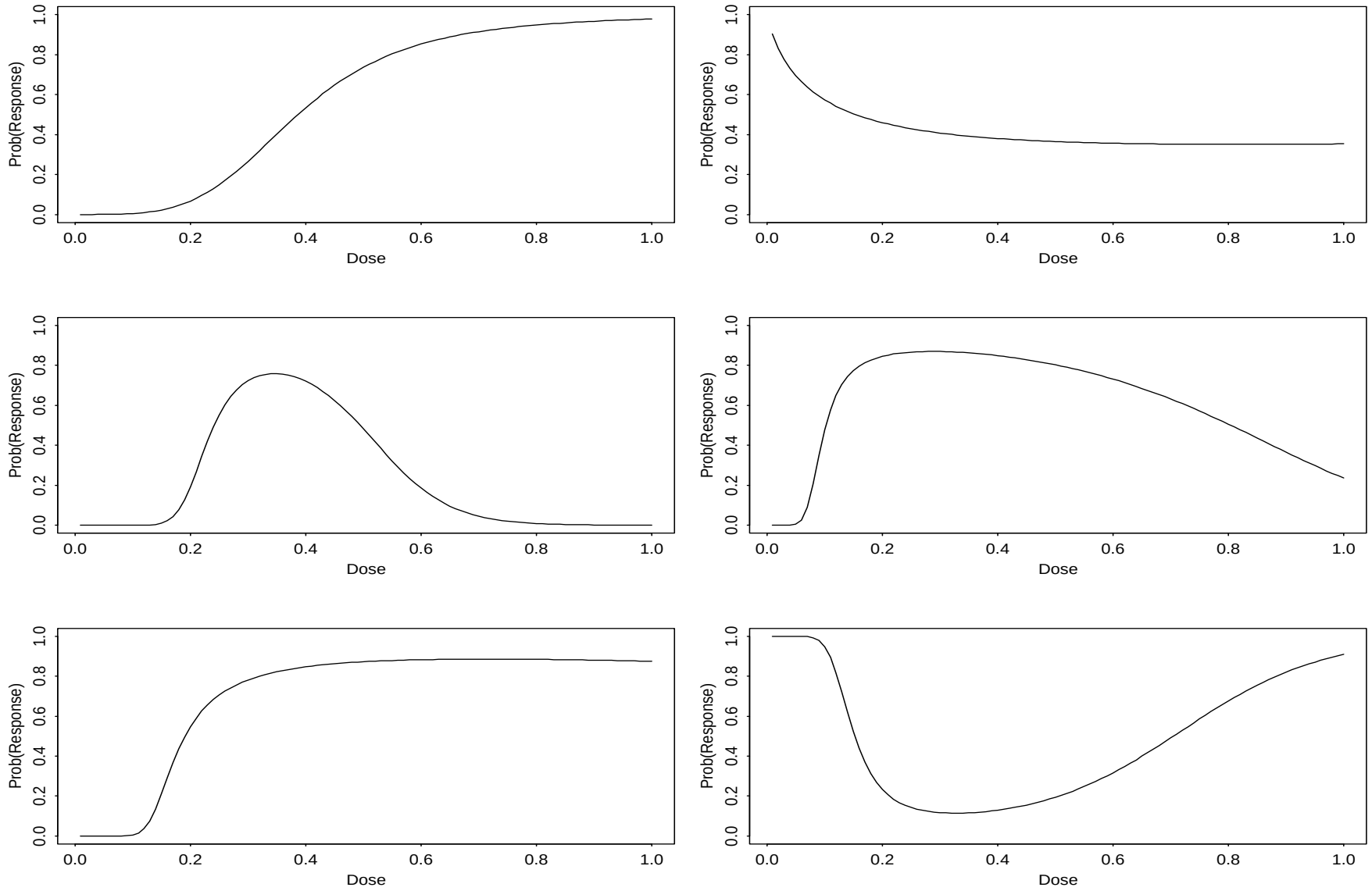
$$\Pr(Y = 1|d, \boldsymbol{\alpha}) = \xi\{\eta(d, \boldsymbol{\alpha}), \lambda\} = 1 - (1 + \lambda e^{\eta(d, \boldsymbol{\alpha})})^{-1/\lambda}, \quad \lambda > 0$$

1. For $\eta(d, \boldsymbol{\alpha}) = \alpha_0 + \alpha_1 log(d)$, $d = 0 \Longrightarrow \xi = 0 \Longrightarrow$ The outcome is impossible if no treatment is given

2. For $\eta(d, \boldsymbol{\alpha}) = \alpha_0 + \alpha_1 d$, $d = 0 \Longrightarrow \xi = 1 - (1 + \lambda e^{\alpha_0})^{-1/\lambda} =$ baseline Pr(Y=1) without treatment

3. λ=1 $\Longrightarrow \xi\{\eta(d, \boldsymbol{\alpha}), 1\} = \frac{e^{\eta(d,\alpha)}}{1+e^{\eta(d,\alpha)}}$ (logistic)

4. $\lim_{\lambda \to 0} \xi(\eta(d, \boldsymbol{\alpha}), \lambda) = 1 - \exp\{-e^{\eta(d,\alpha)}\}$ (compl. log-log)


Prob(Response)
0.0
0.2
0.4
0.6
0.8
1.0
Dose
0.0
0.2
0.4
0.6
0.8
1.0

A Generalized Aranda-Ordaz (GAO) Model

A Generalized Aranda-Ordaz (GAO) Model

To Accommodate Two Linear Terms:

$$\eta_1 \equiv \eta_1(d_1, \boldsymbol{\alpha}_1) \text{ for } d_1 \quad \text{and} \quad \eta_2 \equiv \eta_1(d_2, \boldsymbol{\alpha}_2) \text{ for } d_2$$

A Generalized Aranda-Ordaz (GAO) Model

To Accommodate Two Linear Terms:

$$\eta_1 \equiv \eta_1(d_1, \boldsymbol{\alpha}_1) \text{ for } d_1 \quad \text{and} \quad \eta_2 \equiv \eta_1(d_2, \boldsymbol{\alpha}_2) \text{ for } d_2$$

$$\xi^*\{\eta_1, \eta_2, \lambda, \gamma\} = 1 - \{1 + \lambda(e^{\eta_1} + e^{\eta_2} + \gamma e^{\eta_1+\eta_2})\}^{-1/\lambda}$$

γ accounts for interaction between the two agents

γ = 0 $\implies$ Additive effects e^{η_1} and e^{η_2} in the GAO model

Linear terms determining the marginal of Y_k

Linear terms determining the marginal of Y_k

For j = dose, k = outcome, y = value of Y_k

$$\eta_{k,y}^{(j)}(d_j, \boldsymbol{\alpha}_k^{(j)}) = \alpha_{k,y,0}^{(j)} + \alpha_{k,y,1}^{(j)}\,(d_j - \bar{d}_j)$$

Linear terms determining the marginal of Y_k

For j = dose, k = outcome, y = value of Y_k

$$\eta_{k,y}^{(j)}(d_j, \boldsymbol{\alpha}_k^{(j)}) = \alpha_{k,y,0}^{(j)} + \alpha_{k,y,1}^{(j)}(d_j - \bar{d}_j)$$

1. $\alpha_{k,y,0}^{(1)}$ and $\alpha_{k,y,0}^{(2)}$ are intercepts

Linear terms determining the marginal of Y_k

For j = dose, k = outcome, y = value of Y_k

$$\eta_{k,y}^{(j)}(d_j, \boldsymbol{\alpha}_k^{(j)}) = \alpha_{k,y,0}^{(j)} + \alpha_{k,y,1}^{(j)}(d_j - \bar{d}_j)$$

1. $\alpha_{k,y,0}^{(1)}$ and $\alpha_{k,y,0}^{(2)}$ are intercepts

2. $\alpha_{k,y,1}^{(1)}$ and $\alpha_{k,y,1}^{(2)}$ are dose effects

Linear terms determining the marginal of Y_k

For j = dose, k = outcome, y = value of Y_k

$$\eta_{k,y}^{(j)}(d_j, \boldsymbol{\alpha}_k^{(j)}) = \alpha_{k,y,0}^{(j)} + \alpha_{k,y,1}^{(j)}(d_j - \bar{d}_j)$$

1. $\alpha_{k,y,0}^{(1)}$ and $\alpha_{k,y,0}^{(2)}$ are intercepts
2. $\alpha_{k,y,1}^{(1)}$ and $\alpha_{k,y,1}^{(2)}$ are dose effects
3. $\boldsymbol{\alpha}_k^{(j)} = (\alpha_{k,1,0}^{(j)}, \alpha_{k,1,1}^{(j)}, \alpha_{k,2,0}^{(j)}, \alpha_{k,2,1}^{(j)})$

Linear terms determining the marginal of Y_k

For j = dose, k = outcome, y = value of Y_k

$$\eta_{k,y}^{(j)}(d_j, \boldsymbol{\alpha}_k^{(j)}) = \alpha_{k,y,0}^{(j)} + \alpha_{k,y,1}^{(j)}(d_j - \bar{d}_j)$$

1. $\alpha_{k,y,0}^{(1)}$ and $\alpha_{k,y,0}^{(2)}$ are intercepts
2. $\alpha_{k,y,1}^{(1)}$ and $\alpha_{k,y,1}^{(2)}$ are dose effects
3. $\boldsymbol{\alpha}_k^{(j)} = (\alpha_{k,1,0}^{(j)}, \alpha_{k,1,1}^{(j)}, \alpha_{k,2,0}^{(j)}, \alpha_{k,2,1}^{(j)})$
4. $\boldsymbol{\theta}_k = (\boldsymbol{\alpha}_k^{(1)}, \boldsymbol{\alpha}_k^{(2)}, \lambda_k, \gamma_k)$

Marginal Distributions

Marginal Distributions

For each outcome k = 1, 2 and levels $y = 1, ..., m_k$,

$$\Pr(Y_k \geq y \mid Y_k \geq y-1, \boldsymbol{d}, \boldsymbol{\theta}_k) = \xi^*\{\eta_{k,y}^{(1)}(d_1, \boldsymbol{\alpha}_k^{(1)}), \eta_{k,y}^{(2)}(d_2, \boldsymbol{\alpha}_k^{(2)}), \lambda_k, \gamma_k\}$$

$$\equiv \xi_{k,y}^*(\boldsymbol{d}, \boldsymbol{\theta}_k) \qquad \Longrightarrow$$

Marginal Distributions

For each outcome k = 1, 2 and levels $y = 1, \ldots, m_k$,

$$\Pr(Y_k \geq y \mid Y_k \geq y-1, \boldsymbol{d}, \boldsymbol{\theta}_k) = \xi^*\{\eta_{k,y}^{(1)}(d_1, \boldsymbol{\alpha}_k^{(1)}), \eta_{k,y}^{(2)}(d_2, \boldsymbol{\alpha}_k^{(2)}), \lambda_k, \gamma_k\}$$

$$\equiv \xi_{k,y}^*(\boldsymbol{d}, \boldsymbol{\theta}_k) \qquad \Longrightarrow$$

$$\pi_{k,0}(\boldsymbol{d}, \boldsymbol{\theta}_k) = 1 - \xi_{k,1}^*(\boldsymbol{d}, \boldsymbol{\theta}_k)$$

$$\pi_{k,y}(\boldsymbol{d}, \boldsymbol{\theta}_k) = \{1 - \xi_{k,y+1}^*(\boldsymbol{d}, \boldsymbol{\theta}_k)\} \prod_{j=1}^{y} \xi_{k,j}^*(\boldsymbol{d}, \boldsymbol{\theta}_k), \quad 1 \leq y \leq m_k - 1$$

$$\pi_{k,m_k}(\boldsymbol{d}, \boldsymbol{\theta}_k) = \prod_{j=1}^{m_k} \xi_{k,j}^*(\boldsymbol{d}, \boldsymbol{\theta}_k)$$

In the three-level ordinal outcome case, the unconditional marginal probabilities are

$$\pi_{k,0}(\boldsymbol{d}, \boldsymbol{\theta}_k) = 1 - \xi^*_{k,1}(\boldsymbol{d}, \boldsymbol{\theta}_k)$$

$$\pi_{k,1}(\boldsymbol{d}, \boldsymbol{\theta}_k) = \xi^*_{k,1}(\boldsymbol{d}, \boldsymbol{\theta}_k) - \xi^*_{k,1}(\boldsymbol{d}, \boldsymbol{\theta}_k)\xi^*_{k,2}(\boldsymbol{d}, \boldsymbol{\theta}_k)$$

$$\pi_{k,2}(\boldsymbol{d}, \boldsymbol{\theta}_k) = \xi^*_{k,1}(\boldsymbol{d}, \boldsymbol{\theta}_k)\ \xi^*_{k,2}(\boldsymbol{d}, \boldsymbol{\theta}_k)$$

Bivariate Distribution of (Y_1, Y_2)

Bivariate Distribution of (Y_1, Y_2)

Use a Gaussian copula, given by

$$C_\rho(u, v) \;=\; \Phi_\rho\{\Phi^{-1}(u), \Phi^{-1}(v)\} \qquad \text{for} \quad 0 \le u, v \le 1.$$

Φ_ρ = cdf of a bivariate std normal with correlation ρ

Φ = usual N(0,1) cdf

The cdf of each Y_k is

$$F_k(y \mid \boldsymbol{d}, \boldsymbol{\theta}_k) = \begin{cases} 0 & \text{if} y < 0 \\ 1 - \pi_{k,1}(\boldsymbol{d}, \boldsymbol{\theta}_k) - \pi_{k,2}(\boldsymbol{d}, \boldsymbol{\theta}_k) & \text{if} 0 \leq y < 1 \\ 1 - \pi_{k,2}(\boldsymbol{d}, \boldsymbol{\theta}_k) & \text{if} 1 \leq y < 2 \\ 1 & \text{if} y \geq 2 \end{cases}$$

The cdf of each Y_k is

$$F_k(y \mid \boldsymbol{d}, \boldsymbol{\theta}_k) = \begin{cases} 0 & \text{if} y < 0 \\ 1 - \pi_{k,1}(\boldsymbol{d}, \boldsymbol{\theta}_k) - \pi_{k,2}(\boldsymbol{d}, \boldsymbol{\theta}_k) & \text{if} 0 \leq y < 1 \\ 1 - \pi_{k,2}(\boldsymbol{d}, \boldsymbol{\theta}_k) & \text{if} 1 \leq y < 2 \\ 1 & \text{if} y \geq 2 \end{cases}$$

The joint pmf of $\mathbf{Y}$ is

$$\boldsymbol{\pi}(\boldsymbol{y} | \boldsymbol{d}, \boldsymbol{\theta}) = \sum_{a=1}^{2} \sum_{b=1}^{2} (-1)^{a+b} C_\rho(u_a, v_b)$$

$$u_1 = F_1(y_1 \mid \boldsymbol{d}, \boldsymbol{\theta}), \qquad v_1 = F_2(y_2 \mid \boldsymbol{d}, \boldsymbol{\theta})$$

$$u_2 = F_1(y_1 - 1 \mid \boldsymbol{d}, \boldsymbol{\theta}), \quad v_2 = F_2(y_2 - 1 \mid \boldsymbol{d}, \boldsymbol{\theta})$$

$$\begin{aligned}\boldsymbol{\pi}(\boldsymbol{y}) \;=\;& \Phi_\rho\{\Phi^{-1}\circ F_1(y_1),\ \Phi^{-1}\circ F_2(y_2)\}\\ &- \Phi_\rho\{\Phi^{-1}\circ F_1(y_1-1),\ \Phi^{-1}\circ F_2(y_2)\}\\ &- \Phi_\rho\{\Phi^{-1}\circ F_1(y_1),\ \Phi^{-1}\circ F_2(y_2-1)\}\\ &+ \Phi_\rho\{\Phi^{-1}\circ F_1(y_1-1),\ \Phi^{-1}\circ F_2(y_2-1)\}\end{aligned}$$

$\boldsymbol{\theta} = (\boldsymbol{\theta}_1, \boldsymbol{\theta}_2, \rho)$ and $\dim(\boldsymbol{\theta}) = 21$

Establishing Priors

Establishing Priors

1. **Elicit prior means** of $\pi_{k,1}(\boldsymbol{d})$ and $\pi_{k,2}(\boldsymbol{d})$ for each $\boldsymbol{d}$ and outcome $k = 1, 2$

Establishing Priors

1. **Elicit prior means** of $\pi_{k,1}(\boldsymbol{d})$ and $\pi_{k,2}(\boldsymbol{d})$ for each $\boldsymbol{d}$ and outcome $k = 1, 2$

2. **Use an extension of the least squares method** of Thall and Cook (2004) to solve for prior means of the 21 model parameters

Establishing Priors

1. **Elicit prior means** of $\pi_{k,1}(\boldsymbol{d})$ and $\pi_{k,2}(\boldsymbol{d})$ for each $\boldsymbol{d}$ and outcome $k = 1, 2$

2. **Use an extension of the least squares method** of Thall and Cook (2004) to solve for prior means of the 21 model parameters

3. **Calibrate prior variances** to obtain reasonably small prior effective sample sizes of the priors on $\pi_{k,1}(\boldsymbol{d})$ and $\pi_{k,2}(\boldsymbol{d})$ $\Longrightarrow$ ESS = .20 to .70

Establishing Priors

1. **Elicit prior means** of $\pi_{k,1}(\boldsymbol{d})$ and $\pi_{k,2}(\boldsymbol{d})$ for each $\boldsymbol{d}$ and outcome $k = 1, 2$

2. **Use an extension of the least squares method** of Thall and Cook (2004) to solve for prior means of the 21 model parameters

3. **Calibrate prior variances** to obtain reasonably small prior effective sample sizes of the priors on $\pi_{k,1}(\boldsymbol{d})$ and $\pi_{k,2}(\boldsymbol{d})$ $\Longrightarrow$ ESS = .20 to .70

Establishing Utilities

Establishing Utilities

The Delphi method: A tool for establishing consensus among experts (Dalkey, 1969; Brook, Chassin, Fink, et al., 1986)

Establishing Utilities

The Delphi method: A tool for establishing consensus among experts (Dalkey, 1969; Brook, Chassin, Fink, et al., 1986)

1. Elicit utilites from each of several individuals

Establishing Utilities

The Delphi method: A tool for establishing consensus among experts (Dalkey, 1969; Brook, Chassin, Fink, et al., 1986)

1. Elicit utilites from each of several individuals

2. Show all elicited values (anonymously) to all individuals, and allow them to adjust their utilties

Establishing Utilities

The Delphi method: A tool for establishing consensus among experts (Dalkey, 1969; Brook, Chassin, Fink, et al., 1986)

1. Elicit utilites from each of several individuals

2. Show all elicited values (anonymously) to all individuals, and allow them to adjust their utilties

3. Repeat 2 or 3 times, and compute the mean across experts of the final values

Establishing Utilities

The Delphi method: A tool for establishing consensus among experts (Dalkey, 1969; Brook, Chassin, Fink, et al., 1986)

1. Elicit utilites from each of several individuals

2. Show all elicited values (anonymously) to all individuals, and allow them to adjust their utilties

3. Repeat 2 or 3 times, and compute the mean across experts of the final values

Nadine Houede did this via questionnaire with 8 French medical oncologists who treat bladder cancer patients, using a utility scale of 0 to 100, and finished after 2 rounds

French Utilities Elicited Using the Delphi Method

French Utilities Elicited Using the Delphi Method

	$Y_2 = 0$ **PD**	$Y_2 = 1$ **SD**	$Y_2 = 2$ **CR/PR**	Y_2 Inevaluable
$Y_1 = 0$	25	76	100	–
$Y_1 = 1$	10	60	82	–
$Y_1 = 2$	2	40	52	0

Using Utilities to Select Dose Pairs

Using Utilities to Select Dose Pairs

For $U(\mathrm{y})$ = the numerical utility of outcome y, the **mean utility for a patient treated with $\boldsymbol{d}$** is

$$u(\boldsymbol{d}, \boldsymbol{\theta}) \;=\; \mathrm{E}_{\mathbf{Y}}\{U(\mathbf{Y}) \mid \boldsymbol{d}, \boldsymbol{\theta}\} = \sum_{\boldsymbol{y}} U(\boldsymbol{y})\, \boldsymbol{\pi}(\boldsymbol{y} \mid \boldsymbol{d}, \boldsymbol{\theta})$$

Using Utilities to Select Dose Pairs

For $U(\mathrm{y})$ = the numerical utility of outcome y, the **mean utility for a patient treated with $\boldsymbol{d}$** is

$$u(\boldsymbol{d}, \boldsymbol{\theta}) \;=\; \mathrm{E}_{\mathbf{Y}}\{U(\mathbf{Y}) \mid \boldsymbol{d}, \boldsymbol{\theta}\} = \sum_{\boldsymbol{y}} U(\boldsymbol{y})\, \boldsymbol{\pi}(\boldsymbol{y} \mid \boldsymbol{d}, \boldsymbol{\theta})$$

Given current $data_n = \{(\mathbf{Y}_1, \boldsymbol{d}_1), \cdots, (\mathbf{Y}_n, \boldsymbol{d}_n)\}$, select

$$\boldsymbol{d}^{opt}(data_n) \;=\; \mathrm{argmax}_{\boldsymbol{d} \in \mathcal{D}} \int_{\boldsymbol{\theta}} u(\boldsymbol{d}, \boldsymbol{\theta}) p(\boldsymbol{\theta} \mid data_n) d\boldsymbol{\theta}$$

$$= \;\mathrm{argmax}_{\boldsymbol{d} \in \mathcal{D}} \sum_{\boldsymbol{y}} U(\boldsymbol{y}) \int_{\boldsymbol{\theta}} \boldsymbol{\pi}(\boldsymbol{y} \mid \boldsymbol{d}, \boldsymbol{\theta}) p(\boldsymbol{\theta} \mid data_n) d\boldsymbol{\theta}$$

Additional Safety Rules

Additional Safety Rules

1. **Do Not Skip Untried Dose Pairs**:

If (d_1, d_2) is the current dose pair, then escalation is allowed to as yet untried pairs $(d_1 + 1, d_2)$, $(d_1, d_2 + 1)$, or $(d_1 + 1, d_2 + 1)$.

Additional Safety Rules

1. **Do Not Skip Untried Dose Pairs**:

If (d_1, d_2) is the current dose pair, then escalation is allowed to as yet untried pairs $(d_1 + 1, d_2)$, $(d_1, d_2 + 1)$, or $(d_1 + 1, d_2 + 1)$.

2. **Stop The Trial if All Dose Pairs are Too Toxic**:

For $\pi_{1,2}^{max}$ = fixed upper limit on Pr($Y_2 = 2$), and p_U = a fixed upper probability cut-off (e.g. .80 to .90), **terminate accrual** if

$$\min_{\boldsymbol{d}} \Pr\{\pi_{1,2}(\boldsymbol{d}, \boldsymbol{\theta}) > \pi_{1,2}^{max} \mid data\} > p_U$$

Simulations

Simulations

N_{max} = 48, choose $\boldsymbol{d}$ for cohorts of 3 patients, start at $\boldsymbol{d}$ = (2,2), safety stopping rule applied with $\pi_{1,2}^{max}$ = .33 and p_U = .80.

Simulations

N_{max} = 48, choose $\boldsymbol{d}$ for cohorts of 3 patients, start at $\boldsymbol{d}$ = (2,2), safety stopping rule applied with $\pi_{1,2}^{max}$ = .33 and p_U = .80.

A *simulation scenario* is a vector $\boldsymbol{\pi}^{true}(\boldsymbol{d})$ of fixed probability values for the 12 $\boldsymbol{d}$ pairs, with ρ^{true} = 0.10.

$$u^{true}(\boldsymbol{d}) \;=\; \sum_{\boldsymbol{y}} U(\boldsymbol{y})\, \boldsymbol{\pi}^{true}(\boldsymbol{y} \mid \boldsymbol{d})$$

Simulations

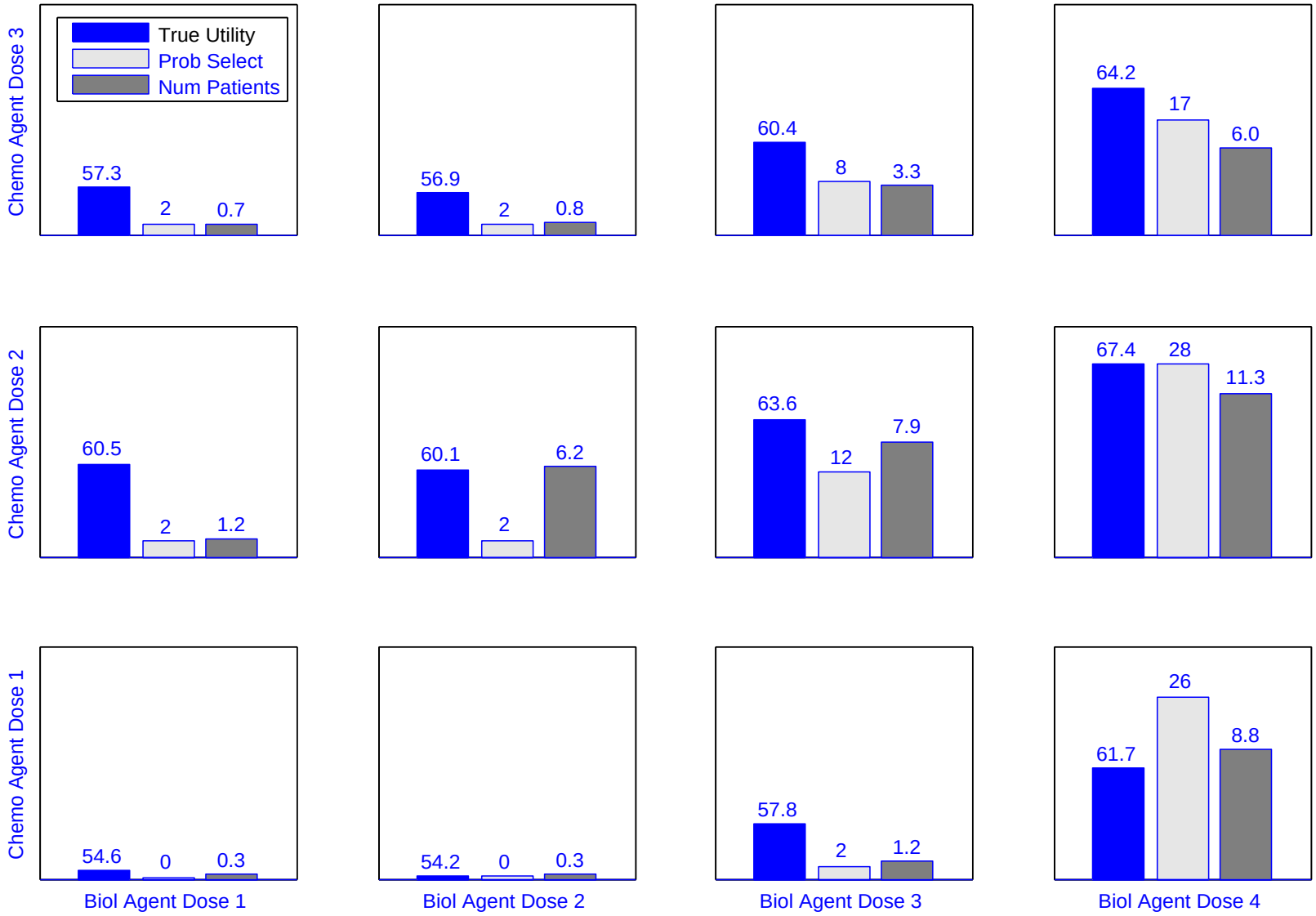
N_{max} = 48, choose $\boldsymbol{d}$ for cohorts of 3 patients, start at $\boldsymbol{d}$ = (2,2), safety stopping rule applied with $\pi_{1,2}^{max}$ = .33 and p_U = .80.

A *simulation scenario* is a vector $\boldsymbol{\pi}^{true}(\boldsymbol{d})$ of fixed probability values for the 12 $\boldsymbol{d}$ pairs, with ρ^{true} = 0.10.

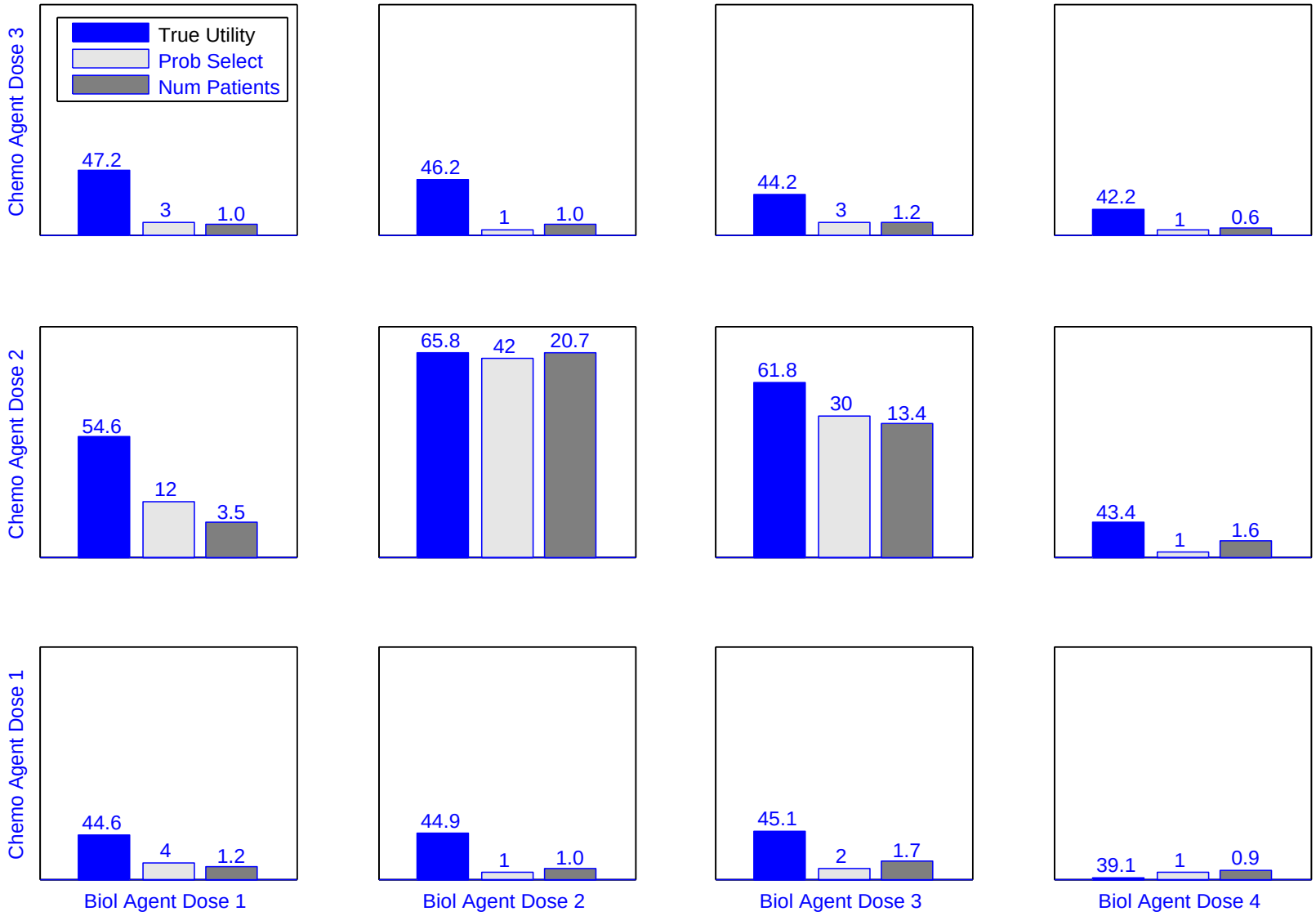
$$u^{true}(\boldsymbol{d}) \;=\; \sum_{\boldsymbol{y}} U(\boldsymbol{y})\, \boldsymbol{\pi}^{true}(\boldsymbol{y} \mid \boldsymbol{d})$$

1000 runs per scenario

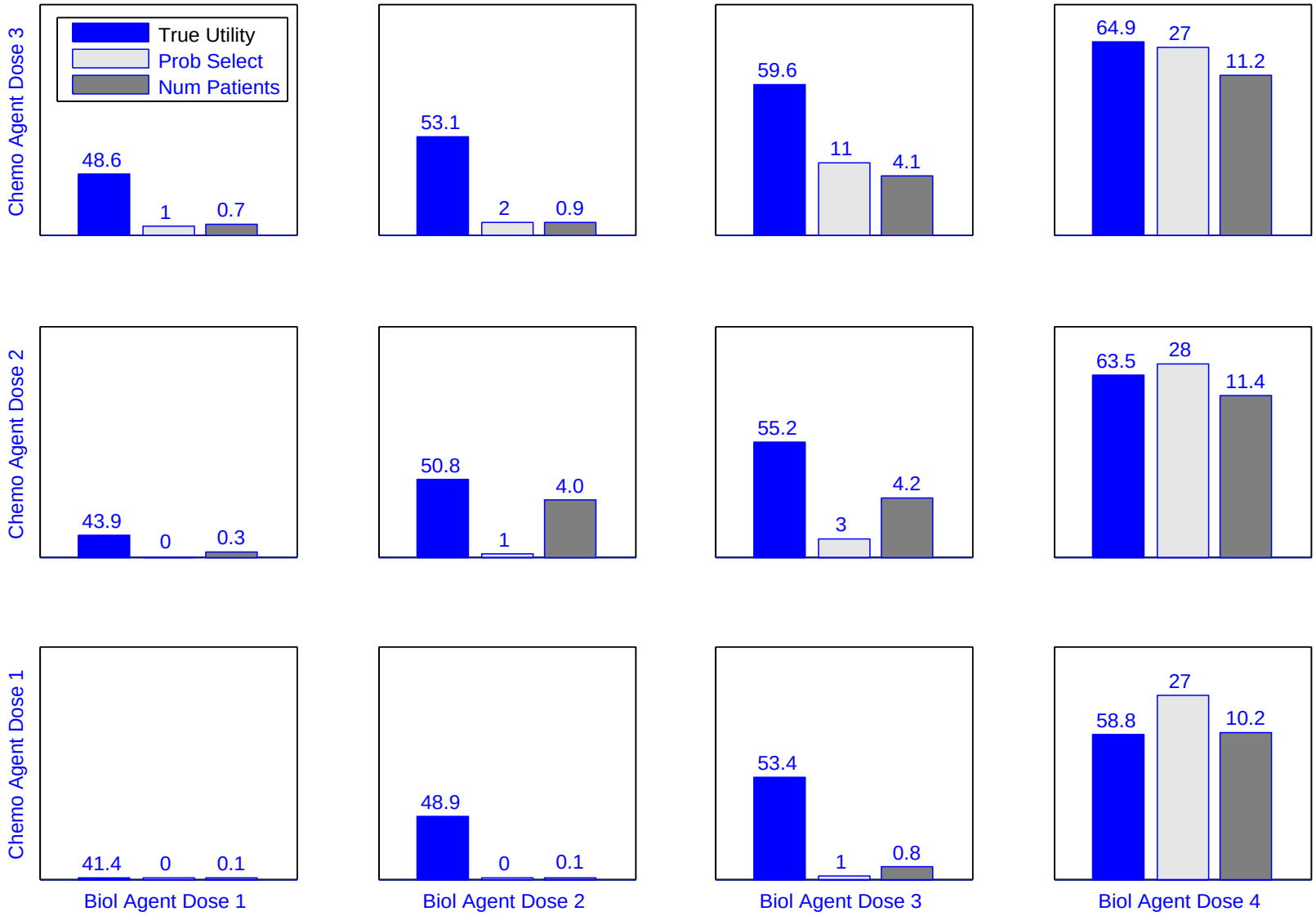
Scenario 1

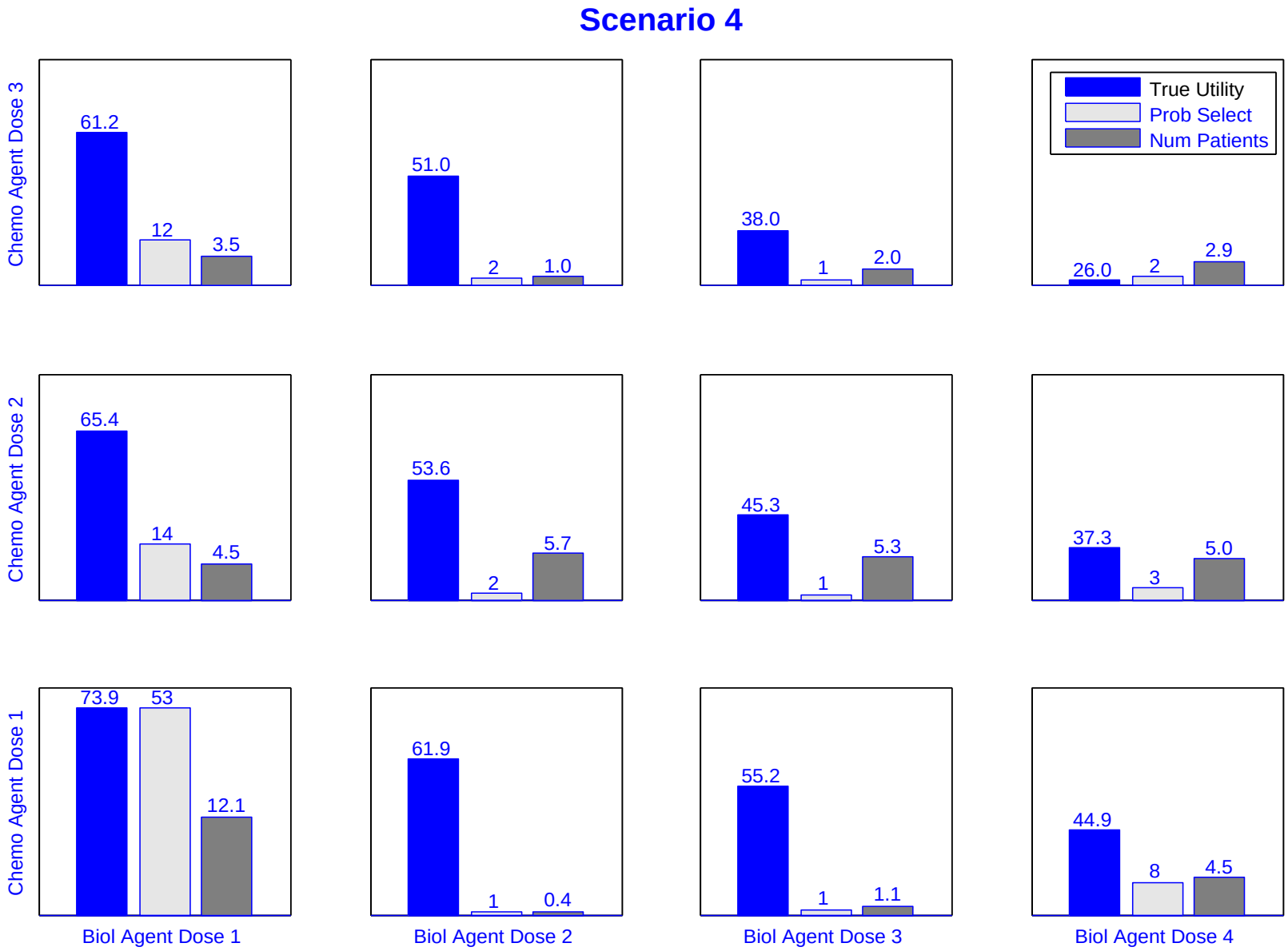

True Utility
Prob Select
Num Patients
Chemo Agent Dose 3
Chemo Agent Dose 2
Chemo Agent Dose 1
57.3
2
0.7
56.9
2
0.8
60.4
8
3.3
64.2
17
6.0
60.5
2
1.2
60.1
2
6.2
63.6
12
7.9
67.4
28
11.3
54.6
0
0.3
54.2
0
0.3
57.8
2
1.2
61.7
26
8.8
Biol Agent Dose 1
Biol Agent Dose 2
Biol Agent Dose 3
Biol Agent Dose 4

Scenario 2


True Utility
Prob Select
Num Patients
Chemo Agent Dose 3
Chemo Agent Dose 2
Chemo Agent Dose 1
47.2
3
1.0
46.2
1
1.0
44.2
3
1.2
42.2
1
0.6
54.6
12
3.5
65.8
42
20.7
61.8
30
13.4
43.4
1
1.6
44.6
4
1.2
44.9
1
1.0
45.1
2
1.7
39.1
1
0.9
Biol Agent Dose 1
Biol Agent Dose 2
Biol Agent Dose 3
Biol Agent Dose 4

Scenario 3


True Utility
Prob Select
Num Patients
Chemo Agent Dose 3
Chemo Agent Dose 2
Chemo Agent Dose 1
Biol Agent Dose 1
Biol Agent Dose 2
Biol Agent Dose 3
Biol Agent Dose 4
48.6
1
0.7
53.1
2
0.9
59.6
11
4.1
64.9
27
11.2
43.9
0
0.3
50.8
1
4.0
55.2
3
4.2
63.5
28
11.4
41.4
0
0.1
48.9
0
0.1
53.4
1
0.8
58.8
27
10.2


Scenario 4
Chemo Agent Dose 3
Chemo Agent Dose 2
Chemo Agent Dose 1
61.2
12
3.5
51.0
2
1.0
38.0
1
2.0
26.0
2
2.9
True Utility
Prob Select
Num Patients
65.4
14
4.5
53.6
2
5.7
45.3
1
5.3
37.3
3
5.0
73.9
53
12.1
61.9
1
0.4
55.2
1
1.1
44.9
8
4.5
Biol Agent Dose 1
Biol Agent Dose 2
Biol Agent Dose 3
Biol Agent Dose 4

Additional Simulation Results

Additional Simulation Results

1. **Safe** : $\pi_{1,2}^{max}$ = .33 and p_U = .80 $\Longrightarrow$ Large PSTOP in toxic scenarios

Additional Simulation Results

1. **Safe** : $\pi_{1,2}^{max}$ = .33 and p_U = .80 $\Longrightarrow$ Large PSTOP in toxic scenarios

2. **Insensitive to Cohort Size** : c = 1 versus c = 3 give the virtually same results under Scenarios 1 – 4, but slightly larger PSTOP for c = 1 (93% versus 90%) under the toxic Scenario 5

Additional Simulation Results

1. **Safe** : $\pi_{1,2}^{max}$ = .33 and p_U = .80 $\Longrightarrow$ Large PSTOP in toxic scenarios

2. **Insensitive to Cohort Size** : c = 1 versus c = 3 give the virtually same results under Scenarios 1 – 4, but slightly larger PSTOP for c = 1 (93% versus 90%) under the toxic Scenario 5

3. **Consistent** : Pr$\{$Select $\boldsymbol{d}$ having largest $u^{true}(\boldsymbol{d})\} \uparrow$ with N_{max}

Additional Simulation Results

1. **Safe** : $\pi_{1,2}^{max}$ = .33 and p_U = .80 $\Longrightarrow$ Large PSTOP in toxic scenarios

2. **Insensitive to Cohort Size** : c = 1 versus c = 3 give the virtually same results under Scenarios 1 – 4, but slightly larger PSTOP for c = 1 (93% versus 90%) under the toxic Scenario 5

3. **Consistent** : Pr$\{$Select $\boldsymbol{d}$ having largest $u^{true}(\boldsymbol{d})\} \uparrow$ with N_{max}

4. **Stupid Priors Give Stupid Designs** : A naive "uninformative" prior with E$(\boldsymbol{\theta})$ = **0** and all prior standard deviations = 1000 gives *terrible* results

Conclusions

Conclusions

1. Utilities including **Future Patient Benefit**, **Cost**, Expected Profit, etc. may lead to **better designs and more publications.**

Conclusions

1. Utilities including **Future Patient Benefit**, **Cost**, Expected Profit, etc. may lead to **better designs and more publications.**

2. **French utilities** are not necessarily the same as **American utilities** $\Longrightarrow$ **Think globally but elicit utilities locally.**

Conclusions

1. Utilities including **Future Patient Benefit**, **Cost**, Expected Profit, etc. may lead to **better designs and more publications.**

2. **French utilities** are not necessarily the same as **American utilities** $\Longrightarrow$ **Think globally but elicit utilities locally.**

3. Many extensions are possible, and this also may lead to **better designs and more publications.**

Conclusions

1. Utilities including **Future Patient Benefit**, **Cost**, Expected Profit, etc. may lead to **better designs and more publications.**

2. **French utilities** are not necessarily the same as **American utilities** $\Longrightarrow$ **Think globally but elicit utilities locally.**

3. Many extensions are possible, and this also may lead to **better designs and more publications.**