Optimizing the Bolus and Concentration of a Drug Administered by Continuous Infusion (to appear in *Biometrics*)

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*Design of Experiments in Healthcare*
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*Cambridge, England*
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Collaborators

Hoang Nguyen, PhD:
Programming and model development

Aniko Szabo, PhD:
Problem formulation, model development, notation & writing

Kate Amlie-Lefond, MD and Sam Zaidat, MD:
Medical motivation, prior, and utilities
Acute ischemic stroke (AIS) is a major cause of disability and death in adults. AIS is caused by a clot in a brain artery that blocks blood flow.

**Intra-arterial (IA) Fibrinolytic Infusion** is a new therapeutic modality for AIS: A thrombolytic agent to dissolve the clot is delivered via 2 telescoping catheters, inserted into the femoral artery. One catheter is supportive, with a microcatheter inside it.

**X-ray fluoroscopic guidance** is used to move the catheters through the arteries to the clot in the brain.

*The agent is infused via the microcatheter.*
Motivating Trial: IA tPA for Acute Ischemic Stroke

1. If treatment can be started within 3 to 6 hours, infuse the thrombolytic agent \textit{tPA (tissue plasminogen activator)} via the arterial micro-catheter to the site of the clot in the brain.

2. Give an initial bolus (10\% or 20\%) of the planned maximum amount of \textit{tPA}.

3. If the initial bolus does not dissolve the clot:

   → Continuously infuse (ci) the remaining \textit{tPA} for up to 120 minutes.
   → Image the clot at 15 minute intervals.
   → Stop the ci early if and when the clot is dissolved.
Outcomes

Response $Y_E = $ Time to dissolve the clot, recorded in 15-minute intervals up to the maximum infusion time of 120 minutes (Faster is much better!!)

Toxicity $Y_T = $ Symptomatic Intra-Cerebral Hemorrhage (SICH) is observed by imaging at 48 hours (much later than response)

**SICH** increases mortality by 50%, and may cause permanent brain damage

$\rightarrow Y_E$ is a time-to-event variable, interval-censored up to 120 minutes and right-censored at 120 minutes

$\rightarrow Y_T$ is a binary variable that depends on $Y_E$

*The Central Problem:* More tPA is more likely to (1) dissolve the clot and (2) cause SICH
Treatment and Efficacy Evaluation Schedule

Bolus

Times of infusion and evaluation (minutes)

\[ Y_E = \text{Time to dissolve the clot is interval censored up to 120 minutes and administratively censored thereafter} \]

Example: If the clot is not dissolved by 30 minutes but dissolved by 45 minutes, it is only known that \(30 < Y_E \leq 45\), and infusion is stopped at the 45 minute evaluation. If \(Y_E > 120\), then \(Y_E^o = 120\) is observed.
Treatment Parameters

- $c$ = concentration of tPA (0.2, 0.3, 0.4, or 0.5 mg/kg)
- $q$ = proportion of maximum total planned tPA given as an initial bolus (0.1 or 0.2)

$4 \times 2 = 8$ possible ($c$, $q$) treatment combinations

<table>
<thead>
<tr>
<th>Treatment parameters (q, c)</th>
<th>(.10, .20)</th>
<th>(.10, .30)</th>
<th>(.10, .40)</th>
<th>(.10, .50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(.20, .20)</td>
<td>(.20, .30)</td>
<td>(.20, .40)</td>
<td>(.20, .50)</td>
<td></td>
</tr>
</tbody>
</table>

Outcome data ($Y_E$, $Y_T$)

(Time to Dissolve the Clot up to 120 Minutes, SICH or Not)
Necessary Properties of the Probability Model

Efficacy:

The distribution of $Y_E$ must be a function of $(c, q)$ that accounts for both
1) $\Pr(Y_E = 0) > 0$, due to possible success with the bolus
2) the rate of $Y_E$ during the continuous infusion

Toxicity (SICH):

\[
\pi_T(Y_E, c, q) = \Pr(Y_T = 1 \mid Y_E, c, q) = \Pr(\text{SICH} \mid Y_E, c, q)
\]

must be a function of both $Y_E$ and $(c, q)$
Probability Model for $Y_E =$ Time to Dissolve the Clot

$p_0(c,q) = \Pr(\text{bolus dissolves the clot instantly})$

$$= \Pr(Y_E = 0) = 1 - \exp\left(-\alpha_0 c^{\alpha_1} q^{\alpha_2}\right)$$

$\lambda(s,c,q) =$ Rate function for $Y_E > 0$

$$= \alpha_3 + \frac{\alpha_4 \alpha_5 \{d(s,c^{\alpha_1},q^{\alpha_2})\}^{\alpha_5-1}}{1 + \alpha_4 \{d(s,c^{\alpha_1},q^{\alpha_2})\}^{\alpha_5}}$$

for $s > 0$.

where the effective delivered dose by time $s$ is

$$d(s,c^{\alpha_1},q^{\alpha_2}) = c^{\alpha_1}\{q^{\alpha_2} + (1 - q^{\alpha_2})s\}$$
Probability Model for $Y_E = \text{Time to Dissolve the Clot}$

Denote the cumulative rate function

$$\Lambda(s, c, q, \alpha) = \int_0^s \lambda(y, c, q, \alpha)\,dy.$$  

The pdf of $Y_E$ is the discrete-continuous mixture

$$f_E(y, c, q, \alpha) = p_0(c, q, \alpha)1(y = 0) +$$

$$\{1 - p_0(c, q, \alpha)\} \lambda(y, c, q, \alpha) \, e^{-\Lambda(y, c, q, \alpha)}1(y > 0)$$

and the cdf is

$$F_E(y, c, q, \alpha) = 1 - \{1 - p_0(c, q, \alpha)\} \, e^{-\Lambda(y, c, q, \alpha)}$$
Possible Forms of the Curve for $p_0(c, q) = \Pr(\text{Dissolve the Clot Instantly with the Bolus})$
Possible Shapes for Rate Function $\lambda(s,c,q)$ of Time to Dissolve the Clot by Continuous Infusion if $Y_E > 0$

$s = \text{standardized time} = \text{minutes} / 120$
The risk of SICH depends on $c$, $q$, and $Y_E$ since infusion is stopped at $Y_E$ or, if the clot is not dissolved by the tPA, at 120 minutes.

\[
\pi_T(Y_E, c, q, \beta) = \Pr(Y_T = 1 \mid Y_E, c, q, \beta) \\
= 1 - \exp\left[-\{\beta_0 + \beta_2 c^{\beta_1} q + \beta_3 c^{\beta_1} (1 - q)(Y_E \land 1) + \beta_4 1(Y_E > 1)\}\right].
\]

- Baseline SICH rate
- Effect of the bolus
- Effect of the continuously infused tPA
- Effect of failure to dissolve the clot within 120 minutes
Possible Shapes for $\pi_T(c,q) = \Pr(\text{SICH} \mid c,q)$
Important Special Case: If No Bolus is Given

$q = 0$, so $p_0(c,q) = 0$, the rate function simplifies to

$$\lambda(s, c, 0, \alpha) = \alpha_3 + \frac{\alpha_4 \alpha_5 (c^{\alpha_1} s)^{\alpha_5-1}}{1 + \alpha_4 (c^{\alpha_1} s)^{\alpha_5}}$$

for $s > 0$.

the cumulate rate becomes

$$\Lambda(s, c, 0, \alpha) = \alpha_3 s + c^{-\alpha_1} \log\{1 + \alpha_4 (c^{\alpha_1} s)^{\alpha_5}\}$$

for $s > 0$

and the SICH probability linear term loses one term:

$$\pi_T(Y_E, c, q, \beta) = 1 - \exp\left[-\{\beta_0 + \beta_2 c^{\alpha_1} q + \beta_3 c^{\beta_1}(1 - q)(Y_E \land 1) + \beta_4 1(Y_E > 1)\}\right]$$
Interval Censoring of $Y_E$

Observation of $Y_E$ at 15-minute intervals $\Rightarrow$

For observation interval $I_E = \left( y_E^a, y_E^b \right)$ and $y_T = 0,1$

the *joint distribution* of $Y_E$ and $Y_T$ is

$$
\pi_{E,T}(I_E, y_T | c, q, \theta) = \Pr(y_E^a < Y_E \leq y_E^b, Y_T = y_T | c, q, \theta)
$$

Dissolve the clot by continuous infusion between $y_E^a$ and $y_E^b$

**SICH** occurs ($y_T = 1$) or does not ($y_T = 0$)
Likelihood Function

For $Y_T = 0$ or $1$,

$$
\mathcal{L}(Y|c, q, \theta) = \left[ p_0(c, q, \alpha) \pi_T(0, c, q, \beta)^{Y_T} \{1 - \pi_T(0, c, q, \beta)\}^{1-Y_T} \right]^{1(Y_E=0)}
\times \prod_{m=1}^{M} \left[ \pi_{E,T}(I_{E,m}, 1 | c, q, \theta)^{Y_T} \pi_{E,T}(I_{E,m}, 0 | c, q, \theta)^{1-Y_T} \right]^{1(Y_E \in I_{E,m})}
\times \left[ \{1 - F_E(1| c, q, \alpha)\} \pi_T(1, c, q, \beta)^{Y_T} \{1 - \pi_T(1, c, q, \beta)\}^{1-Y_T} \right]^{1(Y_E > 1)}
$$

- Dissolve the clot during some 15-minute interval
- Fail to Dissolve the clot within 120 minutes

Dissolve the clot with the bolus at $Y_E = 0$
Utilities of the Possible Bivariate Outcomes:
*(I Elicited these from Sam Zaidat & Kate Amlie-Lefond)*

<table>
<thead>
<tr>
<th>Minutes</th>
<th>0</th>
<th>1-15</th>
<th>16-30</th>
<th>31-45</th>
<th>46-60</th>
<th>61-75</th>
<th>76-90</th>
<th>91-105</th>
<th>106-120</th>
<th>&gt; 120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Std. Time</td>
<td>0</td>
<td>0-.125</td>
<td>.126-.250</td>
<td>.256-.375</td>
<td>.376-.500</td>
<td>.501-.625</td>
<td>.626-.750</td>
<td>.756-.875</td>
<td>.876-1.000</td>
<td>&gt; 1</td>
</tr>
</tbody>
</table>
Utilities of the Possible Bivariate Outcomes: (I Elicited these from Sam Zaidat & Kate Amlie-Lefond)

Time Required to Dissolve the Blood Clot

<table>
<thead>
<tr>
<th>Minutes</th>
<th>0</th>
<th>1-15</th>
<th>16-30</th>
<th>31-45</th>
<th>46-60</th>
<th>61-75</th>
<th>76-90</th>
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<td>.626-.750</td>
<td>.756-.875</td>
<td>.876-1.000</td>
<td>&gt; 1</td>
</tr>
</tbody>
</table>

No SICH

<table>
<thead>
<tr>
<th>Minutes</th>
<th>100</th>
<th>95</th>
<th>90</th>
<th>85</th>
<th>80</th>
<th>75</th>
<th>70</th>
<th>60</th>
<th>50</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>SICH</td>
<td>7</td>
<td>6.5</td>
<td>6</td>
<td>5</td>
<td>4.5</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

1) Dissolving the clot faster is better

2) **SICH** is a disaster
<table>
<thead>
<tr>
<th>$q$</th>
<th>$0.10$</th>
<th>$0.20$</th>
<th>$0.10$ or $0.20$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E{p_0(c, q, \theta)}$</td>
<td>$E{F_E(\frac{1}{2} \mid c, q, \theta)}$</td>
<td>$E{\pi_T(.50, q, 1(Y_E &gt; 1), \theta)}$</td>
<td></td>
</tr>
<tr>
<td>$E{F_E(1 \mid c, q, \theta)}$</td>
<td>$E{\pi_T(0, c, q, \theta)}$</td>
<td>$E{\pi_T(1, c, q, \theta)}$</td>
<td></td>
</tr>
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<td>$E{\pi_T(.50, q, 1(Y_E &gt; 1), \theta)}$</td>
<td></td>
</tr>
</tbody>
</table>
### a. Elicited Prior Mean Probabilities

<table>
<thead>
<tr>
<th></th>
<th>$c = 0.20$</th>
<th>$c = 0.30$</th>
<th>$c = 0.40$</th>
<th>$c = 0.50$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$q = .10$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E{p_0(c, q, \theta)}$</td>
<td>0.10</td>
<td>0.15</td>
<td>0.15</td>
<td>0.25</td>
</tr>
<tr>
<td>$E{F_E(\frac{1}{2}</td>
<td>c, q, \theta)}$</td>
<td>0.25</td>
<td>0.30</td>
<td>0.45</td>
</tr>
<tr>
<td>$E{F_E(1</td>
<td>c, q, \theta)}$</td>
<td>0.35</td>
<td>0.45</td>
<td>0.60</td>
</tr>
<tr>
<td>$E{\pi_T(0, c, q, \theta)}$</td>
<td>0.02</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>$E{\pi_T(1, c, q, \theta)}$</td>
<td>0.04</td>
<td>0.06</td>
<td>0.08</td>
<td>0.12</td>
</tr>
<tr>
<td>$q = .20$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E{p_0(c, q, \theta)}$</td>
<td>0.15</td>
<td>0.20</td>
<td>0.25</td>
<td>0.30</td>
</tr>
<tr>
<td>$E{F_E(\frac{1}{2}</td>
<td>c, q, \theta)}$</td>
<td>0.40</td>
<td>0.45</td>
<td>0.50</td>
</tr>
<tr>
<td>$E{F_E(1</td>
<td>c, q, \theta)}$</td>
<td>0.50</td>
<td>0.60</td>
<td>0.70</td>
</tr>
<tr>
<td>$E{\pi_T(0, c, q, \theta)}$</td>
<td>0.02</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>$E{\pi_T(1, c, q, \theta)}$</td>
<td>0.04</td>
<td>0.06</td>
<td>0.08</td>
<td>0.12</td>
</tr>
</tbody>
</table>

$q = .10$ or .20  \quad E\{\pi_T(.50, q, 1(Y_E > 1), \theta)\} = .15$
$p=11$ model parameters $\rightarrow 22$ normal prior hyper-parameters (11 means + 11 variances). Given the 42 elicited prior mean probabilities from the neurologists, we determined the 22 prior hyper-parameters as follows:

**Algorithm for Establishing a Prior (Hoang Nguyen’s idea)**

1. Treat the elicited values like true probabilities and simulate 1000 large pseudo samples with $n = 400$ (rather than 36) having exactly 50 patients given each $(c,q)$

2. Start with a very non-informative pseudo prior on $\theta$, with $\log(\theta_j) \sim N(0,400)$ for all entries

3. Use the {pseudo prior + pseudo data} to compute a pseudo posterior of $\theta$

4. Set **Prior mean** = mean of the 1000 pseudo posterior means

5. Calibrate prior var{$\log(\theta_j)$} to obtain a non-informative prior, to obtain effective sample size = .17 to .22 for each $F_E(s, c, q, \theta)$ and $\pi_T(s, c, q, \theta)$
Elicit a utility $U(Y_E, Y_T) = U(Y)$ from the physicians.

Given model parameter $\theta$, the mean utility of $(c,q)$ is

$$u(c, q, \theta) = E_Y\{U(Y) \mid c, q, \theta\} = \sum_{y_T=0}^{\infty} \int_{y_E=0}^{\infty} U(y) f_{E,T}(y \mid c, q, \theta) dy_E$$

Under a Bayesian model, given data $D_n$, the optimal $(c,q)$ is the parameter $\theta$ that maximizes the posterior mean utility:

$$u(c, q)^{opt}(D_n) = \arg\max_{c,q} E_{\theta}\{u(c, q, \theta) \mid D_n\}$$

$U(Y)$ = Elicited Numerical Outcome Utilities
Utility Function

Elicit a utility $U(Y_E, Y_T) = U(Y)$ from the physicians

Given model parameter $\theta$, the mean utility of $(c,q)$ is

$$u(c, q, \theta) = \mathbb{E}_{c, q, \theta} [U(c, q, \theta)]$$

Under a Bayesian model, given data $D_n$ the optimal $(c, q)$ maximizes the posterior mean utility:

$$u(c, q)^{opt}(D_n) = \arg \max_{c, q} \mathbb{E}_{\theta} \{ u(c, q, \theta) \mid D_n \}$$

What has been learned from the data $D_n$ about $\theta$, and hence about the expected utility of using $(c, q)$ to treat a patient
Acceptability Criteria

\((c, q)\) has **unacceptably high toxicity** if

\[
\Pr\{\pi_T(1, c, q, \theta) > \bar{\pi}_T \mid D_n\} > p_T
\]

\((c, q)\) has **unacceptably low efficacy** if

\[
\Pr\{F_E(1, c, q, \alpha) < \bar{\pi}_E \mid D_n\} > p_E
\]

large probabilities, like .90 or .95
**Trial Conduct** (Up to a pre-specified $N_{\text{max}}$ patients)

1) Treat 1\textsuperscript{st} patient at lowest pair $(c, q) = (.20, .10)$

2) Treat each patient at the *optimal* $(c, q)$ pair, that maximizes the posterior expected utility

3) Do not skip untried $(c, q)$ pairs when escalating

4) If no $(c, q)$ pair is acceptable $\rightarrow$ Stop the trial

5) Select the *optimal* $(c, q)$ pair at the end of the trial
Simulation Study Design

1) $c = 0.2, 0.3, 0.4, \text{ or } 0.5 \text{ mg/kg}, \quad q = 0.1 \text{ or } 0.2$

2) $N_{\text{max}} = 36 \text{ patients}, \quad \text{cohort size } = 1$

3) Accrual rate = (1 patient /month /site) x 15 sites x 5% eligible = .75 eligible patients per month

4) 10,000 replications per scenario

5) $\bar{\pi}_T = 0.15, \quad \pi_E = 0.50 \quad (\text{elicited from the neurologists})$

6) $p_E = p_T = .95 \text{ for the early stopping (acceptability) criteria}$

We studied 6 basic scenarios, and also performed sensitivity analyses for (i) $N = 24 \text{ to } 240$, (ii) cohort size $= 1, 2, 3$, (iii) prior informativeness, (iv) shapes of true $\lambda$ and $\pi$

→ **14** supplementary tables in the *Biometrics* paper
**Computer Simulation Results** \( (N_{\text{max}} = 36) \)

<table>
<thead>
<tr>
<th>Scenario</th>
<th>( q )</th>
<th>( c )</th>
<th>( u^{\text{true}}(c, q) )</th>
<th>% Sel (No. Pats.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior means</td>
<td>0.1</td>
<td>( 0.2 )</td>
<td>46.9</td>
<td>2% (3.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( 0.3 )</td>
<td>51.5</td>
<td>2% (1.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( 0.4 )</td>
<td>59.2</td>
<td>7% (3.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( 0.5 )</td>
<td>64.4</td>
<td>29% (8.7)</td>
</tr>
<tr>
<td>1.0</td>
<td>0.2</td>
<td>( 0.2 )</td>
<td>56.1</td>
<td>2% (0.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( 0.3 )</td>
<td>60.5</td>
<td>2% (0.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( 0.4 )</td>
<td>65.1</td>
<td>11% (4.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( 0.5 )</td>
<td>70.6</td>
<td>38% (11.5)</td>
</tr>
</tbody>
</table>

Grey shaded utilities correspond to \((c, q)\) with unacceptable efficacy or toxicity.
Computer Simulation Results  \( (N_{\text{max}} = 36) \)

<table>
<thead>
<tr>
<th>Scenario</th>
<th>( q )</th>
<th>( u^{\text{true}}(c, q) )</th>
<th>0.2</th>
<th>0.3</th>
<th>0.4</th>
<th>0.5</th>
<th>% none</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safe, high ( c ) and ( q = 0.2 ) best</td>
<td>0.1</td>
<td>49.0</td>
<td>54.9</td>
<td>62.4</td>
<td>71.5</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( u^{\text{true}}(c, q) )</td>
<td>52.6</td>
<td>58.4</td>
<td>65.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Sel (No. Pats.)</td>
<td>1%  (2.6)</td>
<td>1%  (1.2)</td>
<td>4%  (2.3)</td>
<td>17% (5.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Sel (No. Pats.)</td>
<td>1%  (0.5)</td>
<td>1%  (0.6)</td>
<td>13% (5.3)</td>
<td>60% (16.9)</td>
<td></td>
</tr>
</tbody>
</table>

Grey shaded utilities correspond to \((c, q)\) with unacceptable efficacy or toxicity.
**Computer Simulation Results**  \( N_{\text{max}} = 36 \)

Hardest case: \((q, c) = (0.1, 0.4)\) is best but \((0.1, 0.5)\) has unacceptably low efficacy

<table>
<thead>
<tr>
<th>Scenario</th>
<th>( q )</th>
<th>( u^{\text{true}}(c, q) )</th>
<th>( c )</th>
<th>% Sel (No. Pats.)</th>
<th>% none</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Safe, middle ( c ) and ( q = .1 ) best</strong></td>
<td>0.1</td>
<td>57.3</td>
<td>0.2</td>
<td>3% (2.4)</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.3</td>
<td>8% (3.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.4</td>
<td>33% (9.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.5</td>
<td>33% (9.3)</td>
<td></td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>0.2</td>
<td>57.1</td>
<td>0.2</td>
<td>2% (0.5)</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.3</td>
<td>2% (0.9)</td>
<td></td>
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<td></td>
<td></td>
<td>0.4</td>
<td>7% (5.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.5</td>
<td>3% (2.8)</td>
<td></td>
</tr>
</tbody>
</table>

Grey shaded utilities correspond to \((c, q)\) with unacceptable efficacy or toxicity.
**Computer Simulation Results**  \( N_{\text{max}} = 36 \)

<table>
<thead>
<tr>
<th>Scenario</th>
<th>( q )</th>
<th>( u^{\text{true}}(c, q) )</th>
<th>0.2</th>
<th>0.3</th>
<th>0.4</th>
<th>0.5</th>
<th>% none</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>0.1</td>
<td>( u^{\text{true}}(c, q) )</td>
<td>61.1</td>
<td>58.7</td>
<td>51.6</td>
<td>48.0</td>
<td>12</td>
</tr>
<tr>
<td>Safe, low ( c ) and ( q=.1 ) best</td>
<td>0.2</td>
<td>( u^{\text{true}}(c, q) )</td>
<td>58.2</td>
<td>53.9</td>
<td>49.5</td>
<td>45.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Sel (No. Pats.)</td>
<td>43% (14.4)</td>
<td>7% (3.3)</td>
<td>6% (3.4)</td>
<td>5% (2.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>% Sel (No. Pats.)</td>
<td>22% (5.0)</td>
<td>3% (1.5)</td>
<td>2% (2.2)</td>
<td>1% (0.9)</td>
<td></td>
</tr>
</tbody>
</table>

Grey shaded utilities correspond to \((c,q)\) with unacceptable efficacy or toxicity.
## Computer Simulation Results \( (N_{\text{max}} = 36) \)

<table>
<thead>
<tr>
<th>Scenario</th>
<th>( q )</th>
<th>( \hat{u}(c, q) )</th>
<th>( c )</th>
<th>% Sel (No. Pats.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.1</td>
<td>44.8</td>
<td>0.2</td>
<td>4% (6.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45.2</td>
<td>0.3</td>
<td>1% (1.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45.2</td>
<td>0.4</td>
<td>1% (2.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45.2</td>
<td>0.5</td>
<td>1% (2.2)</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>45.2</td>
<td>0.2</td>
<td>1% (0.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45.0</td>
<td>0.3</td>
<td>0% (0.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45.0</td>
<td>0.4</td>
<td>0% (0.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44.3</td>
<td>0.5</td>
<td>0% (0.6)</td>
</tr>
</tbody>
</table>

Grey shaded utilities correspond to \((c,q)\) with unacceptable efficacy or toxicity.
**Computer Simulation Results**  \( (N_{\text{max}} = 36) \)

<table>
<thead>
<tr>
<th>Scenario</th>
<th>( q )</th>
<th>0.2</th>
<th>0.3</th>
<th>0.4</th>
<th>0.5</th>
<th>% none</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safe, but</td>
<td>0.1</td>
<td>38.2</td>
<td>40.0</td>
<td>41.9</td>
<td>43.3</td>
<td>83</td>
</tr>
<tr>
<td>no ((c, q))</td>
<td>0.2</td>
<td>39.3</td>
<td>41.2</td>
<td>43.1</td>
<td>44.4</td>
<td></td>
</tr>
<tr>
<td>acceptable</td>
<td>( u^{\text{true}}(c, q) )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>% Sel (No. Pats.)</td>
<td>0% (2.8)</td>
<td>0% (1.1)</td>
<td>1% (1.6)</td>
<td>7% (5.2)</td>
<td></td>
</tr>
</tbody>
</table>

Grey shaded utilities correspond to \((c, q)\) with unacceptable efficacy or toxicity.
Conclusions and Addenda

The method is reliable, safe, and robust:

- **Very likely to select a \((c, q)\) pair with high utility**, i.e. optimal or nearly optimal
- **Very likely to stop early if all \((c, q)\) are unacceptable**, i.e. if all pairs have either unacceptably low efficacy (<50%) or unacceptably high toxicity (>15%)
- **Robust** to deviations from the assumed model.

A simpler version of the method with \(q \equiv .10\) will be used for a planned trial of IA tPA *in pediatric patients*, to optimize \(c\) in \(\{.20, .30, .40, .50\}\)

A computer program “CiBolus” is available at [https://biostatistics.mdanderson.org/SoftwareDownload](https://biostatistics.mdanderson.org/SoftwareDownload)
Current Research: Adapt the approach to oncology trials:

**Expand time and reverse the time frames of** $Y_E$ and $Y_T$

$Y_T = $ Time to toxicity, e.g. during first 6 weeks
$Y_E = $ Binary “response” indicator, e.g. at 12, 18, or 24 weeks

- Toxicity may be ordinal to account for severity
- At observation of toxicity, treatment may be stopped, or suspended & later re-started, and the dose given subsequently may be decreased
  (i.e., this is a “Dynamic Treatment Regime”)
- Late-onset toxicities may occur after response evaluation