Improving probabilities of correct decision in population enrichment designs

Heiko Götte\textsuperscript{1}, Margarita Donica\textsuperscript{2*}, and Giacomo Mordenti\textsuperscript{3*}

\textsuperscript{1} Merck KGaA, Darmstadt, Germany
\textsuperscript{2} F. Hoffmann – La Roche LTD (Global Medical Affairs Biometrics), Basel, Switzerland
\textsuperscript{3} Grünenthal GmbH, Aachen, Germany

\* were under employment of Merck Serono S.A. – Geneva, Switzerland, when contributed to the publication work.

Adaptive Designs and Multiple Comparison Procedures workshop in Köln on June 24-26, 2015
End of Phase II

Biomarker suggests treatment is more effective in a subpopulation

- Biological plausibility
  - Biomarker is related to the mode of action of the experimental treatment
  - External data supporting the assumption about the potential predictive effect

- Subpopulation unambiguously defined

- Biomarker test kit is available and result is reliable
Motivating example – Phase II result

Primary end point of randomized phase II trial: PFS

- HR = 0.71 based on 110 events
  - HR ≤ 0.75 is considered as relevant effect
Motivating example – Phase II result

Primary end point of randomized phase II trial: PFS

- HR = 0.71 based on 110 events
  - HR \leq 0.75 is considered as relevant effect
- Biomarker divide population into Subpopulation and Complement
  - HR_s = 0.60 based on 50 events
  - HR_c = 0.89 based on 50 events
Motivating example – Phase II result

Primary end point of randomized phase II trial: PFS

- HR = 0.71 based on 110 events
  - HR≤ 0.75 is considered as relevant effect

- Biomarker divide population into Subpopulation and Complement
  - HRs = 0.60 based on 50 events
  - HRC = 0.89 based on 50 events

- Plan phase III trial with one interim analysis for potential subpopulation selection
Phase III Setting

- $\theta$ is overall treatment effect, i.e. $-\log(HR)$
  - $\theta > 0 \iff HR < 1$

- Hypothesis tested in Sub and Full population
  - $H_s$: $\theta_s \leq 0$ against $\theta_s > 0$
  - $H_F$: $\theta \leq 0$ against $\theta > 0$
Phase III Setting

- $\theta$ is overall treatment effect, i.e. $-\log(HR)$
  - $\theta > 0 \iff HR < 1$

- Hypothesis tested in Sub and Full population
  - $H_s$: $\theta_s \leq 0$ against $\theta_s > 0$
  - $H_F$: $\theta \leq 0$ against $\theta > 0$

- Relationship between $\theta$ and $\theta_s$
  - $\theta = \gamma \theta_s + (1-\gamma) \theta_c$
  - $\gamma$ is subpopulation fraction
Phase III Setting

- $\theta$ is overall treatment effect, i.e. $-\log(HR)$
  - $\theta > 0 \iff HR < 1$

- Hypothesis tested in Sub and Full population
  - $H_s$: $\theta_s \leq 0$ against $\theta_s > 0$
  - $H_F$: $\theta \leq 0$ against $\theta > 0$

- Relationship between $\theta$ and $\theta_s$
  - $\theta = \gamma \theta_s + (1-\gamma) \theta_c$
  - $\gamma$ is subpopulation fraction

- 508 events correspond to 90% Power with one-sided $\alpha=0.025$ and planned $HR=0.75$

- One interim analysis is performed after $\tau\%$ of subjects/events are collected
  - $\tau$ is information fraction
Closed testing procedure

$H_{FS} = H_F \cap H_S$

$H_F$

$H_S$
Trial Design

Stage 1

- Options after Stage 1
  - Continue with the full population
  - Continue with the sub population
  - Stop for futility

- Stop for efficacy: no option

Stage 2
Combine data from stage 1 and 2

- Inverse normal method

\[ C(p_{1,J}, p_{2,J}) = w_1 \Phi^{-1}(1 - p_{1,J}) + w_2 \Phi^{-1}(1 - p_{2,J}) \]

- with \( J \subseteq \{F, S\} \)

- Weights: \( w_1 = \sqrt{\tau} \quad w_2 = \sqrt{1 - \tau} \quad (w_1^2 + w_2^2 = 1) \)
Combine data from stage 1 and 2

- Inverse normal method

\[ C(p_{1,J}, p_{2,J}) = w_1 \Phi^{-1}(1 - p_{1,J}) + w_2 \Phi^{-1}(1 - p_{2,J}) \]

- with \( J \subseteq \{F, S\} \)
- Weights: \( w_1 = \sqrt{\tau} \quad w_2 = \sqrt{1 - \tau} \quad (w_1^2 + w_2^2 = 1) \)

- Intersection hypothesis: Hochberg procedure
- Second stage p-values based on increments in survival setting
Continue with the full population

Stage 1

- $P_{1,FS}$
- $P_{1,F}$
- $P_{1,S}$

Stage 2

- $P_{2,FS}$
- $P_{2,F}$
- $P_{2,S}$

Reject $H_F$ in stage 2, if
$$\min(C(p_{1,FS}, p_{2,FS}), C(p_{1,F}, p_{2,F})) > \Phi^{-1}(1 - \alpha)$$

Reject $H_S$ in stage 2, if
$$\min(C(p_{1,FS}, p_{2,FS}), C(p_{1,S}, p_{2,S})) > \Phi^{-1}(1 - \alpha)$$
Continue with the sub population

Stage 1

\[ P_{1,FS} \]

\[ P_{1,F} \] \[ P_{1,S} \]

Stage 2

\[ P_{2,S} \]

\[ P_{2,S} \]

Reject \( H_0 \) in stage 2, if

\[
\min(C(p_{1,FS}, p_{2,S}), C(p_{1,S}, p_{2,S})) > \Phi^{-1}(1 - \alpha)
\]
Stop for futility

Stage 1

\[ P_{1,FS} \]

\[ P_{1,F} \]

\[ P_{1,S} \]
Main focus of this talk

- How to make an interim decision?
Main focus of this talk

- How to make an interim decision?
- How to make the correct interim decision?
Main focus of this talk

- How to make an interim decision?
- How to make the correct interim decision?
  - Let's say HR ≤ 0.75 is considered as clinically relevant
  - Let's say we know the truth
Main focus of this talk

- How to make an interim decision?
- How to make the correct interim decision?
  - Let’s say $HR \leq 0.75$ is considered as clinically relevant
  - Let’s say we know the truth
  - What would be the decision if (subpopulation fraction $\gamma = 0.5$)
    - $HR_F = 0.75$, $HR_S = 0.75$, $HR_C = 0.75$ ?
Main focus of this talk

- How to make an interim decision?
- How to make the correct interim decision?
  - Let’s say HR ≤ 0.75 is considered as clinically relevant
  - Let’s say we know the truth
  - What would be the decision if (subpopulation fraction $\gamma = 0.5$)
    - $HR_F = 0.75$, $HR_S = 0.75$, $HR_C = 0.75$ ?
    - $HR_F = 0.75$, $HR_S = 0.74$, $HR_C = 0.76$ ?
Main focus of this talk

- How to make an interim decision?
- How to make the correct interim decision?
  - Let’s say HR \leq 0.75 is considered as clinically relevant
  - Let’s say we know the truth
  - What would be the decision if (subpopulation fraction $\gamma=0.5$)
    - $HR_F=0.75$, $HR_S=0.75$, $HR_C=0.75$ ?
    - $HR_F=0.75$, $HR_S=0.74$, $HR_C=0.76$ ?
    - $HR_F=0.75$, $HR_S=0.70$, $HR_C=0.81$ ?
    - $HR_F=0.77$, $HR_S=0.70$, $HR_C=0.85$ ?
Main focus of this talk

- How to make an interim decision?
- How to make the correct interim decision?
  - Let’s say HR≤0.75 is considered as clinically relevant
  - Let’s say we know the truth
  - What would be the decision if (subpopulation fraction $\gamma=0.5$)
    - $HR_F=0.75$, $HR_S=0.75$, $HR_C=0.75$ ?
    - $HR_F=0.75$, $HR_S=0.74$, $HR_C=0.76$ ?
    - $HR_F=0.75$, $HR_S=0.70$, $HR_C=0.81$ ?
    - $HR_F=0.77$, $HR_S=0.70$, $HR_C=0.85$ ?
  - Let’s focus on the unambiguous scenarios
    - $HR_F=0.75$, $HR_S=0.75$, $HR_C=0.75$ \(\Rightarrow\) go with the full population
    - $HR_F=0.87$, $HR_S=0.75$, $HR_C=1$ \(\Rightarrow\) go with the sub population
    - $HR_F=\ ?$, $HR_S=1$, $HR_C=\ ?$ \(\Rightarrow\) stop for futility
Main focus of this talk

- How to make an interim decision?
- How to make the correct interim decision?
  - Let's focus on the unambiguous scenarios
    - $HR_F = 0.75$, $HR_S = 0.75$, $HR_C = 0.75 \Rightarrow$ go with the full population
    - $HR_F = 0.87$, $HR_S = 0.75$, $HR_C = 1 \Rightarrow$ go with the sub population
    - $HR_F = \, \, ?$, $HR_S = 1$, $HR_C = \, \, ? \Rightarrow$ stop for futility
  - Maximally one of these scenarios can be true
    - Make assumption how likely the different scenarios are
Main focus of this talk

- How to make an interim decision?
- How to make the correct interim decision?
  - Let's focus on the unambiguous scenarios
    - $HR_F = 0.75$, $HR_S = 0.75$, $HR_C = 0.75$ ⇒ go with the full population
    - $HR_F = 0.87$, $HR_S = 0.75$, $HR_C = 1$ ⇒ go with the sub population
    - $HR_F = ?$, $HR_S = 1$, $HR_C = ?$ ⇒ stop for futility
  - Maximally one of these scenarios can be true
    - Make assumption how likely the different scenarios are
  - $Q = P(\text{correct decision in interim analysis})$
    $= \sum P(\text{correct decision} \mid \text{true values in sub} \cap \text{in complement}) \times P(\text{true values in sub} \cap \text{in complement})$
Main focus of this talk

- How to make an interim decision?
- How to make the correct interim decision?
  - Let’s focus on the unambiguous scenarios
    - \( HR_F = 0.75, HR_S = 0.75, HR_C = 0.75 \implies \text{go with the full population} \)
    - \( HR_F = 0.87, HR_S = 0.75, HR_C = 1 \implies \text{go with the sub population} \)
    - \( HR_F = ?, HR_S = 1, HR_C = ? \implies \text{stop for futility} \)
  - Maximally one of these scenarios can be true
    - Make assumption how likely the different scenarios are
  - \( Q = P(\text{correct decision in interim analysis}) \)
    
    \[ Q = \sum P(\text{correct decision} \mid \text{true values in sub } \cap \text{in complement}) \ast P(\text{true values in sub } \cap \text{in complement}) \]
    
    \[ = \omega_1 P(\text{continue full } \mid \text{effect in sub } \cap \text{effect in complement}) \]
    
    \[ + \omega_2 P(\text{continue sub } \mid \text{effect in sub } \cap \text{no effect in complement}) \]
    
    \[ + \omega_3 P(\text{stop for futility } \mid \text{no effect in sub}), \quad (\omega_1 + \omega_2 + \omega_3 = 1) \]
How to make the interim decision?

Sign of the observed treatment effect ("Simple rule")

- \( \hat{\theta}_s < 0 \): Stop for futility
- \( \hat{\theta}_s \geq 0 \) & \( \hat{\theta}_c < 0 \): Continue sub
- \( \hat{\theta}_s \geq 0 \) & \( \hat{\theta}_c \geq 0 \): Continue full
How to make the interim decision?

Sign of the observed treatment effect ("Simple rule")

- $\hat{\theta}_s < 0$: Stop for futility
- $\hat{\theta}_s \geq 0$ & $\hat{\theta}_c < 0$: Continue sub
- $\hat{\theta}_s \geq 0$ & $\hat{\theta}_c \geq 0$: Continue full

General "linear rule"

- $\hat{\theta}_s < f_L$: Stop for futility
- $\hat{\theta}_s \geq f_L$ & $a_L \cdot \hat{\theta}_s + \hat{\theta}_c < d_L$: Continue sub
- $\hat{\theta}_s \geq f_L$ & $a_L \cdot \hat{\theta}_s + \hat{\theta}_c \geq d_L$: Continue full
Find optimal decision rule

- $Q_L = P($correct decision in interim analysis$)$
- $= \omega_1 P(X > f_L, Y > d_L \mid E(X) = -\log(0.75), E(Y) = a_L \times (-\log(0.75)) + (-\log(0.75)))$
- $+ \omega_2 P(X > f_L, Y < d_L \mid E(X) = -\log(0.75), E(Y) = a_L \times (-\log(0.75)) + (-\log(1)))$
- $+ \omega_3 P(X < f_L \mid E(X) = -\log(1))$

- Find optimal values $(\max(Q_L))$ for boundaries
  - $a_L, d_L, f_L$
Determine “optimal” boundaries

- Assumption about true effects
  - \((\theta_s, \theta_c) = (0,0)\) stop for futility
  - \((\theta_s, \theta_c) = (\log(1/0.75), 0)\) continue sub
  - \((\theta_s, \theta_c) = (\log(1/0.75), \log(1/0.75))\) continue full
Determine “optimal” boundaries

- Assumption about true effects
  - \((\theta_s, \theta_c) = (0,0)\) \hspace{1cm} \text{stop for futility}
  - \((\theta_s, \theta_c) = (\log(1/0.75), 0)\) \hspace{1cm} \text{continue sub}
  - \((\theta_s, \theta_c) = (\log(1/0.75), \log(1/0.75))\) \hspace{1cm} \text{continue full}

- Subpopulation fraction \(\gamma\)
- Information fraction \(\tau\)
Determine “optimal” boundaries

- Assumption about true effects
  - $(\theta_s, \theta_c) = (0,)$ stop for futility
  - $(\theta_s, \theta_c) = (\log(1/0.75), 0)$ continue sub
  - $(\theta_s, \theta_c) = (\log(1/0.75), \log(1/0.75))$ continue full

- Subpopulation fraction $\gamma$
- Information fraction $\tau$
- Timing of final analysis
  - Continue full population:
    - 508 events in full population, $\sim \gamma \times 508$ events in sub population
Determine “optimal” boundaries

- Assumption about true effects
  - $(\theta_s, \theta_c) = (0,)$ stop for futility
  - $(\theta_s, \theta_c) = (\log(1/0.75), 0)$ continue sub
  - $(\theta_s, \theta_c) = (\log(1/0.75), \log(1/0.75))$ continue full

- Subpopulation fraction $\gamma$

- Information fraction $\tau$

- Timing of final analysis
  - Continue full population:
    - 508 events in full population, ~ $\gamma \times 508$ events in sub population
  - Continue sub population
    - 508 events in sub population
Determine “optimal” boundaries

- Assumption about true effects
  - \((\theta_s, \theta_c) = (0,0)\) stop for futility
  - \((\theta_s, \theta_c) = (\log(1/0.75), 0)\) continue sub
  - \((\theta_s, \theta_c) = (\log(1/0.75), \log(1/0.75))\) continue full

- Subpopulation fraction \(\gamma\)
- Information fraction \(\tau\)
- Timing of final analysis
  - Continue full population:
    - 508 events in full population, \(\sim \gamma \times 508\) events in sub population
    - Power 90%, …
  - Continue sub population
    - 508 events in sub population

- Weights \((\omega_1, \omega_2, \omega_3)\) depending on prior assumption
  - (full, sub, stop)
  - (1/3, 1/3, 1/3)
  - (0.4, 0.4, 0.2)
“Optimal” boundaries for linear rule

- \( \hat{\theta}_s < f_L \): Stop for futility
- \( \hat{\theta}_s \geq f_L \) & \( a_L \cdot \hat{\theta}_s + \hat{\theta}_c < d_L \): Continue sub
- \( \hat{\theta}_s \geq f_L \) & \( a_L \cdot \hat{\theta}_s + \hat{\theta}_c \geq d_L \): Continue full

- \( a_L \) often 0 \( \Rightarrow \) decision between sub and full based on complement
- Usually \( d_L > f_L \)
“Optimal” boundaries for linear rule

- \( \hat{\theta}_s < f_L \): Stop for futility
- \( \hat{\theta}_s \geq f_L \) & \( a_L \cdot \hat{\theta}_s + \hat{\theta}_c < d_L \): Continue sub
- \( \hat{\theta}_s \geq f_L \) & \( a_L \cdot \hat{\theta}_s + \hat{\theta}_c \geq d_L \): Continue full

- \( a_L \) often 0 \( \Rightarrow \) decision between sub and full based on complement
- Usually \( d_L > f_L \)

Example for subpop=0.5, information=0.3, weights (full, sub, stop)=(1/3, 1/3, 1/3)

- \( HR_s > 0.95 \) Stop for futility
- \( HR_s \leq 0.95 \) \& \( HR_c > 0.86 \) Continue sub
- \( HR_s \leq 0.95 \) \& \( HR_c \leq 0.86 \) Continue full
"Optimal" boundaries for linear rule

- $\hat{\theta}_s < f_L$: Stop for futility
- $\hat{\theta}_s \geq f_L$ & $a_L \cdot \hat{\theta}_s + \hat{\theta}_c < d_L$: Continue sub
- $\hat{\theta}_s \geq f_L$ & $a_L \cdot \hat{\theta}_s + \hat{\theta}_c \geq d_L$: Continue full

- $a_L$ often 0 $\Rightarrow$ decision between sub and full based on complement
- Usually $d_L > f_L$

Example for subpop=0.5, information=0.3, weights $(full, sub, stop)=(1/3, 1/3, 1/3)$

- $HR_s > 0.95$ Stop for futility
- $HR_s \leq 0.95$ & $HR_c > 0.86$ Continue sub
- $HR_s \leq 0.95$ & $HR_c \leq 0.86$ Continue full

Example for subpop=0.5, information=0.3, weights $(full, sub, stop)=(0.4, 0.4, 0.2)$

- $HR_s > 1.05$ Stop for futility
- $HR_s \leq 1.05$ & $HR_c > 0.86$ Continue sub
- $HR_s \leq 1.05$ & $HR_c \leq 0.86$ Continue full

Improving probabilities of correct decision in population enrichment designs | 25 June 2015
Performance comparison - Simulation

- Simulation of normalized test statistics based on all pairwise combinations of (0.65, 0.75, 0.85, 1) for (1/exp(θs),1/exp(θc))

- Optimal boundaries for
  - (θs,θc) = (0,) stop for futility
  - (θs,θc) = (-log(0.75),0) continue sub
  - (θs,θc) = (-log(0.75), -log(0.75)) continue full

- Results
  - Rate of correct interim decision
  - Power (reject at least one)
## Probabilities of Interim Decisions (%)

<table>
<thead>
<tr>
<th>Optimal Linear rule</th>
<th>(1/3, 1/3, 1/3)</th>
<th>(0.4, 0.4, 0.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR_S</td>
<td>HR_C</td>
<td>HR_F</td>
</tr>
<tr>
<td>0.650</td>
<td>1.000</td>
<td>0.806</td>
</tr>
<tr>
<td>0.750</td>
<td>0.750</td>
<td>0.750</td>
</tr>
<tr>
<td>0.750</td>
<td>1.000</td>
<td>0.866</td>
</tr>
<tr>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
</tr>
</tbody>
</table>
## Probabilities of Interim Decisions (%)

<table>
<thead>
<tr>
<th>Optimal Linear rule</th>
<th>(1/3,1/3,1/3)</th>
<th>(0.4,0.4,0.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR_S</td>
<td>HR_C</td>
<td>HR_F</td>
</tr>
<tr>
<td>0.650</td>
<td>1.000</td>
<td>0.806</td>
</tr>
<tr>
<td>0.750</td>
<td>0.750</td>
<td>0.750</td>
</tr>
<tr>
<td>0.750</td>
<td>1.000</td>
<td>0.866</td>
</tr>
<tr>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Simple rule</th>
<th>full</th>
<th>sub</th>
<th>futility</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR_S</td>
<td>HR_C</td>
<td>HR_F</td>
<td>full</td>
</tr>
<tr>
<td>0.650</td>
<td>1.000</td>
<td>0.806</td>
<td>48.7</td>
</tr>
<tr>
<td>0.750</td>
<td>0.750</td>
<td>0.750</td>
<td>79.8</td>
</tr>
<tr>
<td>0.750</td>
<td>1.000</td>
<td>0.866</td>
<td>45.6</td>
</tr>
<tr>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
<td>25.3</td>
</tr>
<tr>
<td>HR_S</td>
<td>HR_C</td>
<td>HR_F</td>
<td>P(Reject at least one) (%)</td>
</tr>
<tr>
<td>------</td>
<td>------</td>
<td>------</td>
<td>---------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Optimal Linear rule</strong></td>
</tr>
<tr>
<td>0.650</td>
<td>1.000</td>
<td>0.806</td>
<td>(1/3,1/3,1/3)</td>
</tr>
<tr>
<td>0.750</td>
<td>0.750</td>
<td>0.750</td>
<td>(0.4,0.4,0.2)</td>
</tr>
<tr>
<td>0.750</td>
<td>1.000</td>
<td>0.866</td>
<td>(0.4,0.4,0.2)</td>
</tr>
<tr>
<td>1.000</td>
<td>1.000</td>
<td>1.000</td>
<td>(0.4,0.4,0.2)</td>
</tr>
</tbody>
</table>
Discussion

- Evaluation of decision rules in planning phase is important
  - Optimizing decision rules can substantially improve probabilities of correct decision and power compared to „intuitive“ decision rules

- Assumption or prior knowledge needed
  - Strong impact on results
  - Recommendation with promising results from phase II: not too much weight on stopping for futility

- Extension to other type of decision rule easy
  - For example: conditional power (CP)
    - $CP_1 < f_{CP}$: Stop for futility
    - $CP_1 \geq f_{CP}$ & $CP_2 \geq CP_F + d_{CP}$: Continue sub
    - $CP_1 \geq f_{CP}$ & $CP_2 < CP_F + d_{CP}$: Continue full

- „Optimal“ CP rule lead to similar decisions as „optimal“ linear rule
So far…

- “Points/lines” determine correct decisions
- Weights define how likely each case is (e.g. \(\text{full, sub, stop} = (0.4, 0.4, 0.2)\))
Extension

- “Areas” determine correct decisions
- Prior distribution based on phase II data define how likely each case is

\[ \theta_s \]

Stop for futility
Continue sub
Continue full

\[ \theta_c \]

\[ f_{u_s} : N(-\log(0.6), 4/50), f_{u_c} : N(-\log(0.89), 4/50) \]
References


Back up
"Optimal" boundaries for linear rule

<table>
<thead>
<tr>
<th>$\tau$</th>
<th>$\gamma$</th>
<th>$\omega_1$</th>
<th>$\omega_2$</th>
<th>$\omega_3$</th>
<th>$a_L$</th>
<th>$d_L$</th>
<th>$f_L$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>0.375</td>
<td>1/3</td>
<td>1/3</td>
<td>1/3</td>
<td>0.00</td>
<td>0.15</td>
<td>0.05</td>
</tr>
<tr>
<td>0.3</td>
<td>0.375</td>
<td>0.4</td>
<td>0.4</td>
<td>0.2</td>
<td>0.00</td>
<td>0.15</td>
<td>-0.15</td>
</tr>
<tr>
<td>0.3</td>
<td>0.375</td>
<td>0.5</td>
<td>0.35</td>
<td>0.15</td>
<td>0.00</td>
<td>0.10</td>
<td>-0.20</td>
</tr>
<tr>
<td>0.3</td>
<td>0.375</td>
<td>0.5</td>
<td>0.5</td>
<td>0.0</td>
<td>0.00</td>
<td>0.15</td>
<td>-1.00*</td>
</tr>
<tr>
<td>0.3</td>
<td>0.5</td>
<td>1/3</td>
<td>1/3</td>
<td>1/3</td>
<td>0.00</td>
<td>0.15</td>
<td>0.05</td>
</tr>
<tr>
<td>0.3</td>
<td>0.5</td>
<td>0.4</td>
<td>0.4</td>
<td>0.2</td>
<td>0.00</td>
<td>0.15</td>
<td>-0.05</td>
</tr>
<tr>
<td>0.3</td>
<td>0.5</td>
<td>0.5</td>
<td>0.35</td>
<td>0.15</td>
<td>-0.10</td>
<td>0.05</td>
<td>-0.10</td>
</tr>
<tr>
<td>0.3</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.0</td>
<td>0.00</td>
<td>0.15</td>
<td>-1.00*</td>
</tr>
<tr>
<td>0.6</td>
<td>0.375</td>
<td>1/3</td>
<td>1/3</td>
<td>1/3</td>
<td>0.00</td>
<td>0.15</td>
<td>0.10</td>
</tr>
<tr>
<td>0.6</td>
<td>0.375</td>
<td>0.4</td>
<td>0.4</td>
<td>0.2</td>
<td>0.00</td>
<td>0.15</td>
<td>0.00</td>
</tr>
<tr>
<td>0.6</td>
<td>0.375</td>
<td>0.5</td>
<td>0.35</td>
<td>0.15</td>
<td>-0.05</td>
<td>0.10</td>
<td>-0.05</td>
</tr>
<tr>
<td>0.6</td>
<td>0.375</td>
<td>0.5</td>
<td>0.5</td>
<td>0.0</td>
<td>0.00</td>
<td>0.15</td>
<td>-1.00*</td>
</tr>
<tr>
<td>0.6</td>
<td>0.5</td>
<td>1/3</td>
<td>1/3</td>
<td>1/3</td>
<td>-0.10</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>0.6</td>
<td>0.5</td>
<td>0.4</td>
<td>0.4</td>
<td>0.2</td>
<td>0.00</td>
<td>0.15</td>
<td>0.05</td>
</tr>
<tr>
<td>0.6</td>
<td>0.5</td>
<td>0.5</td>
<td>0.35</td>
<td>0.15</td>
<td>-0.05</td>
<td>0.10</td>
<td>0.00</td>
</tr>
</tbody>
</table>

$\exp(0.15) = 1.16$
$\exp(0.10) = 1.11$
$\exp(0.05) = 1.05$
$\exp(-0.05) = 0.95$
$\exp(-0.10) = 0.90$
$\exp(-0.20) = 0.82$

- $\hat{\theta}_s < f_L$: Stop for futility
- $\hat{\theta}_s \geq f_L \& a_L \times \hat{\theta}_s + \hat{\theta}_c < d_L$: Continue sub
- $\hat{\theta}_s \geq f_L \& a_L \times \hat{\theta}_s + \hat{\theta}_c \geq d_L$: Continue full
Phase II results often not conclusive

Expected outcome

Simulated Study - 12 months recruit 8 months follow up

Simulated Study - 12 months recruit 8 months follow up

Simulated Study - 12 months recruit 8 months follow up

Simulated Study - 12 months recruit 8 months follow up

Simulated Study - 12 months recruit 8 months follow up

Simulated Study - 12 months recruit 8 months follow up

Simulated Study - 12 months recruit 8 months follow up

Simulated Study - 12 months recruit 8 months follow up

Simulated Study - 12 months recruit 8 months follow up

Simulated Study - 12 months recruit 8 months follow up