An Adaptive Design for Survival Studies with Subgroup Selection based on Predictive Biomarkers

RSS / MRC HTMR Workshop on Stratified Medicine

Thomas Hamborg

t.hamborg@warwick.ac.uk

Warwick Medical School
The University of Warwick
Funded by AstraZeneca

30 June 2010
Outline

1. Introduction
2. Adaptive Design Framework
Outline

1. Introduction

2. Adaptive Design Framework

3. Survival Studies
Outline

1. Introduction

2. Adaptive Design Framework

3. Survival Studies

4. Discussion
Problem Definition

Targeted Therapies in Oncology

- Tumours are heterogeneous ⇒ Only some patients may benefit
- Recruit patients with a certain type of cancer
- Might draw wrong conclusion or even miss an effective agent!

Idea

- Presumption (uncertainty!) about a most beneficial subgroup
- Subgroup defined by biomarker: +ve patients vs. -ve patients
- Compare treatment effect in subgroups and adapt recruitment and efficacy claim
Problem Definition

**Targeted Therapies in Oncology**
- Tumours are heterogeneous ⇒ Only some patients may benefit
- Recruit patients with a certain type of cancer
- Might draw wrong conclusion or even miss an effective agent!

**Idea**
- Presumption (uncertainty!) about a most beneficial subgroup
- Subgroup defined by biomarker: +ve patients vs. -ve patients
- Compare treatment effect in subgroups and adapt recruitment and efficacy claim

**Method**
- Seamless phase IIb/III clinical trial design
Problem Definition

Targeted Therapies in Oncology

- Tumours are heterogeneous ⇒ Only some patients may benefit
- Recruit patients with a certain type of cancer
- Might draw wrong conclusion or even miss an effective agent!

Idea

- Presumption (uncertainty!) about a most beneficial subgroup
- Subgroup defined by biomarker: +ve patients vs. -ve patients
- Compare treatment effect in subgroups and adapt recruitment and efficacy claim

Method

- Seamless phase IIb/III clinical trial design
Illustartion: KRAS Biomarker

Panitumumab

- Metastatic colorectal cancer
- Monoclonal antibody directed at EGFR
- Subgroups KRAS mutant & wild-type [Amado et al., 2008]

Figure: Outcome for KRAS mutant tumour patients - Amado et al (2008) JCO, 26
Illustration: KRAS Biomarker

Panitumumab

- Metastatic colorectal cancer
- Monoclonal antibody directed at EGFR
- Subgroups KRAS mutant & wild-type [Amado et al., 2008]

Figure: Outcome for KRAS wild-type tumour patients - Amado et al (2008) JCO, 26
Test Statistics

**Efficient score** $Z = \frac{\partial \ell(0)}{\partial \theta}$: cumulative measure of advantage of experimental treatment $E$ over control $C$

*(Observed) Fisher’s information* $V = -\frac{\partial^2 \ell(0)}{\partial \theta^2}$: amount of information on treatment difference contained in $Z$

- $\theta = \frac{Z}{V}$ - Measure of treatment difference
- Under $H_0$: $\frac{Z}{\sqrt{V}} \sim N(0, 1)$ (Score test)
- Here:
  - +ve patients: $Z_{+,1}$, -ve patients: $Z_{-,1}$, all patients: $Z_{B,1}$
  - Final analysis $Z_S$
  - $V$ correspondingly
General Design Framework

Test Statistics

Efficient score $Z = \frac{\partial \ell(0)}{\partial \theta}$: cumulative measure of advantage of experimental treatment $E$ over control $C$

(Observed) Fisher’s information $V = -\frac{\partial^2 \ell(0)}{\partial \theta^2}$: amount of information on treatment difference contained in $Z$

- $\theta = \frac{Z}{V}$ - Measure of treatment difference
- Under $H_0$: $\frac{Z}{\sqrt{V}} \sim N(0, 1)$ (Score test)
- Here:
  - +ve patients: $Z_{+,1}$, -ve patients: $Z_{-,1}$, all patients: $Z_{B,1}$
  - Final analysis $Z_S$
  - $V$ correspondingly
Design Illustration

\begin{align*}
\text{Interim} & \xrightarrow{\text{select +ve}} \\
+ve & \quad -ve \\
\text{no sel.} & \\
\begin{array}{c}
+ve \\
-ve
\end{array}
\end{align*}

\begin{align*}
\Pr(Z \geq c & \text{ & sel. +ve}) \\
\Pr(Z \geq c & \text{ & no sel.})
\end{align*}
Design Illustration

**Interim**

- **select +ve**
- **no sel.**

**+ve**

- **- ve**

**Pr(\(Z \geq c \& \text{no sel.}\))**

**Pr(\(Z \geq c \& \text{sel. +ve}\))**

**V1**

- **V1**

- **V2**

**Q**

\[ Q = \sum_{i=1}^{m} (\hat{\theta}_i - \hat{\theta})^2 \omega_i \]

In terms of Z and V:

\[ Q = Z + \frac{1}{V} - Z - \frac{1}{V} \sqrt{\left(\frac{V + 1}{V - 1}\right)} \]

Subgroup selection if:

\[ Q \sim N(0, 1) \geq k \]
Design Illustration

Cochran’s Q test

\[
Q = \sum_{i=1}^{m} (\hat{\theta}_i - \hat{\theta})^2 \omega_i
\]

In terms of Z and V:

\[
Q = \frac{Z_{+,1} V_{-,1} - Z_{-,1} V_{+,1}}{\sqrt{(V_{+,1} + V_{-,1}) V_{+,1} V_{-,1}}}
\]

Subgroup selection if: \( Q \sim N(0, 1) \geq k \)
Design Illustration

Cochran’s Q test

\[ Q = \sum_{i=1}^{m} (\hat{\theta}_i - \hat{\theta})^2 \omega_i \]

In terms of \( Z \) and \( V \):

\[ Q = \frac{Z_{+,1}V_{-,1} - Z_{-,1}V_{+,1}}{\sqrt{(V_{+,1} + V_{-,1})V_{+,1}V_{-,1}}} \]

Subgroup selection if: \( Q \sim N(0, 1) \geq k \)
Interim Analysis in Detail

Futility Stopping Criterion

- Cond. power (CP) approach
- CP stopping unlikely if early in study ⇒ stop if:
  \[ \text{CP}_{\theta_R}(V) \leq 1 - \beta_{CP} \]
  or \[ Z_{i,1} \leq 0, \quad i \in \{+, B\} \]
  for respective interim decision

Upper Selection Limit Criterion

- Undesirable to select if drug has certain effect in -ve patients
- Do not select +ve patients if:
  \[ \hat{\theta}_{-,1} \geq \tau \theta_R, \quad 0 < \tau \leq \lambda \]
  Natural choice \( \tau = 1 \)

Thomas Hamborg
Interim Analysis in Detail

**Futility Stopping Criterion**
- Cond. power (CP) approach
- CP stopping unlikely if early in study
  \[ \implies \text{stop if:} \]
  \[ \text{CP}_{\theta_R}(V) \leq 1 - \beta_{CP} \]
  or \[ Z_{i,1} \leq 0, \ i \in \{+, B\} \]
  for respective interim decision

**Upper Selection Limit Criterion**
- Undesirable to select if drug has certain effect in -ve patients
- Do not select +ve patients if:
  \[ \hat{\theta}_{-,1} \geq \tau \theta_R, \ 0 < \tau \leq \lambda \]
  Natural choice \( \tau = 1 \)
**Power Requirements**

**Power Requirement I**
- Study-wise type-I error rate
- \( Pr(Z_S \geq c \mid \theta_+ = \theta_- = 0) = \alpha \)

**Power Requirement II**
- \( Pr(Z_S \geq c \cap \text{no sel.} \mid \theta_+ = \theta_- = \theta_R) = 1 - \beta_B = Power_B \)
- \( \theta_R \) reference improvement

**Diagram**
- Interim
- +ve
- -ve
- select +ve
- no sel.
- Pr(Z>=c) = type-I error rate
- V1
- V2
Power Requirements

Power Requirement I
- Study-wise type-I error rate
- \( \Pr(Z_S \geq c \mid \theta_+ = \theta_- = 0) = \alpha \)

Power Requirement II
- \( \Pr(Z_S \geq c \cap \text{no sel.} \mid \theta_+ = \theta_- = \theta_R) = 1 - \beta_B = \text{Power}_B \)
- \( \theta_R \) reference improvement

Power Requirement III
- \( \Pr(Z_S \geq c \cap \text{sel +ve} \mid \theta_+ = \lambda \theta_R, \theta_- = 0) = 1 - \beta_+ = \text{Power}_+ \)
- \( \lambda \geq 1 \Rightarrow \text{demand larger effect for selection} \)
Power Requirements

**Power Requirement I**
- Study-wise type-I error rate
- \( \Pr(Z_S \geq c \mid \theta_+ = \theta_- = 0) = \alpha \)

**Power Requirement II**
- \( \Pr(Z_S \geq c \cap \text{no sel.} \mid \theta_+ = \theta_- = \theta_R) = 1 - \beta_B = \text{Power}_B \)
- \( \theta_R \) reference improvement

**Power Requirement III**
- \( \Pr(Z_S \geq c \cap \text{sel.+ve} \mid \theta_+ = \lambda \theta_R, \theta_- = 0) = 1 - \beta_+ = \text{Power}_+ \)
- \( \lambda \geq 1 \Rightarrow \text{demand larger effect for selection} \)
Calculation of Design Variables

Score function properties:
1. Approximately $Z \sim N(\theta V, V)$
2. Independent increment structure

Numerical root finding procedure

For each Power Requirement:

$$\Pr(Z_S \geq c) = \sum_{i} \int_{l_i^-}^{u_i^-} \int_{l_i^+}^{u_i^+} \left\{ 1 - \Phi \left( \frac{c - (z_) - \theta_j(V_S - V_{..,1})}{\sqrt{V_S - V_{..,1}}} \right) \right\} f(z_+)f(z_-)dz_+dz_-,$$

where $f(z) = \frac{1}{\sqrt{V}} \phi \left( \frac{z - \theta V}{\sqrt{V}} \right)$
Design Framework for Survival Outcome

Superiority Trial
- Outcome: time to unfavourable event
- \( S_E(t), S_C(t) \) survival probabilities
- \( H_0 : \theta = 0 \) vs \( H_1 : \theta > 0 \)

Proportional Hazard Model
- Assumption: \( h_E(t) = \psi h_C(t), t > 0 \)
- Parameterisation: \( \theta = -\log (h_E(t)/h_C(t)) \)
Design Framework for Survival Outcome

Superiority Trial
- Outcome: time to unfavourable event
- $S_E(t), S_C(t)$ survival probabilities
- $H_0 : \theta = 0$ vs $H_1 : \theta > 0$

Proportional Hazard Model
- Assumption: $h_E(t) = \psi h_C(t), t > 0$
- Parameterisation: $\theta = -\log (h_E(t)/h_C(t))$

Exponential assumption
- Survival times $Weib(\gamma_i, 1) \equiv EXP(\gamma_i)$ distributed
- Loss to follow-up $EXP(\tau)$ distributed
- Analysis: log-rank test: $Z^2 / V$ or $Z / \sqrt{V} \sim N(0, 1)$
Design Framework for Survival Outcome

Superiority Trial
- Outcome: time to unfavourable event
- \(S_E(t), S_C(t)\) survival probabilities
- \(H_0 : \theta = 0\) vs \(H_1 : \theta > 0\)

Proportional Hazard Model
- Assumption: \(h_E(t) = \psi h_C(t), t > 0\)
- Parameterisation: \(\theta = -\log (h_E(t)/h_C(t))\)

Exponential assumption
- Survival times \(\text{Weib}(\gamma_i, 1) \equiv \text{EXP}(\gamma_i)\) distributed
- Loss to follow-up \(\text{EXP}(\tau)\) distributed
- Analysis: log-rank test: \(Z^2/V\) or \(Z/\sqrt{V} \sim N(0, 1)\)
Design Framework for Survival Outcome II

**Design specification**
- Specify trial in terms of time units (weeks) and no. patients
- Conduct trial in terms of $V$
- Recruit +ve and -ve patients according to population proportion

At the design stage calculate:
- $V \approx e/4$ (1:1 allocation ratio)
- Expected no. of events $e = aGp_e \Rightarrow$ determine $p_e$ expected prop. deaths
**Example KRAS study**

Pre-specified values:

- **Power req.:** \( \alpha = 0.025, \ 1 - \beta_B = 0.9, \ 1 - \beta_+ = 0.9 \)
- **Study duration:** recruit 75 weeks, follow up 50 weeks, interim at week 50
- **Treat. effect:** \( S_C(t_0) = 0.10, \ S_E(t_0) = 0.20, \ t_0 = 20, \ \lambda = 2.6 \)

Search procedure results:

<table>
<thead>
<tr>
<th>( S_E^+(t_0) )</th>
<th>( a )</th>
<th>( n )</th>
<th>( n^+ )</th>
<th>( k )</th>
<th>( c )</th>
<th>( V_{1,+} )</th>
<th>( V_{1,-} )</th>
<th>( V_S )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.407</td>
<td>4.9</td>
<td>368</td>
<td>243</td>
<td>1.988</td>
<td>2.233</td>
<td>20.05</td>
<td>18.73</td>
<td>58.250</td>
</tr>
</tbody>
</table>

**Table:** Calculation of design variables for KRAS biomarker study
Example KRAS study

Pre-specified values:
- Power req.: $\alpha = 0.025$, $1 - \beta_B = 0.9$, $1 - \beta_+ = 0.9$
- Study duration: recruit 75 weeks, follow up 50 weeks, interim at week 50
- Treat. effect: $S_C(t_0) = 0.10$, $S_E(t_0) = 0.20$, $t_0 = 20$, $\lambda = 2.6$

Search procedure results:

<table>
<thead>
<tr>
<th>$S_E^+(t_0)$</th>
<th>$a$</th>
<th>$n$</th>
<th>$n^+$</th>
<th>$k$</th>
<th>$c$</th>
<th>$V_{1,+}$</th>
<th>$V_{1,-}$</th>
<th>$V_S$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.407</td>
<td>4.9</td>
<td>368</td>
<td>243</td>
<td>1.988</td>
<td>2.233</td>
<td>20.05</td>
<td>18.73</td>
<td>58.250</td>
</tr>
</tbody>
</table>

Table: Calculation of design variables for KRAS biomarker study
Example: KRAS study

Figure: Interim outcome for mutant type

- 252 patients recruited at interim: $Q = 2.958 \Rightarrow$ select wild-type
- Recruit remaining patients:
  $$Z_S = Z_{+,1} + Z_2 = 38.9, \quad V_S = V_{1,+,1} + V_2 = 47.947$$
- p-value 0.000237 $\Rightarrow$ Panitumumab significantly better for wild-type patients

Figure: Interim outcome for wild type
Simulation study

<table>
<thead>
<tr>
<th>$S_E^+(t_0)$</th>
<th>$S_E^-(t_0)$</th>
<th>$S_C(t_0)$</th>
<th>n</th>
<th>+ve selection</th>
<th>adaptive design</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>358</td>
<td>3.13%</td>
<td>0.049 0.043 0.006</td>
</tr>
<tr>
<td>0.40</td>
<td>0.40</td>
<td>0.25</td>
<td>358</td>
<td>3.5%</td>
<td>0.9329 0.8989 0.034</td>
</tr>
<tr>
<td>0.671</td>
<td>0.25</td>
<td>0.25</td>
<td>358</td>
<td>87.68%</td>
<td>0.9886 0.1119 0.8767</td>
</tr>
</tbody>
</table>

**Table:** Simulation results for the adaptive method. EP denotes the estimated power based on 20,000 simulated trials.

<table>
<thead>
<tr>
<th>$S_E^+(t_0)$</th>
<th>$S_E^-(t_0)$</th>
<th>2 parallel trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.25</td>
<td>0.048 0.001 0.025 0.023</td>
</tr>
<tr>
<td>0.40</td>
<td>0.40</td>
<td>0.839 0.360 0.600 0.599</td>
</tr>
<tr>
<td>0.671</td>
<td>0.25</td>
<td>0.999 0.025 0.999 0.025</td>
</tr>
</tbody>
</table>

**Table:** Simulation results for 2 separate trials for +ve and -ve patients.
Simulation study

<table>
<thead>
<tr>
<th>$S_E^+(t_0)$</th>
<th>$S_E^-(t_0)$</th>
<th>$S_C(t_0)$</th>
<th>n</th>
<th>+ve selection</th>
<th>adaptive design</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>358</td>
<td>3.13%</td>
<td>0.049</td>
</tr>
<tr>
<td>0.40</td>
<td>0.40</td>
<td>0.25</td>
<td>358</td>
<td>3.5%</td>
<td>0.9329</td>
</tr>
<tr>
<td>0.671</td>
<td>0.25</td>
<td>0.25</td>
<td>358</td>
<td>87.68%</td>
<td>0.9886</td>
</tr>
</tbody>
</table>

**Table:** Simulation results for the adaptive method. EP denotes the estimated power based on 20,000 simulated trials.

<table>
<thead>
<tr>
<th>$S_E^+(t_0)$</th>
<th>$S_E^-(t_0)$</th>
<th>2 parallel trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.25</td>
<td>0.048      0.001   0.025   0.023</td>
</tr>
<tr>
<td>0.40</td>
<td>0.40</td>
<td>0.839      0.360   0.600   0.599</td>
</tr>
<tr>
<td>0.671</td>
<td>0.25</td>
<td>0.999      0.025   0.999   0.025</td>
</tr>
</tbody>
</table>

**Table:** Simulation results for 2 separate trials for +ve and -ve patients.
Simulation study

Table: Simulation results for the adaptive method. EP denotes the estimated power based on 20,000 simulated trials.

<table>
<thead>
<tr>
<th>$S_E^+(t_0)$</th>
<th>$S_E^-(t_0)$</th>
<th>$S_C(t_0)$</th>
<th>n</th>
<th>+ve selection</th>
<th>adaptive design</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>358</td>
<td>3.13%</td>
<td>0.049 0.043 0.006</td>
</tr>
<tr>
<td>0.40</td>
<td>0.40</td>
<td>0.25</td>
<td>358</td>
<td>3.5%</td>
<td>0.9329 0.8989 0.034</td>
</tr>
<tr>
<td>0.671</td>
<td>0.25</td>
<td>0.25</td>
<td>358</td>
<td>87.68%</td>
<td>0.9886 0.1119 0.8767</td>
</tr>
</tbody>
</table>

Table: Simulation results for 2 separate trials for +ve and -ve patients.

<table>
<thead>
<tr>
<th>$S_E^+(t_0)$</th>
<th>$S_E^-(t_0)$</th>
<th>2 parallel trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.25</td>
<td>EP_O 0.048 EP_B 0.001 EP_+ 0.025 EP_- 0.023</td>
</tr>
<tr>
<td>0.40</td>
<td>0.40</td>
<td>EP_O 0.839 EP_B 0.360 EP_+ 0.600 EP_- 0.599</td>
</tr>
<tr>
<td>0.671</td>
<td>0.25</td>
<td>EP_O 0.999 EP_B 0.025 EP_+ 0.999 EP_- 0.025</td>
</tr>
</tbody>
</table>

Table: Simulation results for 2 separate trials for +ve and -ve patients.
Simulation study

<table>
<thead>
<tr>
<th>$S_E^+(t_0)$</th>
<th>$S_E^-(t_0)$</th>
<th>$S_C(t_0)$</th>
<th>n</th>
<th>+ve selection</th>
<th>adaptive design</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>358</td>
<td>3.13%</td>
<td>0.049 0.043 0.006</td>
</tr>
<tr>
<td>0.40</td>
<td>0.40</td>
<td>0.25</td>
<td>358</td>
<td>3.5%</td>
<td>0.9329 0.8989 0.034</td>
</tr>
<tr>
<td>0.671</td>
<td>0.25</td>
<td>0.25</td>
<td>358</td>
<td>87.68%</td>
<td>0.9886 0.1119 0.8767</td>
</tr>
</tbody>
</table>

**Table**: Simulation results for the adaptive method. EP denotes the estimated power based on 20,000 simulated trials.

<table>
<thead>
<tr>
<th>$S_E^+(t_0)$</th>
<th>$S_E^-(t_0)$</th>
<th>2 parallel trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.25</td>
<td>0.048 0.001 0.025 0.023</td>
</tr>
<tr>
<td>0.40</td>
<td>0.40</td>
<td>0.839 0.360 0.600 0.599</td>
</tr>
<tr>
<td>0.671</td>
<td>0.25</td>
<td>0.999 0.025 0.999 0.025</td>
</tr>
</tbody>
</table>

**Table**: Simulation results for 2 separate trials for +ve and -ve patients.
## Simulation study

<table>
<thead>
<tr>
<th>$S_E^+(t_0)$</th>
<th>$S_E^-(t_0)$</th>
<th>$S_C(t_0)$</th>
<th>n</th>
<th>+ve selection</th>
<th>adaptive design</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>358</td>
<td>3.13%</td>
<td>0.049 0.043 0.006</td>
</tr>
<tr>
<td>0.40</td>
<td>0.40</td>
<td>0.25</td>
<td>358</td>
<td>3.5%</td>
<td>0.9329 0.8989 0.034</td>
</tr>
<tr>
<td>0.671</td>
<td>0.25</td>
<td>0.25</td>
<td>358</td>
<td>87.68%</td>
<td>0.9886 0.1119 0.8767</td>
</tr>
</tbody>
</table>

**Table:** Simulation results for the adaptive method. EP denotes the estimated power based on 20,000 simulated trials.

<table>
<thead>
<tr>
<th>$S_E^+(t_0)$</th>
<th>$S_E^-(t_0)$</th>
<th>2 parallel trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.25</td>
<td>$EP_O$ $EP_B$ $EP_+$ $EP_-$</td>
</tr>
<tr>
<td>0.40</td>
<td>0.40</td>
<td>0.048 0.001 0.025 0.023</td>
</tr>
<tr>
<td>0.671</td>
<td>0.25</td>
<td>0.839 0.360 0.600 0.599</td>
</tr>
</tbody>
</table>

**Table:** Simulation results for 2 separate trials for +ve and -ve patients.
Simulation study

<table>
<thead>
<tr>
<th>$S^+_E(t_0)$</th>
<th>$S^-_E(t_0)$</th>
<th>$S_C(t_0)$</th>
<th>n</th>
<th>+ve selection</th>
<th>$EP_O$</th>
<th>$EP_B$</th>
<th>$EP_+$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>358</td>
<td>3.13%</td>
<td>0.049</td>
<td>0.043</td>
<td>0.006</td>
</tr>
<tr>
<td>0.40</td>
<td>0.40</td>
<td>0.25</td>
<td>358</td>
<td>3.5%</td>
<td>0.9329</td>
<td>0.8989</td>
<td>0.034</td>
</tr>
<tr>
<td>0.671</td>
<td>0.25</td>
<td>0.25</td>
<td>358</td>
<td>87.68%</td>
<td>0.9886</td>
<td>0.1119</td>
<td>0.8767</td>
</tr>
</tbody>
</table>

**Table:** Simulation results for the adaptive method. EP denotes the estimated power based on 20,000 simulated trials.

<table>
<thead>
<tr>
<th>$S^+_E(t_0)$</th>
<th>$S^-_E(t_0)$</th>
<th>2 parallel trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>0.25</td>
<td>0.048</td>
</tr>
<tr>
<td>0.40</td>
<td>0.40</td>
<td>0.839</td>
</tr>
<tr>
<td>0.671</td>
<td>0.25</td>
<td>0.999</td>
</tr>
</tbody>
</table>

**Table:** Simulation results for 2 separate trials for +ve and -ve patients.
## Impact of Design Changes I

<table>
<thead>
<tr>
<th>Analysis type</th>
<th>$\tau$</th>
<th>$\lambda$</th>
<th>$n$</th>
<th>$k$</th>
<th>$c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>No futility stop</td>
<td>-</td>
<td>3</td>
<td>352</td>
<td>1.8442</td>
<td>1.6980</td>
</tr>
<tr>
<td>Futility stop</td>
<td>-</td>
<td>3</td>
<td>358</td>
<td>1.8667</td>
<td>1.6849</td>
</tr>
<tr>
<td>Fut stop &amp; upper lim</td>
<td>3</td>
<td>3</td>
<td>358</td>
<td>1.8667</td>
<td>1.6836</td>
</tr>
<tr>
<td>Fut stop &amp; upper lim</td>
<td>1</td>
<td>3</td>
<td>372</td>
<td>1.7646</td>
<td>1.6934</td>
</tr>
<tr>
<td>Fut stop &amp; upper lim</td>
<td>0.70</td>
<td>3</td>
<td>468</td>
<td>1.3638</td>
<td>1.7304</td>
</tr>
</tbody>
</table>

**Table:** Impact of interim decision rules on design parameter - standard scenario

- Futility stopping rule is cheap
- Upper selection limit can be cheap
- Lower bound $\tau \approx 0.60$
### Impact of Design Changes I

<table>
<thead>
<tr>
<th>Analysis type</th>
<th>$\tau$</th>
<th>$\lambda$</th>
<th>$n$</th>
<th>$k$</th>
<th>$c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>No futility stop</td>
<td>-</td>
<td>3</td>
<td>352</td>
<td>1.8442</td>
<td>1.6980</td>
</tr>
<tr>
<td>Futility stop</td>
<td>-</td>
<td>3</td>
<td>358</td>
<td>1.8667</td>
<td>1.6849</td>
</tr>
<tr>
<td>Fut stop &amp; upper lim</td>
<td>3</td>
<td>3</td>
<td>358</td>
<td>1.8667</td>
<td>1.6836</td>
</tr>
<tr>
<td>Fut stop &amp; upper lim</td>
<td>1</td>
<td>3</td>
<td>372</td>
<td>1.7646</td>
<td>1.6934</td>
</tr>
<tr>
<td>Fut stop &amp; upper lim</td>
<td>0.70</td>
<td>3</td>
<td>468</td>
<td>1.3638</td>
<td>1.7304</td>
</tr>
</tbody>
</table>

**Table:** Impact of interim decision rules on design parameter - standard scenario

- Futility stopping rule is cheap
- Upper selection limit can be cheap
- Lower bound $\tau \approx 0.60$
## Impact of Design Changes I

<table>
<thead>
<tr>
<th>Analysis type</th>
<th>$\tau$</th>
<th>$\lambda$</th>
<th>$n$</th>
<th>$k$</th>
<th>$c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>No futility stop</td>
<td>-</td>
<td>3</td>
<td>352</td>
<td>1.8442</td>
<td>1.6980</td>
</tr>
<tr>
<td>Futility stop</td>
<td>-</td>
<td>3</td>
<td>358</td>
<td>1.8667</td>
<td>1.6849</td>
</tr>
<tr>
<td>Fut stop &amp; upper lim</td>
<td>3</td>
<td>3</td>
<td>358</td>
<td>1.8667</td>
<td>1.6836</td>
</tr>
<tr>
<td>Fut stop &amp; upper lim</td>
<td>1</td>
<td>3</td>
<td>372</td>
<td>1.7646</td>
<td>1.6934</td>
</tr>
<tr>
<td>Fut stop &amp; upper lim</td>
<td>0.70</td>
<td>3</td>
<td>468</td>
<td>1.3638</td>
<td>1.7304</td>
</tr>
</tbody>
</table>

**Table:** Impact of interim decision rules on design parameter - standard scenario

- Futility stopping rule is cheap
- Upper selection limit can be cheap
- Lower bound $\tau \approx 0.60$
Impact of Design Changes I

<table>
<thead>
<tr>
<th>Analysis type</th>
<th>$\tau$</th>
<th>$\lambda$</th>
<th>n</th>
<th>k</th>
<th>c</th>
</tr>
</thead>
<tbody>
<tr>
<td>No futility stop</td>
<td>-</td>
<td>3</td>
<td>352</td>
<td>1.8442</td>
<td>1.6980</td>
</tr>
<tr>
<td>Futility stop</td>
<td>-</td>
<td>3</td>
<td>358</td>
<td>1.8667</td>
<td>1.6849</td>
</tr>
<tr>
<td>Fut stop &amp; upper lim</td>
<td>3</td>
<td>3</td>
<td>358</td>
<td>1.8667</td>
<td>1.6836</td>
</tr>
<tr>
<td>Fut stop &amp; upper lim</td>
<td>1</td>
<td>3</td>
<td>372</td>
<td>1.7646</td>
<td>1.6934</td>
</tr>
<tr>
<td>Fut stop &amp; upper lim</td>
<td>0.70</td>
<td>3</td>
<td>468</td>
<td>1.3638</td>
<td>1.7304</td>
</tr>
</tbody>
</table>

Table: Impact of interim decision rules on design parameter - standard scenario

- Futility stopping rule is cheap
- Upper selection limit can be cheap
- Lower bound $\tau \approx 0.60$
Impact of Design Changes II

c, k for varying upper selection boundaries

Varying one Power requirement respectively

Thomas Hamborg
Comments

**Multiple interim analyses**

Can be incorporated at design stage

Impose linear relationship on $c_1, \ldots, c_n$

**Family-wise error rate**

Method controls FWER in strong sense
Multiple interim analyses

Can be incorporated at design stage
Impose linear relationship on $c_1, \ldots, c_n$

Family-wise error rate

Method controls FWER in strong sense

Discrete approximation

Anticipate $S_C(t_i), i = 1, \ldots, G + F$
$S_E(t_i)$ found from $\theta_R$ and proportional hazards
Comments

Multiple interim analyses
Can be incorporated at design stage
Impose linear relationship on $c_1, \ldots, c_n$

Family-wise error rate
Method controls FWER in strong sense

Discrete approximation
Anticipate $S_C(t_i), i = 1, \ldots, G + F$
$S_E(t_i)$ found from $\theta_R$ and proportional hazards

Non uniform recruitment rate
Optimal recruitment pattern is u-shaped
### Comments

<table>
<thead>
<tr>
<th><strong>Comment</strong></th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multiple interim analyses</strong></td>
<td>Can be incorporated at design stage</td>
</tr>
<tr>
<td></td>
<td>Impose linear relationship on $c_1, \ldots, c_n$</td>
</tr>
<tr>
<td><strong>Family-wise error rate</strong></td>
<td>Method controls FWER in strong sense</td>
</tr>
<tr>
<td><strong>Discrete approximation</strong></td>
<td>Anticipate $S_C(t_i), i = 1, \ldots, G + F$</td>
</tr>
<tr>
<td></td>
<td>$S_E(t_i)$ found from $\theta_R$ and proportional hazards</td>
</tr>
<tr>
<td><strong>Non uniform recruitment rate</strong></td>
<td>Optimal recruitment pattern is u-shaped</td>
</tr>
</tbody>
</table>
Summary

1. Developed a method that allows to draw inference for all patients in the trial or a subgroup
2. Flexible approach that is useful if uncertainty exists about target population in late stage trial
3. Greater power than fixed sample trial designs in appropriate scenario and allows to draw more accurate conclusion
4. Phase IIb/III design?
Wild-type kras is required for panitumumab efficacy in patients with metastatic colorectal cancer.

Sequential designs for phase iii clinical trials incorporating treatment selection.

*The Design and Analysis of Sequential Clinical Trials.*