Adaptive trial design for early phase trials
Model based dose-finding

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Study specifications

Dose schedule: \( d_1 < \cdots < d_k \)

Response: \( x = \begin{cases} 
1 & \text{for toxic response} \\
0 & \text{otherwise} 
\end{cases} \)

Structure: treat successive cohorts of \( c \) subjects

Objective: find the “highest safe dose”
Typically implemented as adaptive designs:

<table>
<thead>
<tr>
<th>Doses</th>
<th>1</th>
<th>2.5</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
</tr>
</thead>
<tbody>
<tr>
<td># patients</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td># DLT</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

What next?
- More patients on same dose (5)
- More patients on lower dose (2.5)?
- Patients on higher dose (10)?

⇒ Rule such that most patients on MTD, few overexposed
Standard Phase I cancer designs

- "3+3" designs
  - standard, simple up-and-down design
  - no statistical inference, simple data-based rules
  - very popular among clinicians
  - bad statistical properties ("operating characteristics")

- Continual Reassessment Method (CRM)
  - very popular among statisticians
  - good operating characteristics
  - bad on-study properties (non-intuitive dose recommendations)

- Bayesian adaptive dose-response escalation strategies
  - model based using flexible dose-response model
  - Usually very balanced dose-recommendations

Review of advantages Jaki et al. (2013)
Seeking a quantile

\[ MTD \rightarrow \text{maximal dose acceptably tolerated by a particular patient population} \]
\[ \rightarrow \text{vague} \]

\[ TD_{100\pi} \rightarrow \text{dose at which the probability of toxicity is } \pi \]
\[ \text{(for } 0 < \pi < 1\text{), e.g. TD20} \]
\[ \rightarrow \text{more specific} \]
Assume that a 20% risk of toxicity is an acceptable risk to pay for a chance of benefit.
General (Bayesian) approach

1. Make assumptions about the form of $p(d)$
2. Impose a prior distribution for the parameters that determine $p(d)$
3. Choose next dose to optimise treatment for this patient
4. Stop once target dose level can be estimated accurately enough
Two possible purposes:

1. To include relevant additional information
   - Related trial data
   - Expert opinion

2. To control operating characteristics
   - Typically pessimistic - reflecting fears rather than beliefs
   - Often useful to use frequentist final analysis
- Want most patients treated at doses with dark arrows
- Useful to have many doses available
- Skipping doses should be considered
Continual Reassessment method (CRM)  
O’Quigley et al (1990)

Dose schedule: \( d_1 < \cdots < d_k \)

Response: \( x = \begin{cases} 
1 \text{ for toxic response} \\
0 \text{ otherwise} 
\end{cases} \)

Objective: find \( \text{TD}_\vartheta \)

Cohort size: 1
One parameter log-log model

\[ p(d_i) = \pi_i^\theta, \ i = 1, \ldots, k \]

where \( \pi_i \) is the fixed prior guess at the probability of toxicity at \( d_i \), such that

\[ \pi_1 < \pi_2 < \cdots < \pi_k \]

A Bayesian prior for \( \theta \) is imposed: \( \theta \sim Exp(1) \) so that \( E_0(\theta) = 1 \)
Representation of the model

Starting values for the $\pi_i$

<table>
<thead>
<tr>
<th>$\pi_1$</th>
<th>$\pi_2$</th>
<th>$\pi_3$</th>
<th>$\pi_4$</th>
<th>$\pi_5$</th>
<th>$\pi_6$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>0.10</td>
<td>0.20</td>
<td>0.30</td>
<td>0.50</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Graph showing the relationship between dose level and $p(d_i)$ for different values of $\theta$. The graph includes data points for $\theta = 0.5$, $\theta = 1$, and $\theta = 2$.
Assign starting values for the $\pi_i$

\[
\begin{array}{cccccc}
\pi_1 & \pi_2 & \pi_3 & \pi_4 & \pi_5 & \pi_6 \\
0.05 & 0.10 & 0.20 & 0.30 & 0.50 & 0.70 \\
\end{array}
\]

Thus first subject receives $d_3$
Criticisms and modifications

Criticisms:
- Starting dose is usually high
- Treats too many subjects on high doses
- Doses can be skipped
- No appropriate stopping rule

Modifications:
- Start from the lowest dose
- Safety constraints
- No dose skipping
- Formal stopping rules
Bayesian Logistic Regression Model (BLRM)
Neuenschwander et al. (2008)

2-parameter logistic regression model

$\pi(d_i)$

- unsafe
- moderate
- safe
Specifying priors

- Specify two quantiles for probability of toxicity at each dose level
- Define prior distribution for the model parameters such that they are in close agreement with the above
- Requires Markov Chain Monte Carlo (MCMC)
Choose recommended dose, \( d \), such that

- probability of overdosing
  \[ P(\text{DLT rate} > 0.33 \mid d) < 0.2 \]

- probability of target toxicity
  \[ P(\text{DLT rate} \in (0.16, 0.33) \mid d) \geq 0.5 \]

- probability of underdosing
  \[ P(\text{DLT rate} < 0.16 \mid d) < 0.3 \]

is controlled.

**Interval Probabilities by Dose**

- **overdosing**
- **targeted toxicity**
- **underdosing**
Comments

- Widely used in industry now
- Specifying priors can be time consuming
- Requires MCMC
- Very intuitive dose-selection
Open-label, multicenter, dose-escalation cancer trial

Find dose that has 30% risk of toxicity, the TD30.

Use CRM but do not allow for skipping dose levels

After 4 cohorts (4 dose levels) no DLTs

Team decides to skip 2 dose levels

Two DLTs in two patients
Example

<table>
<thead>
<tr>
<th>Dose in mg</th>
<th>1</th>
<th>2.5</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>40</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of DLTs</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Posterior summaries:

Mean

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>0.069</th>
<th>0.085</th>
<th>0.099</th>
<th>0.111</th>
<th>0.123</th>
<th>0.144</th>
<th>0.163</th>
<th>0.242</th>
<th>0.330</th>
<th>0.465</th>
</tr>
</thead>
<tbody>
<tr>
<td>Std. dev.</td>
<td>0.055</td>
<td>0.062</td>
<td>0.068</td>
<td>0.072</td>
<td>0.076</td>
<td>0.082</td>
<td>0.087</td>
<td>0.101</td>
<td>0.109</td>
<td>0.108</td>
<td></td>
</tr>
</tbody>
</table>

Dose recommendation for next cohort:

- **3+3**: Unclear
- **CRM**: 40mg
- **BLRM**: 15mg (from previous figure)
A simple BLRM
Whitehead & Williamson (1998)

2-parameter logistic regression model

\[ p(d_i) \]

Dose level

 unsafe
 moderate
 safe

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Adaptive trial design for early phase trials
Specifying the prior

- Specify two dose levels (low and high)
- Elicit probability of toxicity at these levels from experts
- Determine how many patients this information is worth
- Adjust to start escalation at lowest dose
- Include “pseudo-patients” in analysis based on above

Note: This corresponds to using a beta-prior on $p(d)$. 
Inference

- Treat pseudo-patients as real patients
- Find parameter estimates for logistic model
- Any software that can fit logistic models can be used
Dose escalation and stopping

- **Next dose:**
  - current estimated target toxicity level
  - Usually subject to some additional safety rule

- **Stop**
  - When maximum number of patients has been recruited
  - When the ratio of credibility interval limits is small enough
• Easy to elicit priors from experts
• Any software that can fit a logistic model can be used
• Useful to allow higher TD_{\vartheta^*} during trial when seeking TD_{\vartheta^j}
• Not possible to use more complex rules for dose selection without MCMC
3+3 design as discussed in Lecture 1

Simple BLRM
- Cohort size 1
- Operational prior worth 6 patients
- Accuracy stop if ratio of CI < 4

True probability of toxicity at each dose level

\[
\begin{array}{cccccc}
\pi_1 & \pi_2 & \pi_3 & \pi_4 & \pi_5 & \pi_6 \\
0.05 & 0.10 & 0.20 & 0.30 & 0.50 & 0.70 \\
\end{array}
\]
A comparison

simple BLRM

- no toxicity
- toxicity

Patient

Dose level

0 5 10 15 20 25 30
1 2 3 4 5 6

3+3

Patient

Dose level

0 5 10 15 20 25 30
1 2 3 4 5 6

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