Coherence in early phase dose-finding studies

Ken Cheung
Dept of Biostatistics
Columbia University

March 2007 ENAR
Agenda

• Motivation
  – Phase I cancer trials
  – The conventional method ("3+3")
  – Literature: review & critique

• Coherence
  – Example: Coherent designs
  – Application I: Coherent two-stage CRM
  – Application II: Combined phase I/II trial (if time)
  – Discussion & resources
Phase I cancer trials

- **Primary objective:**
  - Evaluation of clinical safety

- **Dose-finding:**
  - Maximum tolerated dose (MTD) with respect to dose-limiting toxicity (DLT)
  - A presumed optimal dose

- **Complicated issues:**
  - Trade-off between safety and efficacy
A conventional method

- Specify a set of dose levels for the trial
- Start at the lowest dose level:

<table>
<thead>
<tr>
<th>#DLT / #Patients</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/3</td>
<td>Escalate dose</td>
</tr>
<tr>
<td>1/3</td>
<td>Add 3 patients at same level</td>
</tr>
<tr>
<td>1/6</td>
<td>Escalate dose / Called MTD</td>
</tr>
<tr>
<td>$\geq 2/3$ or $\geq 2/6$</td>
<td>De-escalate</td>
</tr>
</tbody>
</table>

- MTD = Max dose with fewer than 2/6 DLTs
A conventional method

• Disadvantages
  1. Quantitative objective is unclear
  2. The operating characteristics arbitrarily depend on the underlying dose-toxicity curve
Phase I Methods: Literature

- Proposals
  - Up-and-down designs (Storer, 1989)
  - Continual reassessment method (O’Quigley et al, 1990)
  - Biased coin design (Durham et al, 1997)
  - EWOC (Babb et al, 1998)
  - Curve-free method (Gasparini and Eisele, 2000)
  - ...

- MTD = a dose that causes DLT with probability $p$
- Operating characteristics validated by simulation
Phase I Methods: Critique

• Critiques
  – Is the “conventional wisdom” respected?
    • De-escalate or stay put if toxicity is observed
    • Escalate or stay put if no toxicity is observed

• Consequence: Pathological behaviors of the methods
A pathological outcome sequence

Each point represents a patient. A circle (o) indicates no toxicity, and a cross (x) indicates toxicity.
Motivation

• Consequence:
  – Deter clinicians from using the more complicated, outcome-adaptive method, which is supposed to be better but now looks dubious

• Prophylaxis:
  – Study whether a design respects the conventional wisdom – coherence
Coherence Principles
Escalations

• An escalation for the next patient is said to be *incoherent* if the most recent patient experiences some toxic side-effects

• A design is said to be coherent in escalation if

$$\Pr(U_i > 0 \mid Y_{i-1} = 1) = 0 \text{ for all } i \text{ (a.s.)}$$

where $U_j$ is dose level increment from patient $j-1$ to patient $j$, and $Y_j$ is the toxicity indicator of patient $j$. 
De-escalations

- A de-escalation for the next patient is said to be *incoherent* if the most recent patient shows no sign of toxicity.

- A design is said to be coherent in de-escalation if
  \[
  \Pr(U_i < 0 \mid Y_{i-1} = 0) = 0 \text{ for all } i \text{ (a.s.)}
  \]
  where \( U_j \) is dose level increment from patient \( j-1 \) to patient \( j \), and \( Y_j \) is the toxicity indicator of patient \( j \).
Incoherent escalation, Pt 11

Each point represents a patient
A circle (o) indicates no toxicity, and a cross (x) toxicity
Coherent designs

- Algorithm-based designs
  - Coherence by construction
  - Up-and-down (Storer, 1989)
  - Biased coin design (Durham et al., 1997)

- Model-based designs
  - Coherence is not obvious, but can be proved
  - CRM (O’Quigley et al., 1990)
One-stage CRM is coherent

• Define the MTD: a dose that causes DLT with probability p
• Assume a dose-toxicity model
  \[ F(d, \beta) = \text{Prob}(\text{DLT at dose } d) \]
• Treat patient at prior MTD.
• Estimate \( \beta \) based on binary toxic outcomes from first \( n \) patients. Denote estimator by \( b_n \).
• Select dose level \( d^* \) for patient \( (n+1) \) such that
  \[ d^* = \arg \min_k |F(d_k, b_n) - p| \]
Initial design

• Practical considerations
  – “Conservative” initial dose assignments
  – No information about dose-toxicity curve until toxicity is seen (especially, likelihood CRM)

• Initial design $D_0$
  – A predetermined monotone sequence of dose levels
    $\{x_{10}, x_{20}, \ldots, x_{n0}\}$ such that $x_{i0} \geq x_{i-1,0}$
  – E.g., Groups-of-three:
    $x_{10} = x_{20} = x_{30} = 1, x_{40} = x_{50} = x_{60} = 2, \ldots$
Two-stage CRM: definition

• Let $D_1(H_i)$ be the design point for patient $i$ by the one-stage CRM, where $H_i$ is the information available upon entry of patient $i$.

• Let $D^*(H_i)$ denote the design point for patient $i$ by a two-stage CRM. Then

\[
D^*(H_i) = \begin{cases} 
  x_{i0} & \text{if } Y_j = 0 \text{ for all } j < i, \\
  D_1(H_i) & \text{if } Y_j = 1 \text{ for some } j < i.
\end{cases}
\]
Two-stage CRM: example

- A one-stage CRM is coherent; a two-stage CRM may not be coherent in escalation.
- Consider the following two-stage CRM:
  - \( F(d_k, \beta) = d_k^\beta \) with \( d = (0.05, 0.10, 0.15, 0.25, 0.35, 0.45) \)
  - \( \log(\beta) \) is normal with mean 0 and variance 1.34
  - Initial design: groups of three
  - Target: \( p = 0.25 \)
Incoherent escalation, Pt 11

Each point represents a patient
A circle (o) indicates no toxicity, and a cross (x) toxicity
Two-stage CRM: example

• Problem:
  – Nontoxic group size before an escalation is too large: too conservative for $p = 0.25$
  – Influence estimation at higher doses via parametric extrapolation

• Let’s fix it:
  – Decrease group size in the initial design, e.g. groups of two
Coherent two-stage CRM

Each point represents a patient
A circle (o) indicates no toxicity, and a cross (x) toxicity
Two-stage CRM: coherence

- Let $M_0 = \min\{i: Y_i = 1\}$
- **Theorem 1 – Condition of coherence**
  If $D^*(H_{M_0+1}) \leq D^*(H_{M_0})$ almost surely, then the (unrestricted) two-stage CRM $D^*$ is coherent.
- In words, **coherence at the transition of stages implies coherence.**
- Computational advantage: Examine $N-1$ sequences instead of $2^{N-1}$ sequences
Two-stage CRM: coherence

• How about enforcing coherence by restriction? – No escalation for next patient if current patient experiences toxicity
  – Goodman et al. (1995)
  – Faries (1994)

• Consider the previous CRM model with
  – Initial design: Groups of three
  – $p = 0.25$
  – **Enforce coherence by restriction**
What is the problem?

Each point represents a patient
A circle (o) indicates no toxicity, and a cross (x) toxicity
Two-stage CRM: compatibility

• Incompatibility:
  – Patient 12 receives dose level 5.
  – If patient 10 did not experience toxicity, patient 12 would have received dose level 4 according to the initial design.
Two-stage CRM: compatibility

• Initial design should represent the fastest escalation scheme that takes place when there is no toxicity ⇒

• Definition: An initial design \( \{x_{i0}\} \) is said to be compatible with the CRM component \( D_1 \) in an unrestricted two-stage CRM \( D^* \) with respect to \( p \) if \( D^*(H_i) \leq x_{i0} \) for all \( i \) with probability one.
Two-stage CRM: compatibility

• *Theorem 2*: With some mild conditions on $F$, if an unrestricted two-stage CRM is coherent in escalation, then its initial design is compatible with its CRM component.
Two-stage CRM: discussion

• Enforce coherence by restriction:
  – Does not enforce compatibility
  – Gives no insight to the choice of initial design

• Enforce coherence by applying Theorem 1
  – Enforce also compatibility
  – Calibrate initial design with respect to $p$
  – Choose $p$ with respect to an initial design
Application II:

Combined phase I/II trial
Combined phase I/II Trials

• Bivariate binomial outcomes
  – $T = \text{indication of Toxicity}$
  – $R = \text{indication of Response}$

• Monotone dose-toxicity and dose-response
  – $P(T = 1 \mid \text{dose} = x)$ increases in $x$
  – $P(R = 1 \mid \text{dose} = x)$ increases in $x$
Combined phase I/II Trials

• Use coherence structure to guide dose assignments:
  – Stuck when (T,R) = (1,0)?
  – Stay or stop

<table>
<thead>
<tr>
<th>T</th>
<th>R</th>
<th>Escalation</th>
<th>De-escalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>Ok</td>
<td>X/X</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>Ok</td>
<td>X</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>X</td>
<td>Ok</td>
</tr>
</tbody>
</table>
Summary & resources

- **Motivation:** Study coherence, whose ethical implication is immediately observed in dose-finding studies.


- **Software:** An R function “cohere” in the “titecrm” library at CRAN