Shaping the Future of Drug Development

Dose Escalation with East®

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Before joining Cytel, Pantelis Vlachos was a Principal Biostatistician at Merck Serono, and taught statistics at Carnegie Mellon for 12 years.

His research focus is adaptive designs, mainly from a Bayesian perspective, as well as hierarchical model testing and checking, although his personal passion is Text Mining.

Pantelis is the Managing Editor of the journal “Bayesian Analysis” and on editorial boards of several other journals and online archives.
Agenda

• Quick Intro into the new functionality of East® 6.3
• Introduction of the methods considered in East® ESCALATE
• Demo of East® ESCALATE
• Q&A
Where are we today?

- *East®* on the *Architect™* platform is backed up by 20 years of R&D
- Its algorithms have been thoroughly battle-tested
- It is the *industry standard* for designing adequate and well-controlled clinical trials
What is special about the new East?

• Broad coverage of designs for biostatisticians
• One integrated tool for all types of designs: fixed sample, group sequential or adaptive
• Superior User Interface
  – Multiple windows with graphs and tables
  – Organized storage of designs in workbooks
• Rapid creation, viewing and filtering of multiple scenarios for design parameters
• Commitment to continuous improvement and expansion of features
New Statistical Capabilities
Module: *East® EXACT*

Phase I

Phase II

Phase III

Enrollment prediction
Conditional simulation
Predicted intervals plots
Module: *East® PREDICT*

- **Phase I**
- **Phase II**
- **Phase III**

- Simon’s two-stage designs
- Enrollment prediction
- Conditional simulation
- Predicted intervals plots

*East® PREDICT*
Module: East® ESCALATE

Phase I
- Dose escalation designs

Phase II
- Simon’s two-stage designs

Phase III
- Enrollment prediction
- Conditional simulation
- Predicted intervals plots
East® ESCALATE

• Dose Escalations Designs
  – 3+3
  – Modified Toxicity Probability Interval (mTPI)
  – Continual Reassessment Method (CRM)
  – Bayesian Logistic Regression Model (BLRM)

Two modes
1. Simulation
2. Interim Monitoring
Phase I dose-finding (general frame)

Only consider trials with fixed doses.

- A sequence of $D$ doses as candidates.
- Dose $i$ has a toxicity probability of $p_i$ (unknown).
- Monotonicity: $p_i < p_{i+1}$
- **Goal**: to find the MTD, defined as the highest dose with toxicity rate lower (or close to) a fixed rate, $p_T$, e.g., $p_T = 0.30$.

- Default practical rules:
  - Do not skip when escalation: $i \rightarrow (i + 1)$
  - Early stopping if dose 1 is toxic.
The 3+3 design

• Rule based design
• Start by allocating lowest dose level to first cohort
• Adaptively Escalate/De-escalate based on observed DLTs
• Repeat until MTD obtained or trial is stopped for excessive toxicity
• Two different versions: $3+3^L$ and $3+3^H$
The 3+3 design (schematic)

Step 1: treat 3 patients at dose i

0 DLT
- Escalate to dose i+1, Repeat Step 1

1 DLT
- Enroll 3 more patients at dose i
  - >2 DLT in 6 patients
    - If (i = 1), stop the trial;
    - If (i > 1), De-escalate to dose i-1
  - 3+3^H
    - Escalate to dose i+1, Repeat Step 1
  - 3+3^L
    - Stop the trial; Dose i is the MTD

>1 DLT
- 3+3^L
  - 6 patients treated at i-1
    - Stop the study
  - 3 patients treated at i-1
    - Enroll 3 more patients at i-1, Repeat Step 1

Yuan Ji,
KOL Lecture Oct. 2013
Sample output (3+3)

<table>
<thead>
<tr>
<th>Dose ID</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
<th>D5</th>
<th>D6</th>
<th>D7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>25</td>
<td>40</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>Percentage</td>
<td>4.8</td>
<td>20</td>
<td>33</td>
<td>24.5</td>
<td>10.2</td>
<td>4.4</td>
<td>0.7</td>
</tr>
</tbody>
</table>
The mTPI design

Yuan Ji,
KOL Lecture Oct. 2013
The mTPI design in a nutshell

• Bayesian like CRM, BLRM
• Rule-based like 3+3
• Independent Betas assumed for the probability of toxicity at each dose
• Set of decision intervals specified
• Subsequent dosing decisions determined by computing the normalized posterior probability in each interval at the current dose.
The mTPI design (cont)

• Start at dose 1.
• At any time, suppose dose \( i \) is used.
  
  Escalate to \((i + 1)\) if dose \( i \) is safe \((p_i << p_T)\)
  Stay at \( i \) if \( p_i \) is close to \( p_T \)
  De-escalate to \((i - 1)\) if dose \( i \) is toxic \((p_i >> p_T)\)
• Must not Escalate/De-escalate to \((i \pm k)\) for \( k \geq 2 \)
Interval rules

• How do we capture $p_i$ is safe, close to $p_T$, or toxic?
• Divide (0; 1) into three intervals:
  - $(0; p_T - e_1)$
  - $(p_T - e_1; p_T + e_2)$
  - $(p_T + e_2, 1)$

  Equivalence Interval

E  S  D

• Measure the unit probability mass (UPM) of each interval under the posterior of $p_i$.
• Decide the action corresponding to the largest UPM
UPM

UPM (interval) = \textit{post. prob (interval)} / \textit{length (interval)}
Sample output (mTPI)

Dose-wise Summary

<table>
<thead>
<tr>
<th>Dose ID</th>
<th>Dose</th>
<th>True Prob. of Toxicity</th>
<th>No. of Simulations Tried</th>
<th>Averages given the Dose was Tried</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Allocations</td>
</tr>
<tr>
<td>D1</td>
<td>5</td>
<td>0.05</td>
<td>1000</td>
<td>4.323</td>
</tr>
<tr>
<td>D2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dose Limiting Toxicity - mTPI

- Average Number of Subjects
- Dose: 5, 10, 15, 25, 40, 50, 60
- Allocated and Responded
The Continual Reassessment Method (CRM)

• Bayesian model-based method
• Uses all available information from doses to guide dose assignment
• To be specified:
  – Target toxicity (usually at 33%)
  – A single-parameter dose-toxicity curve
  – Prior distribution for curve parameter
• Next recommended dose is the one with posterior toxicity probability close to the target
The CRM: The process

• Dose-toxicity curves:
  – Logistic  \[ p(d) = \frac{\exp(p(c + d\mu))}{1 + \exp(p(c + d\mu))} \]
  – Power  \[ p(d) = p^\mu \]
  – Hyperbolic tangent  \[ p(d) = \left( \frac{\tanh d + 1}{2} \right)^\mu \]

• Prior distribution on \( \theta \)
• Prior mean toxicity probabilities at each dose level
The CRM: The process

1. Patient cohorts treated at each dose level
2. Toxicity outcome observed
3. Using Bayes theorem, prior distribution and observed outcomes are used to calculate the posterior mean of the probability of toxicity at each dose level, $\hat{p}_i$
4. Next cohort of patients assigned to dose level that has its $\hat{p}_i$ closest to target toxicity
5. Repeat 1-4 until termination criteria met
Sample output (CRM)

Dose-wise Estimates:

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>5</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.064</td>
<td>0.002</td>
<td>0.046</td>
</tr>
<tr>
<td>D2</td>
<td>10</td>
<td>0.1</td>
<td>0.1</td>
<td>0.4</td>
<td>0.444</td>
<td>0.002</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Model Fit - CRM

![Graph showing dose-response relationship](image)
The Bayesian Logistic Regression Model (BLRM)

- More advanced version of the CRM
- Two-parameter logistic dose-toxicity curve assumed
- In addition to target toxicity, a set of decision intervals are specified:

<table>
<thead>
<tr>
<th>Toxicity Intervals</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>Losses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under dosing</td>
<td>0.000</td>
<td>0.200</td>
<td>1</td>
</tr>
<tr>
<td>Targeted toxicity</td>
<td>0.200</td>
<td>0.350</td>
<td>0</td>
</tr>
<tr>
<td>Excessive toxicity</td>
<td>0.350</td>
<td>0.600</td>
<td>1</td>
</tr>
<tr>
<td>Unacceptable toxicity</td>
<td>0.600</td>
<td>1.000</td>
<td>2</td>
</tr>
</tbody>
</table>
The Bayesian Logistic Regression Model (BLRM)

• Based on these decision intervals dosing decisions are made by either:
  – specifying associated losses with each interval; as data accumulate next recommended dose is the one with lower Bayes risk, or by
  – imposing constraint on probability of overdosing; next recommended dose is the one that maximizes probability of targeted toxicity
The BLRM: Components

- Basic model: logistic regression
  - DLT rate $\rho$, Dose $d$

$$\log \frac{\rho}{1 - \rho} = \log(\hat{\rho}) + \log(d)$$

- Bivariate normal prior distribution assumed for $(\log(\alpha), \log(\theta))$
Sample output (BLRM)

Posterior p(DLT) Quantiles for Simulation3 – BLRM

Posterior Probability that DLT Rate lies in each Toxicity Interval for Simulation10 – BLRM

Dose

Pr(Under dosing) Pr(Target) Pr(Excessive) Pr(Unacceptable)
References

**3+3**

**mTPI**

**CRM**

**BLRM**
Thank you!
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Connect with Pantelis on LinkedIn
Next: Q&A with Pantelis

Download slides
www.cytel.com/software-solutions/east

Replay available by end of this week

Conclusion survey
Thank you!

Connect with Pantelis on LinkedIn

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Backup slides
3+3 Design: Limitations

• Ignores dosage history other than previous cohort
  – 0/3, 0/3, 0/3, 0/3, 0/3, 2/6 provides more information than 0/3, 2/6

• Same action under qualitatively different situations
  – 0/3 and 1/6 lead to same action (escalate to the next provisional dose)
  – 2/3, 3/3, 2/6, 3/6, and 4/6 lead to same action (de-escalate to the last provisional dose)

• Cannot re-escalate

• Inflexible cohort sizes (either 3 or 6)
3+3 Design: Limitations

- **Low probability** of selecting true MTD (e.g. Thall and Lee. 2003)
- **High variability** in MTD estimates (Goodman *et al.* 1995)
- **Poor targeting** of MTD on study:
  - **Low MTD**: Can assign toxic doses to relatively large number of patients
  - **High MTD**: Tends to declare MTD at dose levels below the true MTD
  - Behavior depends on number of cohorts before MTD – too many leads to underdosing, too few leads to overdosing
Prior Elicitation?

• Based on information on \((\log(\alpha), \log(\beta))\)
  
  – \(\log(\alpha)\) is the log-odds of a DLT at reference dose \(d^*\)
    
    • Set \(d^*\) to the \textit{a priori} anticipated MTD
    
    • The mean of \(\log(\alpha)\) results from the targeted probability (e.g. 0.30) and only an additional quantile would be required to obtain the SD.
  
  – For two doses \(d_i\) and \(d_j\), \(\beta\) is the log-odds ratio of a DLT, i.e.,
    
    \[
    \logit(p(d_j)) - \logit(p(d_i)) = \log(d_j = d_i) 
    \]
Prior Elicitation?

- Based on elicitation of “observable quantities” and converting them to a prior on \((\log(\alpha),\log(\beta))\)
  - Ask for user to supply for the lowest dose \(d_1\) a guess for its prior probability of toxicity
  - Also ask the user to supply his/her estimate of the MTD \((d_{MTD})\)
  - Using the assumption that the doses are linear in log-odds scale we can calculate the best guess for the toxicity probability at all doses
  - Fit a Beta distribution at each dose level and the bivariate log-normal prior which matches the Beta at its quantiles

These steps are done by East in the background following paper by Huson and Kinnersley
Prior Elicitation (cont)

Design: Bayesian Logistic Regression Model

<table>
<thead>
<tr>
<th>Simulation Parameters</th>
<th>Response Generation</th>
<th>Simulation Control Info</th>
</tr>
</thead>
</table>

- **Max Sample Size:** 30
- **Cohort Size:** 3
- **Starting Dose:** Lowest Dose
- **Dose Selection Method:**
  - EWOC
  - Bayes Risk

<table>
<thead>
<tr>
<th>Toxicity Intervals</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under dosing</td>
<td>0</td>
<td>0.2</td>
</tr>
<tr>
<td>Targeted toxicity</td>
<td>0.2</td>
<td>0.35</td>
</tr>
<tr>
<td>Excessive toxicity</td>
<td>0.35</td>
<td>0.6</td>
</tr>
<tr>
<td>Unacceptable toxicity</td>
<td>0.6</td>
<td>1</td>
</tr>
</tbody>
</table>

- **Target Probability of Toxicity (P<sub>T</sub>):** 0.3
- **Distribution:** Bivariate Lognormal
- **Prior Specification:**
  - Specify prior on: Lowest dose & MTD
  - P(DLT) at D1: 0.05
  - Estimate of MTD: 25
  - # Beta Samples: 1000

- **Prob. (Overdosing) <=:** 0.25
- **Reference Dose (d*):** 25

Simulate
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