An Escalation With Overdose Control for bivariate binary outcomes (bEWOC) in early oncology clinical trials

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Contents

- Early phase oncology trials: from cytotoxic toward Molecular Targeted Agents (MTA)
- Escalation with overdose control for bivariate outcomes
- Comparison with bCRM through a simulation study
**Objective**
- Evaluate safety and activity
- Aim MTD
- Escalate dose levels
- Recommend several dose for Phase II

**Constraints**
- Sequential designs
- Avoid overdosing
- Patient’s clinical benefit

**Binary data**
- Dose-Limiting Toxicity
- Activity
Several designs

- **Algorithmic designs**
  - « 3+3 » (« A+B »)
  - Accelerated Titration Design
  - Hunsberger

- **Model-based dose-response designs**
  - CRM: Continual Reassessment Method
  - Designs derived from the CRM: Escalation With Overdose Control (EWOC)
  - bCRM: CRM applied on two binary outcomes (safety and efficacy)

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\( ^c \) Hunsberger S., Statistics in Medicine 2005 - \( ^d \) O'Quigley J., Biometrics 1990
\( ^g \) Braun .T., Controlled Clinical Trials 2002
New drugs in development

- **Cytotoxic drugs**
  - Assumption: Monotonic Dose-Efficacy relationship
  - Dose level recommended: Maximum Tolerated Dose (MTD)
    - A dose with a probability of DLT closest to a target proportion

- **Molecularly Targeted Agents (MTA)**
  - Non-monotonic Dose-Efficacy relationship
  - Two endpoints: Toxicity and Efficacy (binary outcomes)

Cytotoxic profile

MTA profile
Contents

● Early phase oncology trials: from cytotoxic toward Molecular Targeted Agents (MTA)

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EWOC for bivariate outcome
Dose-response models

● Safety model

$$\text{logit}(P^{i \text{DLT}}) = \alpha_1 + \exp(\beta_1) \times \log(d_i / d_1^*)$$

Slope > 0 => Monotonic dose-toxicity relationship

● Activity model

$$\text{logit}(P^{i \text{Act}}) = \alpha_2 + \beta_2 \times \log(d_i / d_1^*) + \gamma_2 \times \log(d_i / d_2^*)^2$$

$P^{\text{DLT}}$ : Probability of DLT
$P^{\text{Act}}$ : Probability of Activity
$d_1^*$, $d_2^*$ : Reference doses

Non-monotonic dose-activity relationship
EWOC for bivariate outcome
Dose-response models

Activity model parameters

<table>
<thead>
<tr>
<th>Example</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha_2 )</td>
<td>-1</td>
<td>1.5</td>
<td>3.5</td>
</tr>
<tr>
<td>( \beta_2 )</td>
<td>3</td>
<td>2</td>
<td>3.5</td>
</tr>
<tr>
<td>( \gamma_2 )</td>
<td>0</td>
<td>-0.75</td>
<td>-2.2</td>
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</tbody>
</table>

![Graph showing dose-response models with three examples: Example 1, Example 2, and Example 3.](image)
EWOC for bivariate outcome
Dose-response models

Bayesian Inference

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Sd error</th>
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<tbody>
<tr>
<td>$\alpha_1$</td>
<td>-2</td>
<td>3</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>0,5</td>
<td>1,2</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>0</td>
<td>1,5</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>1,5</td>
<td>1</td>
</tr>
<tr>
<td>$\gamma_2$</td>
<td>0</td>
<td>0,5</td>
</tr>
</tbody>
</table>
EWOC for bivariate binary outcome

- **Binary endpoints**
  - DLT
  - Activity (Tumour Response)

- **Areas of interest:**
  - Over-Toxicity Area ($A_{OT}$)
  - Useless Area ($A_U$)
  - Moderate Area ($A_M$)
  - Target Area ($A_T$)
  - $T_1=0.35, T_2=0.25$ et $T_3=0.5$

- EWOC for bivariate binary outcome

  - $\text{IP}(\text{Act} \mid \text{di})=0.48$
  - $\text{IP}(\text{DLT} \mid \text{di})=0.18$
EWOC for bivariate outcome
Predictions for dose level escalation decision

<table>
<thead>
<tr>
<th>Doses</th>
<th>50</th>
<th>75</th>
<th>100</th>
<th>125</th>
<th>150</th>
<th>200</th>
<th>250</th>
<th>300</th>
<th>400</th>
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<tbody>
<tr>
<td>Patients</td>
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<td>3</td>
<td>9</td>
<td>6</td>
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<tr>
<td>DLT</td>
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<td>0</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Activity</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
</tbody>
</table>
EWOC for bivariate outcome
Predictions for dose level escalation decision
EWOC for bivariate outcome
Predictions for dose level escalation decision
Contents

● Early phase oncology trials: from cytotoxic toward Molecular Targeted Agents (MTA)

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● Comparison with bCRM through a simulation study
Comparison with bCRM

- bCRM looks for the non over-toxic dose which minimize the distance:

\[
d^n_{ij} = \sqrt{0.75(P^i_{DLT} - p^*_{DLT})^2 + 0.25(P^i_{Act} - p^*_{Act})^2}
\]

- bCRM is based on 2 logistics models

- Stopping rules
  - After 4 recommendations for the same dose
  - After 3 consecutive recommendations for the same dose
  - After 15 cohorts of patients
  - bEWOC: Trial stops when a safe dose level (twice administered) induces more than 50% of Activity
Simulation study - Scenario

Scenario 1

Scenario 2

Scenario 3
Dose-recommendation ratio
Simulation study (36 patients)

Scenario 1

Scenario 2

Scenario 3

bEWOx

bCRM
Dose-recommendation ratio – Overdose Control Simulation study (36 patients)

Scenario 2

<table>
<thead>
<tr>
<th>Dose</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>bEWOC</td>
<td>26,4%</td>
<td>30,4%</td>
<td>29,8%</td>
<td>11,4%</td>
<td>1,9%</td>
</tr>
<tr>
<td>bCRM</td>
<td>7,8%</td>
<td>30%</td>
<td>41,8%</td>
<td>16,8%</td>
<td>3,4%</td>
</tr>
</tbody>
</table>
Simulation study – Reasons for stopping

Over Toxicity

At least one good dose found

Max recommendations

Max Cons. Recommend.

Max cohorts
Conclusion

● **bEWOC characteristics**
  - Assess both Toxicity and Efficacy
  - Activity model more flexible for Molecularly Targeted Agents
  - Decision and communication tool (clinician team)

● **Comparison with bCRM**
  - Similar dose-escalations but different dose-recommendations
  - bEWOC better controls overdosing
  - bEWOC includes less patients
    (“At least one good dose” rule)
  - bEWOC is more conservative (Over Toxicity rule) and can lead to unnecessary stopping decision
Thank you for your attention