Introduction to CRM and Dose Finding

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Disclosures

The presenter has no commercial or financial interests, relationships, activities, or other conflicts of interest to disclose.
Outline

• Phase 1 Trials: Objectives and NeuSTART

• Continual Reassessment Method (CRM)

• Dose Finding with other endpoints
Phase 1 Trial

- **Objective:** Evaluate safety and tolerability of a new drug
  - A “first in humans” drug
  - An approved drug for new population/indication
  - When used in combination with other drugs

- **Objective:** Finding the maximum tolerated dose (MTD)
  - Determine a high & potentially efficacious dose with acceptable toxicity (RP2D); Nitrogen mustard (1940s)
  - Define an upper limit of dose for future investigation
Translational Research

In 2011, 5,408 medicines* were in clinical development worldwide.

*Defined as single products which are counted exactly once regardless of the number of indications pursued.

Because many of the 5,408 medicines in development are in trials for more than one indication, the total number of projects in development is close to 8,000.

Pharmaceutical Research Manufacturers of America. 2013 Biopharmaceutical Research Industry Profile
Phase 1 Trial

- **Endpoints:** Adverse event, Dose-limiting toxicity (DLT), Tolerability or feasibility, PK

- A DLT should include the specific type of adverse event over a specified observation schedule

- An example of “Hypothesis” statement: To determine the maximum dose of drug $X$ that causes a DLT with probability $p$ in patients with disease D
NeuSTART

- Neuroprotection with Statin Therapy for Acute Recovery Trial (Elkind et al., 2008, Int J Stroke)
- A phase 1 dose escalation study of high-dose lovastatin in acute ischemic stroke: Determine the highest dose of lovastatin that can be administered in AIS patients with <10% probability of myotoxicity or hepatotoxicity

- **DLT:**
  - ALT/AST/CK exceeding predefined thresholds on days 1, 2, 3, 5, 7, and 30
  - Clinical liver and muscle toxicity during 30d
NeuSTART

- **Maximum tolerated dose:** Allow 10% of DLT
- **Feasibility:** Completers (got at least 9 doses out of 12)
- **Dose escalation Method:** Two-stage Continual Reassessment Method (CRM)
- **Sample size:** Total \( N = 33 \)
NeuSTART

Table 2. Dose escalation plan in case of no dose-limiting toxicity (DLT)

<table>
<thead>
<tr>
<th>Phase 1B Cohort #</th>
<th>Cohort size (N)</th>
<th>Lovastatin Dose q6h for 72h</th>
<th>Dose days 3-30</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>1mg/kg/day</td>
<td>20 mg/day</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>3mg/kg/day</td>
<td>20 mg/day</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>6mg/kg/day</td>
<td>20 mg/day</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>6mg/kg/day</td>
<td>20 mg/day</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>8mg/kg/day</td>
<td>20 mg/day</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>8mg/kg/day</td>
<td>20 mg/day</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>8mg/kg/day</td>
<td>20 mg/day</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>10mg/kg/day</td>
<td>20 mg/day</td>
</tr>
<tr>
<td>9</td>
<td>3</td>
<td>10mg/kg/day</td>
<td>20 mg/day</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>10mg/kg/day</td>
<td>20 mg/day</td>
</tr>
<tr>
<td>11</td>
<td>3</td>
<td>10mg/kg/day</td>
<td>20 mg/day</td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The DSMC will meet and discuss continuation to the next cohort after every cohort of three patients. These dose levels apply before any dose-limiting toxicity (DLT) is observed. Dose (de-)escalation will be conducted according to the time-to-event CRM once a DLT is observed.

Experimental regimen: Acute high-dose lovastatin in acute ischemic stroke

Elkind et al. (2008) Int J Stroke
NeuSTART

CRM:

• Stage 1: Follow dose escalation plan in Table
• Once, a DLT is observed ➔ Stage 2:
  – Reassess the dose-toxicity model based on interim data
  – Treat the next patient at the model-based MTD; reassess the dose-toxicity model with new data
CRM: How it operates

• Model-based
• Require prior guesses
• Estimate dose-toxicity curve continually using accrued data
• Treat next patient(s) at estimated MTD
CRM: How it operates

- Model-based
- Require prior guesses
- Estimate dose-toxicity curve continually using accrued data
- Treat next patient(s) at estimated MTD: dose level 3
CRM: How it operates

- Model-based
- Require prior guesses
- Estimate dose-toxicity curve continually using accrued data
- Treat next patient(s) at estimated MTD: dose level 4
CRM: How it operates

- Model-based
- Require prior guesses
- Estimate dose-toxicity curve continually using accrued data
- Treat next patient(s) at estimated MTD: dose level 4
CRM: How it operates

- Model-based
- Require prior guesses
- Estimate dose-toxicity curve continually using accrued data
- Treat next patient(s) at estimated MTD: dose level 4
CRM: Clinical inputs

1. DLT: AE definition and observation period
2. Maximum DLT rate tolerated; e.g., 10%
3. Number of dose levels to be tested
4. Starting dose and/or starting dose escalation plan
5. Sample size: N
How to choose DLT rate

• Some useful questions to ask:
  – What is the convention? E.g., p = 0.20 to 0.25 for cancer chemotherapy
  – What is the safety endpoint? E.g., hypotension; elevated liver enzymes; etc.
  – “Is it acceptable if one in 10 patients experience hypotension?” , “How about one in 5?” , etc.
How to choose number of dose levels

• Doses should be sufficiently distinct
• Some useful questions to ask:
  – What is the largest dose? And the smallest dose?
  – Use PK to determine increment
  – Use convention to determine increment
  • Fixed dose increment (pills)
  • Exponential increment (vaccine; antibody)
  • Fibonacci – not particularly right or wrong
How to choose starting dose

- A “safe” choice: start with the lowest experimental dose (level 1)
  - Also ask about “fall back dose”, level 0
- CRM allows starting in the middle of the dose panel – if the dose is considered safe
How to choose N

• Preliminary sample size can be determined for an approximate accuracy ("power") at an effect size ("odds ratio")
  – For initial budgeting purposes
  – Odds ratio of toxicity rate of two adjacent doses
  – Accuracy = probability of correctly choosing the MTD

• Final planning: Use simulation to fine tune CRM model and sample size
Sample size calculation

```r
> library(dfcrm)
> theta = 0.1  # Target toxicity rate
> K = 4       # Number of dose levels to be tested
> psi = 2     # Effect size (slope of logistic dose-toxicity curve)
> acc = 0.6   # An accuracy index; to be explained later
> nobj = getn(acc, theta, K, psi)
> nobj

Target rate: 0.1
Number of dose levels: 4
Effect size (odds ratio): 2
Required accuracy: 0.6
Calculated sample size: 40

> 
```
Fine-tuning using simulation

<table>
<thead>
<tr>
<th>N = 40</th>
<th>Probability selecting MTD when the true MTD is dose**</th>
<th>Ave</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Four dose-toxicity scenarios</td>
<td>.81</td>
<td>.43</td>
</tr>
</tbody>
</table>

**Under an odds ratio of 2.0
CRM: Why

- **Higher efficiency**
- Target rate: **10%**
- Toxicity odds increases **2.5** times per dose level
- Logistic regression was used to estimate the MTD at trial’s end

Cheung and Kaufmann (2011, *Stroke*)
## CRM: Why

<table>
<thead>
<tr>
<th>Design characteristics</th>
<th>CRM</th>
<th>Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Probability of correctly selecting the MTD&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.54</td>
<td>0.47</td>
</tr>
<tr>
<td>(b) Probability of selecting an overdose&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.17</td>
<td>0.26</td>
</tr>
<tr>
<td>(c) Average number of subjects treated at</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>(d) Average number of subjects treated at an overdose</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>(e) Median of toxicity odds ratio estimate&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.2</td>
<td>2.6</td>
</tr>
</tbody>
</table>
Other considerations

- Hybrid decision: model recommendation and DSMC

- Secondary outcomes are important, and are sometimes more important than DLT for next clinical phase: Feasibility, PK, pilot efficacy

- Use these other endpoints for dose escalation
Example: Phase 1/2 Trial

• Thrombolytic agent for acute stroke
• Trinary outcome (efficacy-toxicity)
  – Intracranial hemorrhage (Toxicity; $Y=2$)
  – Reperfusion without hemorrhage (Response; $Y=1$)
  – Neither ($Y=0$)
• Objective: Find dose with highest desirability, which increases with response rate and decreases with toxicity rate
Example: Phase 1/2 Trial

5 dose levels
Size of dot indicates desirability

Thall and Cook (2004, Biometrics)
Example: Phase 1/2 Trial

- CRM-like design
- Model-based:
  (A) Dose-toxicity relationship
  (B) Dose-response relationship
  (C) Correlation between toxicity and response
    - Estimate (A), (B), (C) continually using accrued data
    - Treat next patient(s) at dose with highest desirability based on most recent update
- Modeling is complicated, relies on simulation, and requires more upfront work
Example: CMD

- Congenital muscular dystrophies (CMD) are genetically heterogeneous neuromuscular disorders
- No pharmacological treatments available
- Phase 1 dose finding trial of omigapil in LAMA2 and COL6-related CMD
- Previously evaluated in adults pts with Parkinson’s disease and ALS; volunteers for PK
- Objective of CALLISTO:
  - Find a dose with PK activity and safety in pediatrics and adolescents
Example: CMD

Specific PK target:

- AUC (0 – 24h), averaged at first 2 post-baseline visits

**PK activity:** Find a dose with AUC > 3 ng h/ml

- Safety (Maximum tolerated dose, MTD): A dose that exceeds 33 ng h/ml with 10% probability or less
Example: CMD

Specific PK target:

• AUC (0 – 24h), averaged at first 2 post-baseline visits

• **PK activity:** Find a dose with AUC > 3 ng h/ml

• **Safety** (Maximum tolerated dose, **MTD**): A dose that exceeds 33 ng h/ml with 10% probability or less
Example: CMD

- Leach et al. (2017) Neuromuscular disorders
- N = 16-20 enrolled in cohorts of 4 in a dose escalation manner
- Pre-selected doses: 0.02, 0.08 and 0.2 mg/kg
- Start at 0.02 mg/kg. Use Continual Reassessment Method (CRM) for subsequent dose assignment
- Hybrid decision process: Investigators convened to discuss dosing and DSMB convened to approve
- Switch from CRM to SAVOR, a new class of dose escalation method that allows dose interpolation
SAVOR: 0.04 or 0.05 mg/kg
Hybrid decision: 0.04 mg/kg

Post hoc model-based estimate

Exceed 33 ng·h/ml
On target [3, 33] ng/ml
SAVOR: 0.05 or 0.06 mg/kg
Hybrid decision: 0.06 mg/kg

Post hoc model-based estimate

n = 12
SAVOR: 0.05 mg/kg
Hybrid decision: 0.06 mg/kg

Average AUC (log scale)

Dose (mg/kg)

Exceed 33 ng*h/ml
On target [3, 33] h*ng/ml

Post hoc model-based estimate

Probability

Dose (mg/kg)
SAVOR: 0.06 or 0.07 mg/kg
Final MTD: 0.06 mg/kg

Post hoc model-based estimate

- Exceed 33 ng*h/ml
- On target [3, 33] ng/h*ml

n = 20

SAVOR: 0.06 or 0.07 mg/kg
Final MTD: 0.06 mg/kg
Stochastic approximation with virtual observations for dose-finding on discrete levels

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- **Stochastic Approximation with Virtual Observation Recursion**
- Second-generation adaptive dose finding that allows dose addition/deletion, and improves efficiency by using continuous (e.g., PK) data instead of dichotomized data (in CRM)
Discussion

• Early phase dose finding trials are critical to the eventual success of drug development. Worst case scenario: wrong dose of the right drug treated at phase 3
• Adaptive designs such as the CRM and SAVOR can improve the accuracy of dose finding, and enhance how patients are dosed during a trial
• Require \textit{prospective} planning
• With new class of targeted therapies, interests in orphan drugs, and rare diseases, dose finding with non-DLT endpoint may be used