Trial Designs for the Development of Treatment Parameters

SHARON D. YEATTS, PH.D.
ASSISTANT PROFESSOR OF BIOSTATISTICS
DATA COORDINATION UNIT
DEPARTMENT OF PUBLIC HEALTH SCIENCES
MEDICAL UNIVERSITY OF SOUTH CAROLINA
Disclosures

• None
Clinical Development

- Phase I - “Dose Finding”
  - Pharmacokinetics
  - Safety, feasibility

- Phase II - “Safety and Efficacy”
  - Safety, feasibility
  - Therapeutic activity
  - Informal comparisons

- Phase III - “Confirmatory”
  - Safety
  - Definitive evidence of efficacy
  - Formal comparisons designed to maintain acceptable statistical operating characteristics
Dose-Finding Objectives

- To establish an optimal biological dose to move to Phase II studies

- May involve
  - Estimation of pharmacokinetic parameters
  - Assessment of tolerability and feasibility
  - Quantification of the toxicity profile
Dose-Response Curve

- No-effect range
- Range of increasing effect with increasing dose
- Maximum effect range

Total Exposure
Defining the Optimal Dose

- Maximum Tolerated Dose (MTD): the highest dose without unacceptable toxicity
- Minimum Effective Dose (MED): the lowest dose with clinically significant efficacy
Idealized Phase I Design:

- Treat dose-finding like a Phase III clinical trial with randomization, etc.
## Dose-Finding Designs

<table>
<thead>
<tr>
<th>Rule-based</th>
<th>Model-based</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Outcome: occurrence of target event (DLT)</td>
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</tr>
<tr>
<td>• Dose levels pre-specified</td>
<td>• Pre-specifying dose levels not necessary</td>
</tr>
<tr>
<td>• Stopping rule pre-specified</td>
<td>• Stopping rule pre-specified</td>
</tr>
<tr>
<td>• (De-)escalation rules pre-specified</td>
<td>• (De-)escalation determined by estimation of the dose-toxicity curve</td>
</tr>
<tr>
<td>• Targets a 33% DLT probability</td>
<td>• Can target a pre-specified DLT probability in its search for the MTD</td>
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</table>
Traditional 3 + 3 (escalation and de-escalation):

- 3 subjects receive dose $k$
  - >1 DLT?
    - De-escalate to dose $k-1$
      - 6 subjects treated at dose $k-1$? (Yes)
        - Stop the study
      - No
        - 3 more subjects receive dose $k-1$
  - 1 DLT?
    - >1 DLT in 6 subjects?
      - No DLT?
    - No DLT?
  - Escalate to next higher dose $k+1$
Clinical Perspective:
## Rule-based Designs

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple to implement</td>
<td>Pre-specified dose levels</td>
</tr>
<tr>
<td>Small sample size</td>
<td>Patients treated well below therapeutic range</td>
</tr>
<tr>
<td>Familiar</td>
<td>MTD too conservative</td>
</tr>
<tr>
<td>Do not require special software</td>
<td>Takes a long time for the MTD to be reached</td>
</tr>
<tr>
<td></td>
<td>Decision rules do not use all available data</td>
</tr>
<tr>
<td></td>
<td>Estimate of the optimal dose is biased and variable</td>
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</tbody>
</table>
### Clinical Perspective
- Concentrate dosing around the MTD
- Minimize the number of patients treated at subtherapeutic levels
- Obtain information re: inter-patient variability and cumulative toxicity

### Statistical Perspective
- High probability of terminating at/near the true MTD
- Low probability of stopping before the true MTD
- Small probability of escalating beyond the MTD
Continual Reassessment Method (CRM)

- First cohort is treated at the MTD identified based on a hypothesized dose-toxicity curve.
- After each outcome (absence/presence of a DLT) is known: the curve is re-estimated, and the MTD identified, using all of the available data.
- The next cohort is treated at the current estimate of the MTD.
  - Process repeated until stopping rule reached.
    - Target sample size treated at MTD
    - Convergence/precision achieved
    - Maximum sample size reached
  - After the planned N subjects have been treated, the MTD is considered to be the dose of the N+1st subject.
Variations

- **Modifications to the CRM**
  - Treat a small cohort of subjects at each dose
  - Restrict escalation process so that doses do not increase too quickly
    - Choose low starting dose selected using conventional criteria
    - Incremental increases in dose until a DLT has been observed
    - Do not allow skipping over untried doses

- **CRM with Expansion Cohort**: enroll additional (6-15) subjects to be treated at the final MTD
CRM Simulated Trial
## Continual Reassessment Method

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<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>• Clinical judgment and statistical rigor</td>
<td>• Comparatively complex – statistical software and statistical input required</td>
</tr>
<tr>
<td>• Statistical model uses cumulative information from all patients</td>
<td>• Potential to expose patients to high (and thus toxic) doses.</td>
</tr>
<tr>
<td>• Estimates MTD from a continuous spectrum of doses</td>
<td></td>
</tr>
<tr>
<td>• Unbiased estimation</td>
<td></td>
</tr>
<tr>
<td>• Reaches MTD sooner</td>
<td></td>
</tr>
<tr>
<td>• Requires only a starting dose</td>
<td></td>
</tr>
<tr>
<td>• Does not depend strongly on the starting dose</td>
<td></td>
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</tbody>
</table>
Variations

- Escalation with Overdose Control (EWOC): constrains the predicted proportion of patients who receive an overdose
- Time-to-Event CRM (TITE-CRM): extends the CRM for late-onset effects
- Ordinal CRM: extends the CRM to allow for ordinal toxicity ratings
Defining the Optimal Dose

- Non-toxic, Non-efficacious Dose
- Non-toxic, Efficacious Dose
- Toxic Dose

MED → Non-toxic, Efficacious Dose → MTD

Therapeutic Window
Finding Effective Doses

- Use CRM to target Minimum Effective Dose, rather than Maximum Tolerated Dose

- Trichotomous outcome (Tri-CRM)
  - No toxicity, no efficacy
  - No toxicity, efficacy
  - Toxicity

- Joint modeling of bivariate outcome (bivariate CRM)
Phase II Objectives

- **Safety**
  - Estimate the frequency of side effects (tolerability)

- **Efficacy**
  - Identify drugs/doses with potential efficacy
  - Quickly discard drugs/doses without promise

- **Feasibility**
  - Compliance
  - Route of administration
  - Delivery
  - Cost
  - Recruitment
Selection Designs

- **Goal:** Select the “best” among $K$ interventions (or $K$ interventions and a control) to move forward
- **Sample size** determined to ensure that, if the “best” treatment is superior by at least $D$, then it will be selected with high probability
  - the probability of correct selection may be less than desired if the difference is less than $D$
  - Estimation of the difference between two treatments?
  - Evidence that the “best” treatment is worth moving forward?
- **Sequential Selection Designs**
  - Selection + Superiority
  - Selection + Futility
A two-stage design for a phase II clinical trial of coenzyme Q10 in ALS (Levy et al, 2006)

Figure. Two-stage phase II design of the Clinical Trial of High Dose Coenzyme Q10 in ALS (QALS study; total: 185 patients, 105 in stage 1 and 80 in stage 2).
Early Two-Stage Design with Adaptive Randomization

- There may **not** be strong rationale to assume that the MTD is the optimal one
  - Interventions with low toxicity
  - Dose-toxicity and dose-efficacy relationships are not monotonically increasing
- More relevant to use efficacy-driven dose finding designs with safety boundaries
  - Binary toxicity information (yes/no DLT)
  - Continuous efficacy outcomes
  - Modeled independently
Two-Stage Design with Adaptive Randomization

- **Goals:**
  - Identify the optimal dose to maximize efficacy while maintaining safety
  - Higher allocation to more therapeutic doses and lower percentage of untreated patients
  - Easy to understand and implement (frequentist approach, standard software)
  - Flexible to accommodate a variety of continuous efficacy outcomes (fold-change, absolute count, etc.)

- **Two-stage design:**
  - **Stage 1:** establish safety profile of prespecified doses and collect efficacy outcomes
  - **Stage 2:** adaptively randomize subjects to safe doses with emphasis towards those with higher efficacy
Two-Stage Design with Adaptive Randomization Application to an Immunotherapy Cancer Trial

- Adoptive T-cell transfer for patients with metastatic melanoma
- Immunologic (efficacy) outcome: T-cell percent persistence at 15/30 days compared to baseline
  - Percent persistence is a prognostic factor of clinical outcome (complete & partial response in solid tumors)

Findings
- More patients treated at doses with higher efficacy
- Improvement in efficacy estimation
- Design can accommodate any cohort size
Exploratory phases take time...

- Adaptive designs may take even more
  - Statistical effort in the planning phase

- ... but the time spent can provide valuable information
  - Optimal dosing
  - Safety assessment
  - Preliminary evidence of efficacy
  - Logistics (blinding, randomization, outcomes assessment)