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Clinical Trial Designs

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Outline

- Overview of drug development
- Key Elements of Study Designs
- Exploratory studies
- Adequate and Well-Controlled Studies
- Some Regulatory Guidance
Traditional paradigm
Drug Research & Development
Emerging Trend for Drug R&D

Search for promising COMPOUND

Search for promising DRUG

Search for promising Statistical Analysis PLAN

Target discovery and validation

PoC clinical trials

Clinical development

Exploratory Stage

Confirmatory Stage

Target

Proof-of-Concept

Efficacy

Approval

Market
Key Elements of Study Design (1)

- What question(s) does the study want to address?
- What is the experimental unit?
- What measures clinical benefit and/or risk?
- What dose regimens to study?
Key Elements of Study Design (2)

- Does the study have a comparator?
- If so, are there available (approved) therapies?
- Is the study design ethically sound?
  - For patients in the study
  - For future patients to be studied
- Are there important prognostic factors of disease?
Key Elements of Study Design (3)

• How large is the number of experimental units needed?
• Will the experimental treatment be evaluated sequentially or concurrently?
• Will the design elements be fixed or may change?
• What constitutes a successful trial?
  • Trials in early phase or early stage
  • Trials that are adequate and well-controlled (A&WC)
Aims in Early Phase or Early Stage

- Understand tolerability of a compound
- Is there drug activity?
- Is there dose response?
- Research mode - Plenty of flexibility
- Little interest to commit large resources yet – generally small sample size
- Not unusual to see PI-initiated phase I trial
Types of Exploratory Studies

- Dose escalation
  - Placebo-controlled?
  - Single vs. multiple doses

- Dose-Response
  - Dose-Ranging
  - Exposure-response

Target dose(s) estimation
Dose Regimen of Interest

Phase I – primary interest is **Tolerability**
- Maximum Tolerated Dose (MTD)

Phase II – primary interests: **POC, Dose Selection**
- Minimum Effective Dose (MED)
- Maximum Safe Dose (MSD)
- Maximum Utility Dose (MUD) based on current info
- Minimally acceptable dose (MAD): the lowest dose that has a utility of at least, say, 70%
Box 1  A standard "3 + 3" dose escalation design starting at dose k. The maximum tolerated dose (MTD) is usually defined as the highest dose at which 0 or 1 dose-limiting toxicities (DLTs) are observed in six patients (although some "3 + 3" rules call the highest dose with two or fewer dose-limiting toxicities in six patients the MTD). If de-escalation occurs at the first dose level, then the study is discontinued.
Continual Reassessment Method

Define DLT, e.g., any grade 3 or higher toxicity occurred in 1st 4-wks on study

TITE CRM*

Define DLT, e.g., any grade 3 or higher toxicity occurred in three months or longer of the patients being on study

Allow staggered entry ➔ shorten study duration

MTD, e.g., dose level achieved a DLT closest to λ%

*Braun (2005 SIM)
### Point est. vs. Interval est.

<table>
<thead>
<tr>
<th>DLTs per patient treated at a dose level</th>
<th>Toxicity Point Estimate</th>
<th>Exact 95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 of 3</td>
<td>0%</td>
<td>0-71%</td>
</tr>
<tr>
<td>0 of 6</td>
<td>0%</td>
<td>0-46%</td>
</tr>
<tr>
<td>1 of 6</td>
<td>16.7%</td>
<td>0.4-64%</td>
</tr>
<tr>
<td>2 of 6</td>
<td>33.3%</td>
<td>4.3-77.7%</td>
</tr>
</tbody>
</table>

Wide interval estimates based on 3 and 6 patients. When 2 of 6 patients have DLT, the MTD may have been exceeded, but there is a very good chance that it has not. With the 3+3 design, the summary data may be too sparse to be reliable.
Continual Reassessment Method
Often PI-Initiated in oncology

22 patients studied at 4 dose levels (30-45 mg/m2), JCO 2004

27 patients studied at 5 dose levels (4 mg/m2 to 20 mg/m2/wk)
JCO 2004

Phase I Trial of Preoperative Doxorubicin-Based Concurrent Chemoradiation and Surgical Resection for Localized Extremity and Body Wall Soft Tissue Sarcomas

37 patients (from 2 centers) studied at 14 dose levels (10 to 6400ng/kg) EJC 2006

Using the continual reassessment method: Lessons Learned from an EORTC phase I dose finding study
CRM and its Modifications

- Objective: Estimate MTD
- Sequential Design
- Bayesian or Maximum Likelihood
- Assume Dose Response Curve
- Data Source for Dose Response Curve
- Assumptions for Dose Response Model
- Start Dose
- Target Dose Estimation based on % DLT
Phase 1 Trial  CRM Method

Patient population: Androgen Independent Prostate Cancer

Proposed Dose Levels  30, 35, 40, 45

DLT: any toxicity resulted in a delay of ≥ 1wk in Docetaxel or Gleevec or resulted in a dose-reduction during combo

Estimated MTD – Dose that achieved a DLT closet to 30%

<table>
<thead>
<tr>
<th>Cohort No.</th>
<th>Dose Level (mg/m²)</th>
<th>First-Cycle DLTs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Proportion</td>
</tr>
<tr>
<td>1</td>
<td>30</td>
<td>0/6</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>3/4</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>5/6</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>3/6</td>
</tr>
</tbody>
</table>

Abbreviation: DLT, dose-limiting toxicity.

JCO 22:3323-3329, 2004
To determine MTD

In principle, the probability of DLT should depend on the context of the disease and the treatment, the toxicity rates that are seen in alternative therapies available to the patient (if any) and the balancing of the relationship between potential toxicities and potential benefit of the treatment. In some trials, a 20% DLT rate may be too high, while in others it may be too low.
Early Assessment of Drug Activity

Dose ranging, dose response studies
What is an appropriate dose range?
Will there be dose-response?

*Plenty of learning and exploration*

Might add higher dose(s) or lower dose(s)

Preliminary assessment of drug activity

Internal decision making for further development

Fixed, Adaptive vs Model-based Design
Study Designs

- Balanced Design
- Adaptive Frequentist
- Optimal Design
- Adaptive Bayesian
POC and Dose-Response

♦ POC: Is there evidence of dose-response?
   Any evidence of treatment effect?

♦ How well dose-response curve is estimated?

♦ Dose-Finding: Which dose to bring to next stage or next phase of the drug development?

♦ ICH E-4: the purpose of dose-response information is to find the smallest dose with a discernible useful effect
Figure 4.1. Dose-response profiles used in simulation.
Utility Function – an example
Figure 2  Objectives of the trial.
When is adaptive design useful compared to optimal design under Bayesian framework?

- If differences b/t possible dose-effect scenarios are large (in relation to variability of data in interim analysis), there is gain from adaptive dosing.

- If scenarios similar enough or variability large, decisions based on interim data could lead into wrong direction – especially if assumed dose-range is the relatively uninformative part, given true DR unknown.

Miller et al, 2007
The purpose of dose-response information is to find the smallest dose with a discernible useful effect

(ICH E-4)
Early Phase or Stage of Drug Development

♦ Uncertainty about drug activity

♦ Should be an exploratory or learning mode of investigation

♦ Trade-off between false negative vs. false positive vs. estimation problem

♦ Prerequisites before launching a confirmatory trial
Early stage in Drug Development

*Dose-ranging; Dose-response; Exposure-response; promising dose profile*

have plenty of flexibility for learning & for quantifying many early uncertainties

AIM: hope to maximize probability of correct selection for future planning
Dealing with Learning (i)

Combine Learn and Formalizes Learn in Exploratory Trials - Hypothesis generation

- Global $H_0$
- Learn
- Change $H_0$
- Selection
- Final Analysis
- Wide Flexibility
- Estimation & Quantify Uncertainty

Patient pop’n? Corr (Early, late endpoints)? Dose range? Dose regimen(s)? Effect size? etc.
Dealing with Learning (ii)

(ii) Formalize learning to plan confirmatory trial

Use of point estimate of effect size from ph II to plan ph III can be valuable in prediction of useful doses.

But, may be too optimistic on effect size to detect at usual $\alpha$-level and $1-\beta$ level

→ possibly regression toward mean

“Learn Trial” versus “Confirm Trial”

Clinical questions to be addressed in *early stage trials for decision making* are naturally different from *late stage trials for rigorous inference*

*Caveats:*
if pursued as one-trial for inference, learning data is a part of inference data that are subject to multiplicity correction (can be very heavy)
if pursued as learn vs. confirm, adaptive elements can be built-in within learn trial versus within confirm trial, but, separately
Learn and Confirm Within Trial of Most Enthusiastic Interest

Statistical theory has shown that learn and confirm within the same study yield liberal type I error rate and overestimate performance characteristics if multiplicity adjustment is not formally accounted for, e.g., commonly used internal cross-validation of model built using the same or a part of the data e.g., in gene expression or whole genome screening or gene association studies, rigorous confirmation of the prediction accuracy should be performed in an independent dataset

Multiplicity issue and regression to the mean issue
Adaptive Design

- **Prospectively planned opportunity** for modification of one or more specified aspects of the **study design and hypotheses** based on analysis of data (usually interim data) from subjects in the study.

- Analysis of the accumulating study data are performed at **prospectively planned time-points** within the study.

- **Analyses** can be performed in a **fully blinded** manner or in an **unblinded** manner, and can occur with or without formal statistical hypothesis testing.
Clinical Trial Designs and Objectives

- Randomized Controlled Trials
- Crossover trials
- Randomized withdrawal trials
- Enrichment strategy
- Group sequential trials
- Superiority
- Non-inferiority
Concepts & Terminology

• **Design**: Conventional vs. Adaptive
• **Adaptation**: Prospective Plan vs Reactive Changes
• **Adaptations**: Unblinded vs Blinded non-comparative
• **Interim Analysis**: beyond ICH E9
• **Bias**: Statistical vs Operational
• **Study**: Exploratory vs A&WC (can have expl element)
  • Ph I, II, III, confirmatory, seamless ph 2/3 – not used
• **Group Sequential Trial & Beyond**: Firewalls Adaptive Monitoring Process/Procedure/Documentation
Some Design Considerations

◆ When large amount of data collection is not feasible in early phase studies
◆ When large amount of data collection is routinely practiced in late phase studies
◆ Accurate modeling relies on large amount of data
◆ Desired to pursue modeling in early phases because of little data
Design with Little vs More

- Philosophy 1
  - Mine the data and what do the data tell?
  - Many slices of the data, then, give the clinical question and simultaneously the answer.
  - What the new compound/drug behaves in the trial, not what the design should be to answer if the new compound/drug is useful

- Philosophy 2
  - What is the clinical question or objective?
  - Choice of study design to address the Qs.
Learn/preliminary confirm for Decision

- Correct go/no-go decision is critical
- To improve the probability of correct selection based on early phase exploration relies upon
  - Being able to make no-go decision
  - Being able to also make go decision
- Patient population starts narrow
  - cannot anticipate degree of heterogeneity, effect size(s)
- Dose groups start a few (or more) in exploratory trials
  - If still in a narrow patient population, even if picked promising dose, uncertainty in phase III with broad patient population – M&S for planning A&WC
Adequate & Well-Controlled (A&WC) 21CFR314.126

- Not exploratory adaptive design clinical trial
- In addition to experimentwise type I error rate control
- Should possess the following characteristics
  - clear statement of the objectives, proposed and actual methods of analysis in protocol, SAP, and reports
  - design that permits a valid comparative evidence of T-effect
  - methods of adequate assurance of patient selection
  - patient assignments that minimize bias, group comparability
  - minimize bias on all parties: pts, investigator, data analyst
  - endpoints well-defined that address clinical primary hypo.
  - analysis results - interpretability of the effects of drug
Scientific Principles

- For a trial that is exploratory in nature – statistical validity may not necessarily be controlling the statistical error of making a wrong statement of at least one possible clinical conjecture
- Not intended as primary basis for efficacy evaluation
- A stage to better quantify uncertainty and parameter estimates as such the study is well designed to learn, explore or address plausible effect sizes, dose regimens, patient populations, primary efficacy endpoints, etc.
- If active controlled, explore useful study objectives
Scientific Principles

- For a trial that is adequate and well-controlled (A&WC) or otherwise known as confirmatory trial
- First principle: statistically valid (ICH E-9)
- Design induced bias vs operationally induced bias due to trial conduct
- Study results are interpretable