Design of Dose Response Clinical Trials

BASS XIII
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Drug Development Process

- Drug Discovery
- Non-clinical Development
- Clinical Development
  - Phase I Clinical pharmacology (PK/PD, MTD)
  - Phase II Drug efficacy/safety, dose ranging
  - Phase III Long-term, large scale, confirmatory
  - Phase IV Post-market
FIGURE 1  A THEORETICAL DOSE–RESPONSE CURVE
Phase I Studies (Drugs developed for non-life-threatening diseases)

- Healthy normal volunteers
- Single dose
- Double-blind, placebo controlled, randomized, dose escalation
- Clinical pharmacology – PK/PD, MTD
- Cross-over studies (BA, BE)
- Answer the question – how often should we dose the patient?
Phase II Studies (Non-life-threatening diseases)

- Patients with the disease under study
- Dose ranging, efficacy dose response
- Double-blind, placebo controlled, randomized, fixed doses
- Clinical efficacy and safety endpoints
- Exploratory, estimation of efficacy, dose,…
- Answer the question – how much should we dose the patient?
FIGURE 1.1  INDIVIDUAL AND AVERAGE DOSE–RESPONSE CURVES
FIGURE 3 OBSERVATIONS FROM A SIMULATED DOSE RESPONSE STUDY
Phase III, IV Studies

- Phase III studies are for registration purposes
- Confirmatory, hypothesis testing
- Study for target dose(s)
- Phase IV studies are for larger scale safety surveillance, or new indication
- Change of labeled dose post market is possible
Concerns in Developing Drugs for Life-Threatening Diseases

- May not be ethical to use placebo control
- May not be ethical to recruit normal healthy volunteers
- Open label, single arm, dose titration study designs
Challenges in dose selection

- Every stage of drug development - from drug discovery to post market
- What is the right range of doses
- Individual dose response curves vs population curve
- Exposure-response vs dose-response
- Other challenges (choice of primary endpoint, multiple comparison, …)
WHAT ARE THE ISSUES IN DOSE FINDING?

- Individual versus global responses
- What are you looking for?
- What range of doses should we consider?
- How many doses to be tested?
- What are we measuring?
- The differences in exploration and confirmation
FIGURE 2  DOSE–RESPONSE FOR EFFICACY AND TOXICITY
INDIVIDUAL VERSUS GLOBAL RESPONSES

- In most of drugs, we need to recommend a few fixed doses
- For wide Therapeutic Index (TI), it is possible to use one dose
- Dose response relationship vs concentration response relationship
PHARMACOKINETICS (PK), PHARMACODYNAMICS (PD)

- PK, PD, PK/PD
  - PK: body act on drug
  - PD: drug act on body
- Concentration response uses PK, but should we consider PD?
WHAT ARE YOU LOOKING FOR

- A single dose or a range of doses
- Fixed dose or titration doses
- As needed or chronic treatment
- How many doses a day
DRUG LABEL (Package Insert)

- Summary Information of the Drug
- Agreed with Regulatory Agencies
- Target Product Profile
- Competitors on Market
- Easy for Physicians to prescribe
Forward: Accumulating information

Backward: Planning Based on Label

Pre-clinical  Phase I  Phase II  Phase III  Drug Label
DETERMINING DOSING FREQUENCY

- When determining dosing frequency, the pharmacodynamics of a compound should be considered as critical as the pharmacokinetics.
- In contrast to the pharmacokinetic half-life, the pharmacodynamic half-life will be dose dependent.
- Will a control release formulation be needed?
DETERMINING DOSING FREQUENCY

QD Feasible if high levels are well tolerated, otherwise will need to default to BID dosing or change shape of curve with CR.

- Q day dosing at 2x dose
- Bid Dosing at 1x dose
- Minimal effective level by PD marker
WHAT RANGE OF DOSES SHOULD WE CONSIDER

- In early Phase II, not much information available (pre-clinical, PK, MTD)
- We know 0 (Placebo), we know MTD
- Exploring an Adequate Dose Range
- Selecting Doses for Early Dose-ranging Studies
STUDY 1 - WHAT’S NEXT?

![Bar chart showing the comparison of different dosage levels: Placebo, 20 mg, 30 mg, and 40 mg.](chart.png)
STUDY 2

![Bar chart showing Placebo, 5 mg, 10 mg, and 20 mg comparisons]
FIGURE 4  SEVERAL POSSIBLE DOSE—RESPONSE CURVES
WHAT RANGE OF DOSES SHOULD WE CONSIDER

- Examine a wide dose range in early development and follow this study with a narrower dose range study.
- Use pharmacological response or biological markers from animal studies and phase I studies to guide the selection in dose range for the early studies.
- Although not always attainable in early studies, a goal should be to try and define the Maximally Tolerated Dose (MTD), the Maximally Effective Dose (MaxED), and the Minimum Effective Dose (MinED).
IS THERE A DOSE RESPONSE?

![Bar chart showing dose response]

- Low
- Medium
- High

Series 1
IMPORTANCE OF PLACEBO RESPONSE

![Bar Chart]

- Placebo
- Low
- Medium
- High

Series 1
ACTIVE CONTROL

![Bar Chart]

- Placebo
- Low
- Medium
- High
- Active

Bars represent Series 1.
ACTIVE CONTROL

![Bar graph showing the comparison of different conditions (Placebo, Low, Medium, High, Active) with Series 1.](image-url)
Active control is not strictly necessary

It serves as a useful control in case the test drug “doesn’t work” or works poorly

Active control “worked” or not?

An active comparator may also be critical if there is an effective competitor on the market

How appropriate are Phase II comparisons?

Statistically valid vs “looks similar”? 
HOW MANY DOSES TO BE TESTED

- Can we set all possible doses to test
- Do we include control groups
- If so, which controls
- Spacing between doses
LIMITED NUMBER OF FIXED DOSES

- Multiple center designs
- Formulation considerations
- Placebo and maximally tolerable dose (MTD)
- Incorporate active control?
- Concerns in interpreting titration dose
## TREATMENT BY CENTER INTERACTION

<table>
<thead>
<tr>
<th>Center</th>
<th>Placebo</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Center 1</td>
<td>6</td>
<td>7</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Center 2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Center 3</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>
DOES THE DRUG WORK?

- Test hypothesis - does the drug work?
- Null hypothesis \((H_0)\) - no difference between test drug and placebo
- Alternative hypothesis \((H_a)\) - there is a difference
## TYPES OF ERRORS

<table>
<thead>
<tr>
<th></th>
<th>Null True</th>
<th>Null False</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accept Null</td>
<td>OK</td>
<td>II</td>
</tr>
<tr>
<td>Reject Null</td>
<td>I</td>
<td>OK</td>
</tr>
</tbody>
</table>

If there is no true difference, but concluded there is => Type I error
If there is a difference, but concluded there isn’t => Type II error
TYPES OF ERRORS

- Regulatory agencies focus on the control of Type I error
- Probability of making a Type I error is not greater than $\alpha$
- In general, $\alpha = 0.05$; i.e., 1 in 20
- Avoid inflation of this error
- Change method of analysis to fit data will inflate $\alpha$
MULTIPLE COMPARISONS

- For 20 independent variables (clinical endpoints), one significant at random
- For 20 independent treatment comparisons, one significant at random
- For 20 small studies, one sig. At random
- Multiple comparison adjustment
MULTIPLE COMPARISONS

- Consider a dose response study with high and low dose against placebo
- 2 comparisons each dose vs placebo
- Bonferroni is to divide $\alpha$ by 2
- Step-down
- Special contrasts
- Fisher protected LSD
MULTIPLE COMPARISONS

- Other types of multiple comparisons
  - compare test drug with placebo and active control
- Multiple endpoints
- Subset analysis
- Various statistical methods available to handle these situations
INTERIM ANALYSIS

- Final analysis: LPV -> closed database -> break blind -> final analysis
- Any analysis before final is interim
- Objectives
  - claim efficacy
  - stop for no efficacy (for safety, ...)
  - help decision making for other studies
  - other
Randomized Double-Blind study to control for bias

Multiple look at data will inflate $\alpha$

Statistical penalty

- inflation of $\alpha$ -> need adjustment
- enough efficacy data to help decision?
CONTROL OF TYPE I ERROR

- Experiment-wise Type I error is controlled by specifying primary endpoint, primary comparison, primary time point for the primary study population
- Keep analysis method as stated in the protocol
- If interim analysis is needed, we should pre-specify, and plan for it
WHAT ARE WE MEASURING

- PD marker, clinical endpoint (hard, soft) or safety
- Efficacy can’t be observed from normal volunteer
- Early Phase or late phase
- Time after baseline (short, long)
- Multiple endpoints
Efficacy vs Dose

- Low dose: Efficacy 30
- Medium dose: Efficacy 20
- High dose: Efficacy 10
EXPLORATION AND CONFIRMATION

- Phase I, II, III clinical trials
- Exploratory – estimation
- Confirmatory – hypothesis testing
- Learning process
EXPLORATION AND CONFIRMATION

- Design considerations for exploratory and confirmatory are different
- Analysis method depending on objective
- For labeling, may consider the entire database to select doses