

PHASE I/II CLINICAL TRIAL  
DESIGN AND DOSE  
FINDING (PART I)  
(CHAPTER 1, 7)

NAITEE TING, BOEHRINGER-INGELHEIM

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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

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PHASE I CLINICAL TRIALS - NON  
LIFE-THREATENING DISEASES

Healthy normal volunteers

Primarily for PK properties

Help recommend dosing frequency

Estimate maximally tolerated dose (MTD)

Dose escalation design or crossover designs are popular in Phase I

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### 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 escalation study designs

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### DOSE-FINDING IN ONCOLOGY

Cancer patients in Phase I  
Not ethical for placebo control  
Dose limiting toxicity (DLT)  
 $P[\text{toxicity at MTD}] = \Gamma$   
Where  $\Gamma$  is the target probability of toxicity

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### DOSE-FINDING IN ONCOLOGY TRADITIONAL 3+3 DESIGN

The most widely used design in oncology  
Subjects are assigned in groups of 3  
If only 3 subjects on the current dose, then

- no toxicity -> 3 on next higher dose
- one toxicity -> add 3 on the same dose
- two or more toxicity -> MTD is exceeded

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## DOSE-FINDING IN ONCOLOGY TRADITIONAL 3+3 DESIGN

If 6 patients on the same dose, then:

- If at most one toxicity -> 3 on next higher dose
- If two or more toxicities -> MTD exceeded

The estimated MTD is the highest dose level with observed toxicity rate less than 0.33.

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## PHASE II CLINICAL TRIALS

First Phase II is Proof of Concept (PoC)

Followed by dose-ranging trials

Objective is to propose dose(s) for Phase III design

Moving doses down to MinED

If dose-range is not found in Phase II, it will be too expensive in later Phases

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## PROOF OF CONCEPT (POC) STUDY

➤ Typically two treatment groups

➤ Parallel design

➤ Placebo controlled

➤ Use a dose at MTD or close to MTD

➤ Short term, clinical efficacy endpoint (surrogate markers may be used at times)

➤ Moderate sample size

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### SAMPLE SIZE FOR A POC DESIGN

People come to statistician asking for sample size  
This is the opportunity for a statistician to contribute to the study design  
Assuming  $\delta$  is positive  
Assuming variance = 1  
N is calculated given  $\alpha$  and  $\beta$

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### PROOF OF CONCEPT

Hypothesis testing  
Primary endpoint is clinical efficacy  
Pre-specified two-sided alpha could be  $\geq 0.05$   
Power may be greater than 80%  
Go/No Go decision

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### PROPOSE A TOOL TO HELP WITH COMMUNICATIONS

A communication tool is proposed to help the team members in understanding the risks  
Discussions should happen before breaking blind  
After the design is finalized  
Clear Go/No Go criteria can be documented

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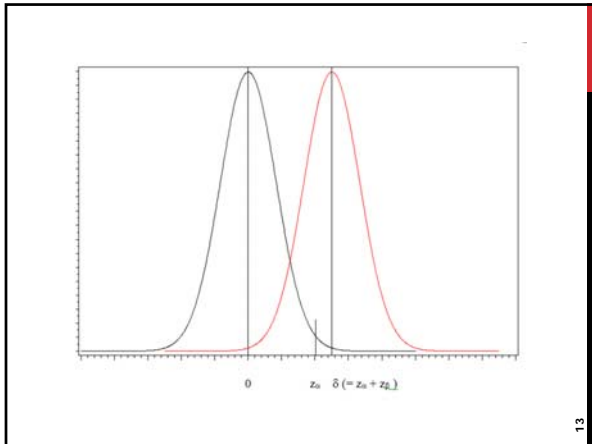
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### STATISTICAL HYPOTHESIS

$H_0: \mu_T \leq \mu_P$  vs  $H_1: \mu_T > \mu_P$   
 is tested at Type I error  $\alpha$

The distance between  $z_\alpha$  and  $\delta$  reflect the absolute value of  $z_\beta$   
 Hence  $\delta = z_\alpha + z_\beta$

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### DECISION PROCESS

- If  $\hat{\delta} > z_\alpha + z_{\beta/}$ , then a "Go" decision is made, because the study results meet both statistical significance, and clinically meaningful improvement. Under this situation, the potential Type I error is much smaller than  $\alpha$ ;
- If  $z_\alpha < \hat{\delta} < z_\alpha + z_{\beta/}$ , then a "Go" decision is made, then the Type I error is controlled under  $\alpha$ , however, the clinically meaningful

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### DECISION PROCESS

- If  $z_{\alpha} < \hat{\delta} < z_{\alpha} + z_{\beta}$ , but a "No Go" decision is made, then the Type II error is inflated;
- If  $0 < \hat{\delta} < z_{\alpha}$ , then a "No Go" decision is made, then there is no inflation of Type II error;
- If  $0 < \hat{\delta} < z_{\alpha}$ , but the team inclined to make a "Go" decision, knowing that Type I error is inflated, this is the case where clear communications of risks are necessary.

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### DOSE RANGING STUDY

- Parallel dose groups
- Placebo controlled
- Duration of treatment limited by animal tox coverage
- Many doses of test drug
- Objective is to explore a range of efficacious doses

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### MINIMUM EFFECTIVE DOSE (MINED)

Imagine the difficulty in a PoC study  
It was MTD in PoC  
From a dose ranging design, there are multiple test doses  
When each dose is compared with placebo, there is a PoC discussion  
Which dose is efficacious? And the minimal dose?

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**WHAT IS DOSE RANGE?**

Suppose study A is designed with placebo, 20 mg, 40 mg, and 80 mg

Study B with placebo, 0.1 mg, 1 mg, and 10 mg

Which design has a wider range?

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**WHAT IS DOSE RANGE?**

Dose range for a given study is defined as the high dose divided by the low dose in the design

Design A has a dose range of 4

Design B has a dose range of 100

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**CONCERNS IN DOSE RANGING STUDIES**

- Number of doses to be tested
- Need an active control?
- Dose spacing
- Choice of endpoints
- Length of study

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### WHY POC AND DOSE RANGING SEPARATE?

- Not sure if test drug works
- Formulation (dose strength) limitations
- Extrapolation from PD endpoints to clinical efficacy endpoints
- Investment/cost
- Possible ethical concerns

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### IMPACT OF POC DECISIONS

- Drug formulation
- Ordering large quantity of raw materials?
- Long term toxicity studies?
- Clear Go/No Go decision very critical
- Avoid inconclusiveness

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### RISKS OF INCONCLUSIVENESS

- Clinical trial process: design -> conduct -> unblind -> results ?? Decision ??
- To go? Or not to go? is the question
- This decision has to be made
- Delay in this decision impact formulation, order of raw materials, and tox studies
- Inconclusiveness happens between study results and decision

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## RISKS OF INCONCLUSIVENESS

After results are ready, there is very little a statistician can do

The critical time for statisticians to help the team is at the design stage

Clearly communicate the Type I and II risks

Define Go/No Go criteria

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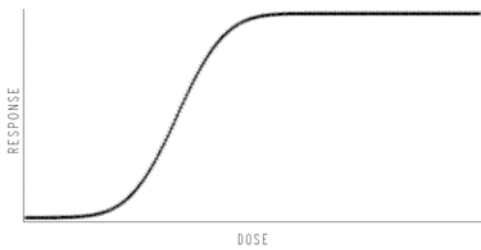
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FIGURE 1 A THEORETICAL DOSE-RESPONSE CURVE



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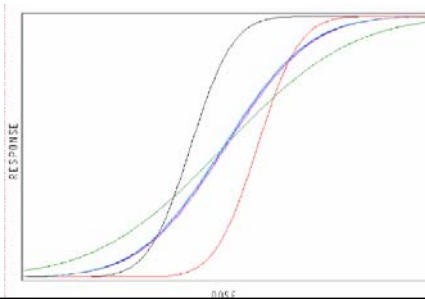
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## INDIVIDUAL DOSE RESPONSE AND POPULATION DOSE RESPONSE



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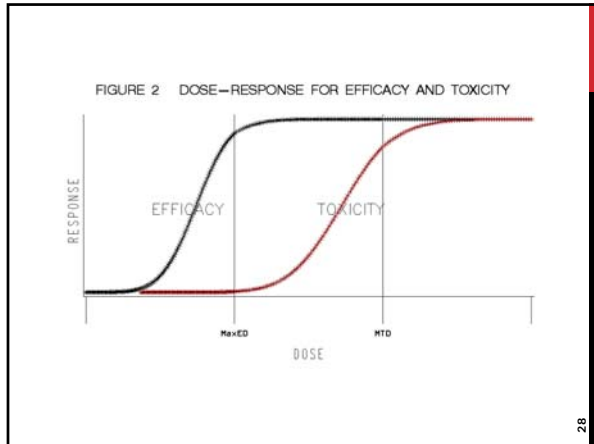
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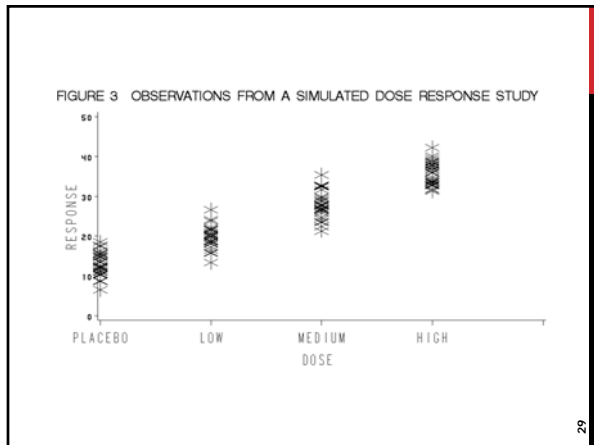
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**DRUG LABEL (PACKAGE INSERT)**

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

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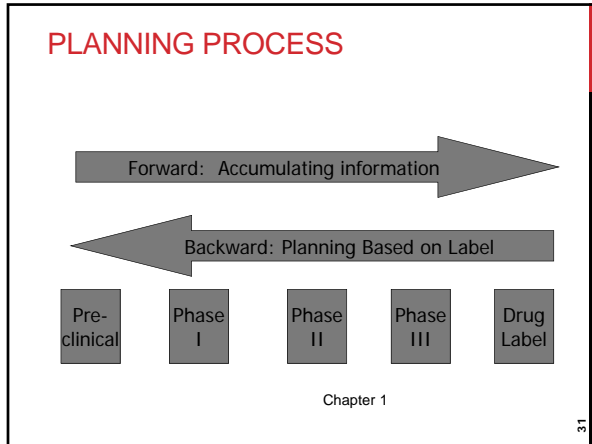
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### WHAT ARE THE ISSUES IN DOSE FINDING?

- 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

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### 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

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### 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?**

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### 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?

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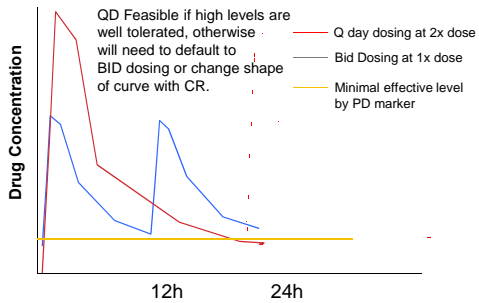
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### DETERMINING DOSING FREQUENCY



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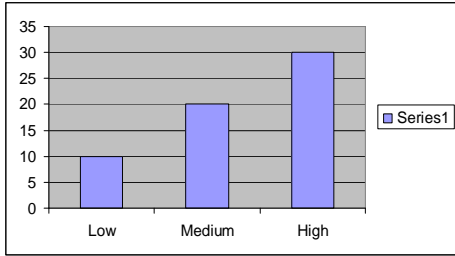
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### IS THERE A DOSE RESPONSE?



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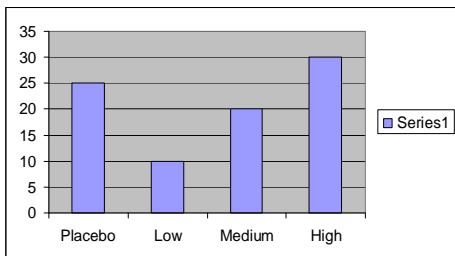
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### IMPORTANCE OF PLACEBO RESPONSE



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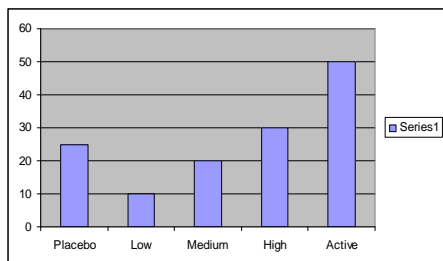
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### ACTIVE CONTROL



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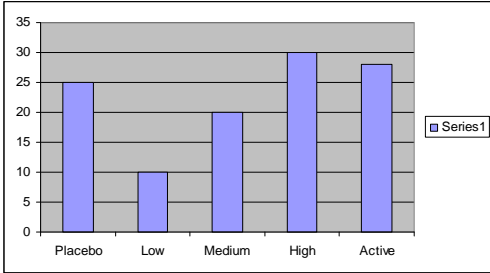
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### ACTIVE CONTROL



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### ACTIVE CONTROL

- 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”?

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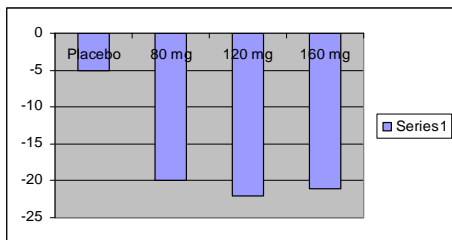
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### DRUG A STUDY 1 - WHAT'S NEXT?



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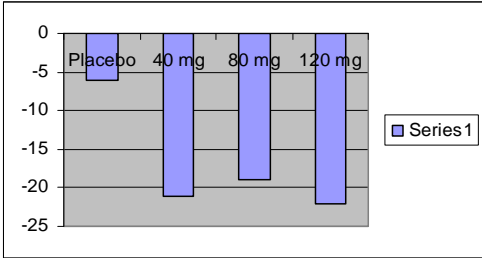
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### DRUG A STUDY 2 - WHAT'S NEXT?



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### DRUG A

After study 2, the Phase III study started with dose 120 mg  
At end of Phase II meeting, FDA questioned about dose  
We designed the third dose finding study to look at doses 2.5 mg, 10 mg and 40 mg

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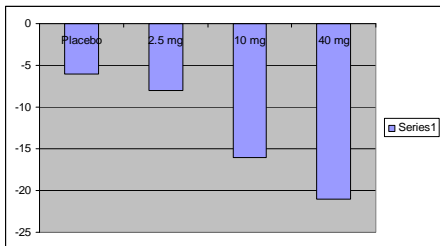
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### DRUG A - STUDY 3



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### DRUG A

Redesigned Phase III studies with 20 mg and 40 mg  
It took 3 studies to find the efficacy dose response  
The large scale study with 120 mg cannot be used for registration  
Filing was delayed by many years

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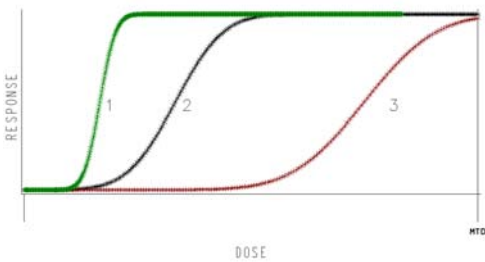
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FIGURE 4 SEVERAL POSSIBLE DOSE-RESPONSE CURVES



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### MULTIPLE-ARM DOSE-RESPONSE TRIAL

Monotonic dose-response relationship is very common in practice.  
Two groups are not sufficient to characterize the nonlinear nature of dose-response.  
Multiple-arm trial is specially informative for drug with a wide therapeutic window.

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### 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

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### 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)

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### 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

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### LIMITED NUMBER OF FIXED DOSES

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

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### TREATMENT BY CENTER INTERACTION

	Placebo	Low	Medium	High
Center 1	6	7	6	8
Center 2	1	1	0	1
Center 3	4	2	3	2

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### LIMITED NUMBER OF FIXED DOSES

- Too few doses may not cover a wide range
- Can we study all possible doses?
- Under fixed total sample size, too many doses left very few subjects per dose
- Based on intensive simulation, it is recommended to use 4 to 5 doses, plus placebo

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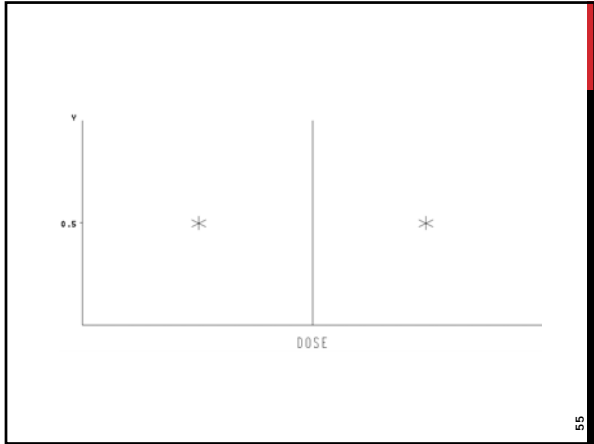
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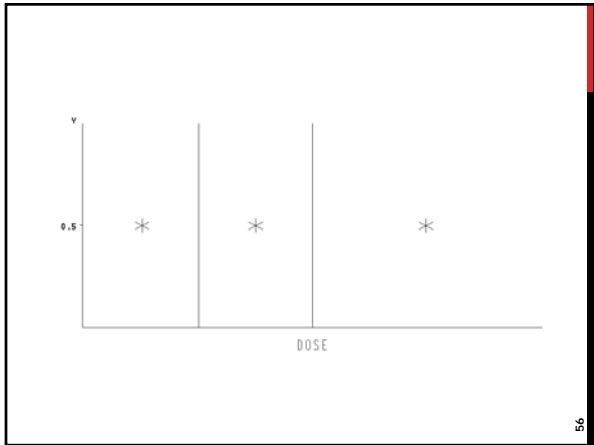
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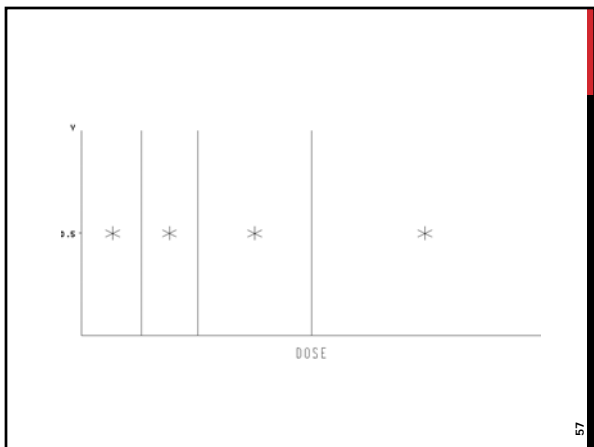
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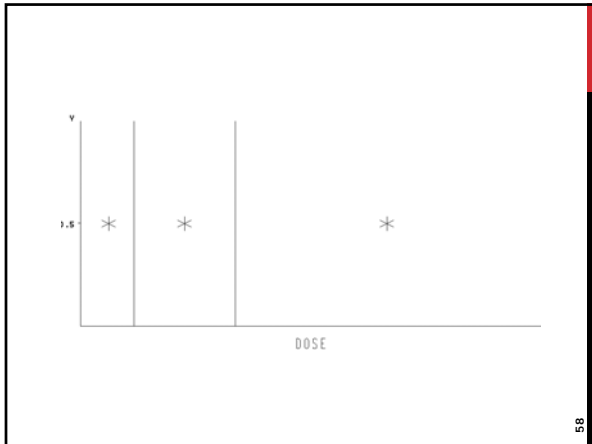
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**BINARY DOSE SPACING**

- For 2 test doses, one above 1/2, one below
- Continue with this fashion to the lower end
- Any cut for  $1/p$ , where  $p \geq 2$
- Non-parametric, model independent
- Applies to titration design, sequential design, active control, early or late Phase

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**BINARY DOSE SPACING**

- Assume MTD known and non-decreasing relationship
- Intuitive and with wide applications
- Model independent
- A general recommendation, not one size fits all

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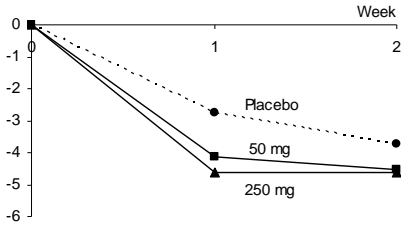
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### DRUG B: EXPLORATORY STUDY - PRIMARY ENDPOINT



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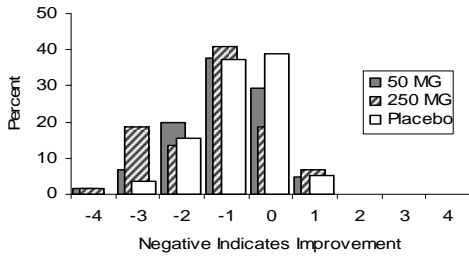
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### DRUG B: EXPLORATORY STUDY - SECONDARY ENDPOINT



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### DRUG B: DESIGN CONSIDERATIONS

The safety profile indicates the high dose could be too high  
Secondary endpoints are used to help design the next study  
Use of MCP-Mod  
Consider a linear model

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## DRUG B: DOSE RANGING STUDY DESIGN

Length of study restricted by toxicity coverage  
Placebo controlled  
Including an active control  
Proposed 5 test doses – 2.5 mg, 5 mg, 12.5 mg, 25 mg and 75 mg

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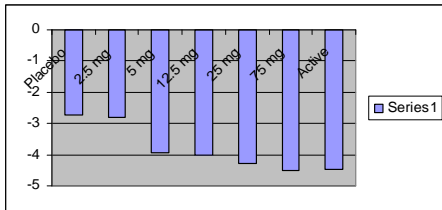
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## DRUG B STUDY RESULTS



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## 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

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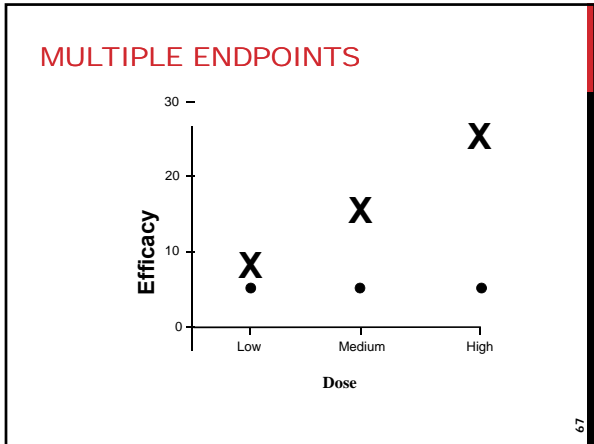
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### STUDY DESIGN -> ANALYSIS PLAN -> STUDY REPORT

Sample size calculation  
Primary and secondary endpoints  
Efficacy and safety  
Other analyses of interest  
Statistical Analysis Plan (SAP) – more details  
Clinical Study Report (CSR)

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### DESIGN CONSIDERATIONS

A stepwise approach  
Confirmatory – go/no go decision  
After confirmation, then explore –

- Secondary endpoints
- Multiple treatment comparisons
- Dose response modeling
- Safety analyses
- Subset analyses

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## DESIGN CONSIDERATIONS

Clinical question ->

Clinical objectives ->

Study design

Are these objectives clear enough?

Are they sequential?

Which part is confirmatory?

What are the exploratory objectives?

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## EFFICACY VS SAFETY

In most studies, sample size calculation is based on efficacy, or PK

Safety data are observed after study read out

Efficacy or PK is for confirmatory purposes

Safety is exploratory

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PHASE I/II CLINICAL TRIAL  
DESIGN AND DOSE  
FINDING (PART II)

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OUTLINE

	Topic
1:00-1:45	Phase I dose escalation design
1:45-2:45	Phase II dose finding study: Hypothesis Testing
2:45-3:00	Break
3:00-3:45	Modeling of dose response, including Emax model.
3:45-4:00	Optimal Design.

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PHASE I DOSE  
ESCALATION STUDY  
3+3, BLRM AND EWOC  
(CHAPTER 3, 4, 5)

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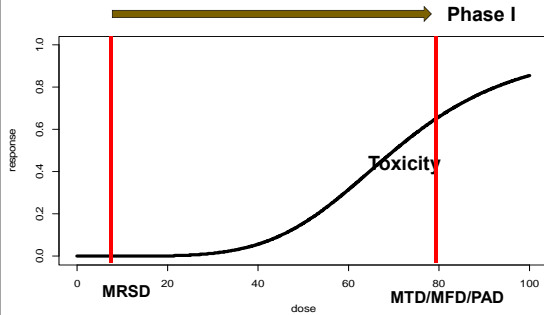
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### OBJECTIVE FOR PHASE I DOSE FINDING



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### PHASE I DOSE FINDING STUDY

Primary objective(s):

- Estimate the maximum tolerable dose (MTD) or maximum feasible dose (MFD)
- For a compound with limited toxicity, a dose based on PAD may be used
- For oncology, to define the recommended phase 2 dose (RP2D)

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### PHASE I: TERMINOLOGY

- MRSD:** Maximum recommended starting dose
- NOAELs:** No-observed adverse effect levels
- HED:** Human equivalent dose
- MTD:** Maximal tolerable dose
- MFD:** Maximal feasible dose
- PAD:** Pharmacologically active dose

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### DOSE SELECTION FOR FIH

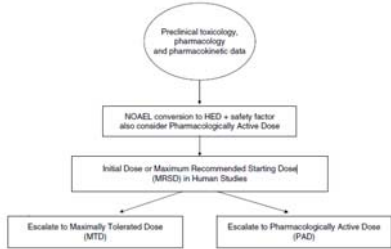


Figure 3.3. Overview of dose selection for FIH studies.

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### CAVEATS FOR PHARMACOLOGICALLY ACTIVE DOSE

- **PAD may not be possible**
  - Knowledge of animal models of disease or mechanism of action (MoA)
  - Target site and receptors may be absent or modified
- **PAD may not be reliable**
  - Extrapolation from animal to human
  - Route of administration often different
  - PD effect vs clinical effect
- **PAD often helpful in guiding the dose escalation, but over-confidence may lead to inconclusive results in phase II.**

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### PD MARKER OR CLINICAL ENDPOINT

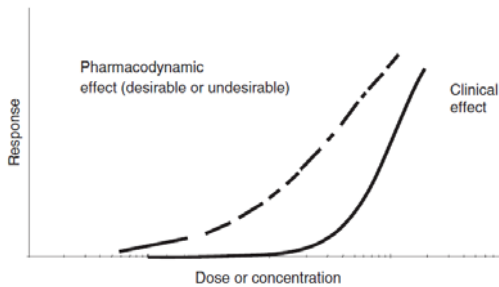


Figure 3.4. PD effect vs. clinical efficacy dose- or exposure-response relationships.

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### PHASE I DESIGN IN HEALTHY VOLUNTEER

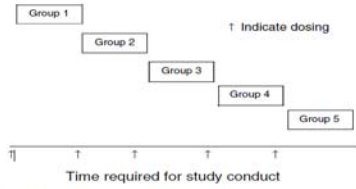


Figure 3.2. Parallel-group, placebo-controlled, randomized, double-blind ascending dose Phase I study design.

- **SRD: Single rising study**
- **MRD: Multiple rising study**

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### TRADITIONALLY IN ONCOLOGY DF

- Generally assumed toxicity is a prerequisite for optimal antitumor activity for cytotoxic agents (Wooley and Schein, 1979)
- Monotonicity for efficacy
- Dose limiting toxicity (DLT)
  - usually defined based on CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events), e.g. as treatment related nonhematological toxicity  $\geq$  Grade 3, or treatment related hematological toxicity  $\geq$  Grade 4.
- => **RP2D are often close to MTD ( $\gamma$ ), where**

$$Prob(DLT|Dose = \gamma) = \theta$$

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### SELECTION OF DOSE FOR ONCOLOGY

- **Too low a starting dose or slow escalation is a concern**
- **Murine LD<sub>10</sub>:** Dose with approximately 10% mortality mice
- **1/10 or 2/10 of murine equivalent of LD<sub>10</sub>** (milligrams per m<sup>2</sup>) as starting dose
- **Based on estimated MTD**
- **Modified Fibonacci is often used:**
  - (x, 2x, 3x, 5x, 7x, 9x, 12x, and 16x) or
  - Increase of (100, 65, 50, 40, and 30% thereafter)

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### PHASE I DESIGN FOR ONCOLOGY

- **Nonparametric Methods (Rule-based design)**
  - E.g. 3+3, A+B Design, Accelerated titration
- **Parametric method (Model-based design)**
  - E.g. Continual Reassessment method (CRM) (O'Quigley et al., Biometrics, 1990, 1996)
  - Bayesian Logistics regression model (BLRM)
  - Escalation with over dose control (EWOC)
- **Hybrid design**
  - mTPI (Yuan Ji et al 2010)

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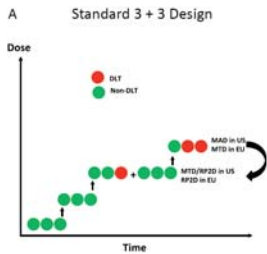
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### ILLUSTRATION OF 3+3 DESIGN



**Phase 1 Trial Design: Is 3 + 3 the Best?**  
 Aaron R. Hansen, MBBS, Donna M. Graham, MBCh, Gregory R. Pond, PhD, and Lillian L. Siu, MD

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### 3+3 DESIGN

**MTD: highest dose with 0 or 1DLT out of 6 patients**

**Problem:**

- **Not flexible**
  - target rate of toxicity
  - cohort size
  - order of dose
  - level of accuracy before stopping
  - Incorporating other data, e.g. biomarker, PK, efficacy
- **Memory-less (using data only from most recent cohort)**
- **Insufficient operation characteristics:**
  - Reiner et al. 1999; Lin et al. 2001

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### BLRM (BAYESIAN LOGISTIC REGRESSION MODEL)

Two-parameter model, dose as **continuous** variable

$$\text{logit}(p(d)) = \log\alpha + \beta \log\left(\frac{d}{d^*}\right)$$

$p(d)$ : probability of having a DLT in the first cycle at dose  $d$

$d^*$ : reference dose

$\alpha$ : intercept, odds of a DLT at  $d^*$

$\beta$ : slope, steepness of curve

Neuenschwander et al (2008), Statist.Med. 27: 2420-2439

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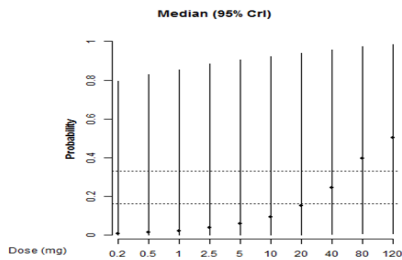
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### PLOTS



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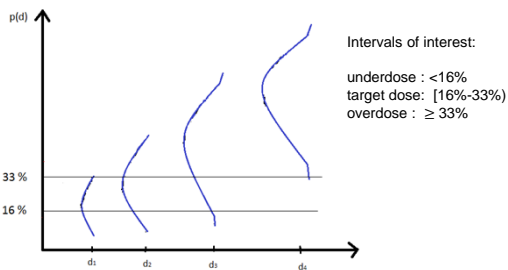
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### ESCALATION: INTERVALS OF INTEREST



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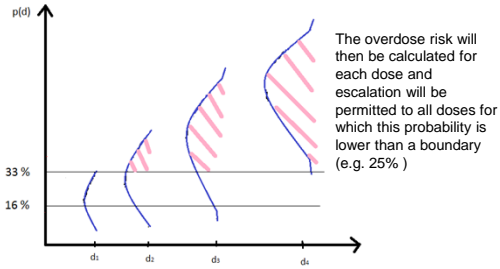
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### ESCALATION WITH OVERDOSE CONTROL (EWOC)




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### ESCALATION

**Overdose control: Probability for overdosing should be less than 25%**

**Escalation maximal 100% compared to already tested levels (e.g. Modified Fibonacci)**

- In-between dose levels are possible

**The MTD may be considered found, e.g. if the posterior probability of the true DLT rate in the target interval is above 50% or at least 12 patients overall have been treated at this dose**

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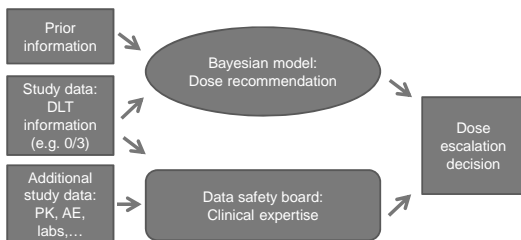
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### DECISION - COMBINATION OF CLINICAL AND STATISTICAL EXPERTISE




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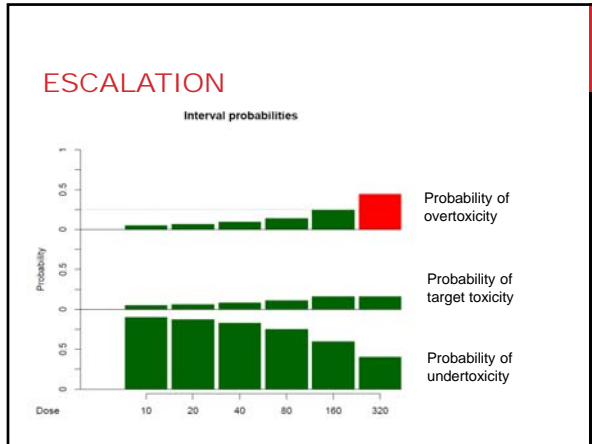
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### FINAL ANALYSIS

**Recommended Phase II Dose**

At the end of the trial, run model for dose confirmation using all patient (including an expansion cohort)

**Sensitivity analysis**

Run the model using a new DLT definition

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### BLRM – Combination trials / Motivation

**Combinations**

- May lead to synergistic efficacy
- May help to overcome resistance mechanisms

**But:**

**Potential for interaction and in-/decreased safety risk**

<p><b>Protective:</b> The toxic effect of the drug combination is <b>less</b> than that obtained if the drugs act independently in the body.</p>	<p><b>No interaction:</b> The toxic effect of the drug combination is <b>equal</b> to that obtained if the drugs act independently in the body.</p>	<p><b>Synergism:</b> The toxic effect of the drug combination is <b>greater</b> than that obtained if the drugs act independently in the body.</p>
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## SOFTWARE

- EAST: ESCALATE
- ADDPLAN DF
- R package: e.g. bcrm
- NextGen-DF (online web tool)
  - <http://www.compgenome.org/NGDF/>
- Various resource online
  - <http://onbiostatistics.blogspot.com/2015/01/alternative-phase-i-dose-escalation.html>

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## HYPOTHESIS TEST IN PHASE II DOSE-FINDING TRIALS: PARALLEL SETTING (CHAPTER 10, 14)

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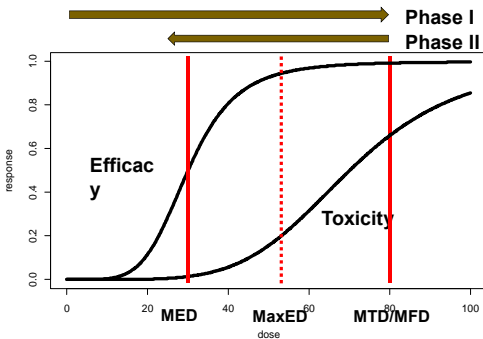
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## OVERVIEW OF DOSE FINDING PROCESS (NON-ONCOLOGY)



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## OBJECTIVE OF PHASE II DOSE FINDING STUDY

### Proof-of-Concept (PoC)

- Contrast based test for Proof of Concept (PoCx, PoC)
- Contrasts based on ranks (OLCT)
- Model-based contrast (MCPMod)
- Other contrast test

### Recomend dose for phase III (Estimation and modeling)

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## A COMBINED POC AND DOSE-RANGING DESIGN

For illustration purpose, three active dose are used. However, it is generally recommended to have 4-5 doses in a full dose-ranging study.

- Four parallel treatment groups
- Low, medium, and high doses
- Placebo controlled
- Contrast test to combine information from multiple doses

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## POTENTIAL POC CONTRASTS

- A**  $H_0: \mu_H = \mu_P$  vs  $H_1: \mu_H > \mu_P$
- B**  $H_0: -3\mu_P - \mu_L + \mu_M + 3\mu_H = 0$  vs  $H_1: -3\mu_P - \mu_L + \mu_M + 3\mu_H > 0$
- C**  $H_0: -\mu_P - \mu_L + \mu_M + \mu_H = 0$  vs  $H_1: -\mu_P - \mu_L + \mu_M + \mu_H > 0$
- D**  $H_0: -\mu_P - \mu_L - \mu_M + 3\mu_H = 0$  vs  $H_1: -\mu_P - \mu_L - \mu_M + 3\mu_H > 0$
- E**  $H_0: -3\mu_P + \mu_L + \mu_M + \mu_H = 0$  vs  $H_1: -3\mu_P + \mu_L + \mu_M + \mu_H > 0$

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### FOUNDATION OF CONTRAST TEST

Let  $\mu_i$  be the population mean for group  $i$ . The null hypothesis of no treatment effect can be written as follows:

$$H_0 : \mu_0 = \mu_1 = \dots = \mu_k \quad (14.4)$$

or

$$H_0 : L(\mu) = \sum_{i=0}^k c_i \mu_i = 0 \quad (14.5)$$

where contrasts satisfy the condition that  $\sum_{i=0}^k c_i = 0$ .

Note that if  $H_0$  in Eq. (14.5) is rejected for some  $\{c_i\}$  satisfying  $\sum_{i=0}^k c_i = 0$ , then  $H_0$  in Eq. (14.4) is also rejected. We are particularly interested in the following alternative hypothesis:

$$H_a : L(\mu) = \sum_{i=0}^k c_i \mu_i = \varepsilon \quad (14.6)$$

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### POWER OF A CONTRAST TEST IN A DOSE-FINDING STUDY

For normal distributed data

$$H_0: L(\mu) = \sum_{i=0}^k c_i \mu_i = 0 \quad H_a: L(\mu) = \sum_{i=0}^k c_i \mu_i = \varepsilon$$

where  $\sum_{i=0}^k c_i = 0$ .

And power of the test is

$$1 - \beta = \Phi \left( \frac{\varepsilon}{\sigma} \sqrt{\frac{n}{\sum_{i=0}^k c_i^2 / f_i}} \right)$$

Where  $c_i$  is the contrast coefficient,  $f_i$  is the sample size fraction for the  $i$ th group,  $n$  is the total sample size ( $n = \sum f_i$ )

$$n = \left[ \frac{(z_{1-\alpha} + z_{1-\beta}) \sigma}{\varepsilon} \right]^2 \sum_{i=0}^k \frac{c_i^2}{f_i}$$

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### CONTRAST TEST #1: OPTIMAL CONTRAST FOR A SINGLE MODEL

•For given set of means of all treatment groups ( $\mu_i$ ), and given allocation ratio ( $f_i$ ), find contrast coefficient ( $c_i$ ) which maximize the power of PoC test.

•Optimal contrast is independent of total sample size  $n$ , but is dependent on allocation ratio.

•Only the values of response at selected dose groups impact the power.

$$c_i \propto n_i(\mu_{0i} - \bar{\mu}), \quad i = 1, \dots, k, \quad (3)$$

where  $\bar{\mu} = N^{-1} \sum_{i=1}^k \mu_{0i} n_i$  (Bornkamp 2006, p. 88; Casella and Berger 1990, p. 519). A

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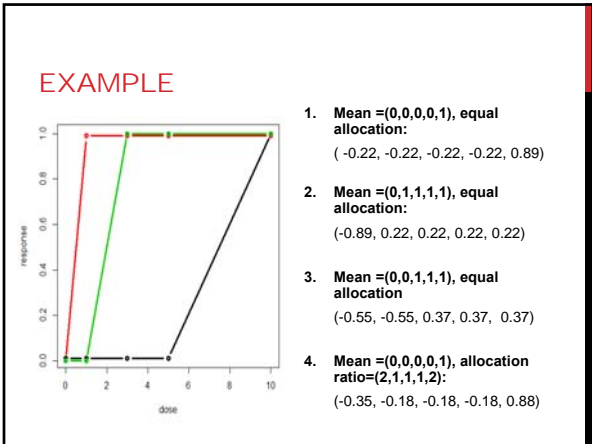
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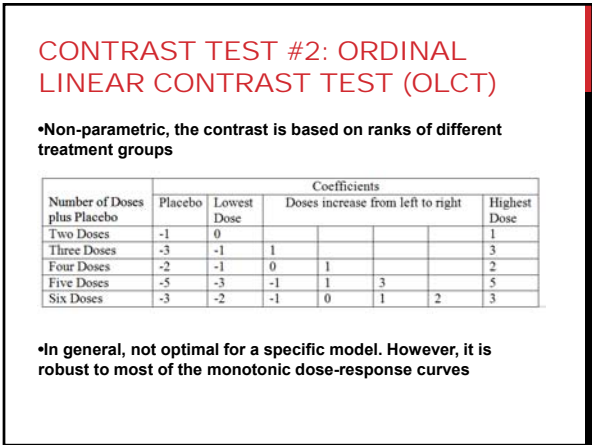
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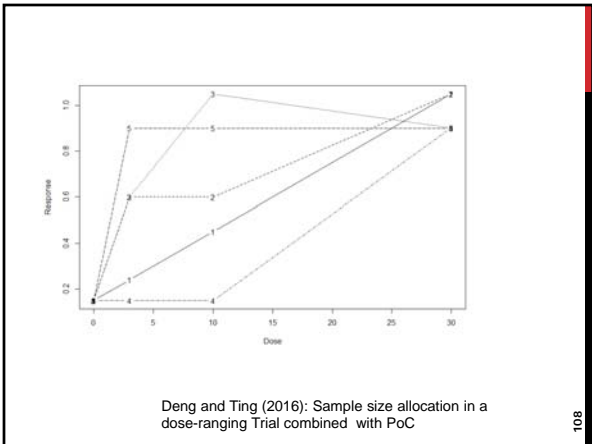
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### CONTRAST TEST #4: MCP-MOD (MCP STEP)

- One optimal Contrast for each model in candidate set
- Multiplicity from multiple contrast tests are adjusted by multivariate normal/t distribution in a similar fashion as Dunnett test and other testing in #3.

The final detection of a significant dose-response signal (i.e., demonstrating PoC), is based on the maximum contrast test statistic

$$T_{max} = \max\{T_1, \dots, T_M\}.$$

Under the null hypothesis of no dose-response effect  $\mu_{d_1} = \dots = \mu_{d_k}$  and under the distributional assumptions stated in Equation 1,  $T_1, \dots, T_M$  jointly follow a central multivariate  $t$  distribution with  $N - k$  degrees of freedom and correlation matrix  $R = (\rho_{ij})$ , where

$$\rho_{ij} = \frac{\sum_{l=1}^k c_{il}c_{jl}/n_l}{\sqrt{\sum_{l=1}^k c_{il}^2/n_l \sum_{l=1}^k c_{jl}^2/n_l}} \quad (4)$$

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### DOSE RESPONSE STUDY WITH MCPMOD

MCPMod is an approach

1. Primary objective: Show that the drug works
2. Secondary objective: Show how the drug works w.r.t doses

Under one methodological umbrella

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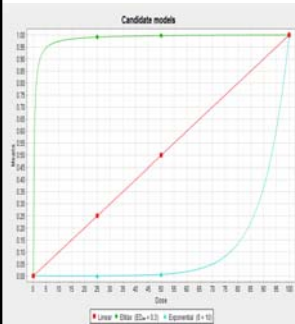
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### DETERMINE THE OPTIMAL WEIGHT FOR TEST OF NON-FLAT RESPONSE



- Four doses: 0, 25, 50, 75 for illustration
- Green (emax): (-3, 1, 1, 1)
- Red (linear): (-3, -1, 1, 3)
- Blue (exponential): (-1, -1, -1, 3)

**MCP step:** apply the 3 contrast tests, and claim success if at least one test is significant

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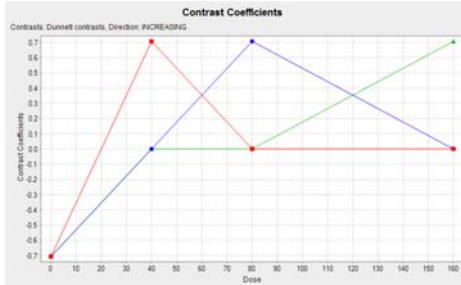
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### DOSE RESPONSE SHAPES WHERE PAIR-WISE COMPARISON IS OPTIMAL



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### EXAMPLE: COMPARISON OF DIFFERENT METHODS

- 80% power, one-sided alpha of 0.025,
- treatment difference of 0.36 with SD=0.67
- Five treatment groups: PBO, 1 mg, 3mg, 10mg, 30mg

- Candidate set
  - Emax 1: 3mg -> 50% of effect
  - Emax 2: 1mg -> 70% of effect
  - Linear
  - Exponential : 10mg -> 20% of effect
  - Logistic: 3mg -> 10% of effect, 10mg -> 80% of effect

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### EXAMPLE (CONTINUED)

- What is the sample size for
- MCPMod
  - OLCT
  - Highest dose vs PBO
  - Dunnett
  - Williams contrast
  - Marcus contrast

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### SOFTWARE -- MCPMOD

- ADDPLAN DF
- EAST: PROC MCPMod
- R package: DoseFinding (Design of trial requires additional coding for non-normal endpoint)

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### SOFTWARE - OLCT WITH ANCOVA

```
PROC MIXED DATA=one METHOD=reml ORDER=formatted;  
CLASS trt stratmed ;  
MODEL chgept = baseline stratmed trt ;  
LSMEANS trt / CL DIFF OM ;  
LSMESTIMATE 'OLCT PoC Test' trt -2 -1 0 1 2 ;  
RUN ;
```

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### OLCT FOR BINARY DATA (COCHRAN-ARMITAGE TREND TEST)

```
proc freq data=Pain;  
tables Adverse*odnDose;  
exact trend / maxtime=60;  
title 'Cochran-Armitage trend test';  
run;
```

•It is critical that the ordinal value of dose should be used (as "odnDose") instead of the actual value of doses.  
•For example, for a trial with placebo, 1mg, 3mg, 10 mg and 30mg, odnDose should be 0, 1, 2, 3, 4 or 1, 2, 3, 4, 5 (something equally spaced). If you use 0, 1, 3, 10, 30, it will not give you correct output.

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# MODELING AND ESTIMATION (CHAPTER 9, 10)

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### MODELS AVAILABLE IN MCPMOD

$$f(d, \theta) = \theta_0 + \theta_1 f^0(d, \theta^0)$$

Name	$f(d, \theta)$	$f^0(d, \theta^0)$	(*)	(‡)
linear	$E_0 + \delta d$	$d$		
linlog	$E_0 + \delta \log(d + c)$	$\log(d + c)$		$c$
quadratic	$E_0 + \beta_1 d + \beta_2 d^2$	$d + \delta d^2$ if $\beta_2 < 0$	$\delta$	
emax	$E_0 + E_{max} d / (ED_{50} + d)$	$d / (ED_{50} + d)$	$ED_{50}$	
logistic	$E_0 + E_{max} / (1 + \exp\{-[ED_{50} - d] / \delta\})$	$1 / (1 + \exp\{-[ED_{50} - d] / \delta\})$	$(ED_{50}, \delta)^T$	
exponential	$E_0 + E_1 (\exp(d/\delta) - 1)$	$\exp(d/\delta) - 1$	$\delta$	
sigEmax	$E_0 + E_{max} d^h / (ED_{50}^h + d^h)$	$d^h / (ED_{50}^h + d^h)$	$(ED_{50}, h)^T$	
betaMod	$E_0 + E_{max} B(\delta_1, \delta_2) (d/D)^{\delta_1} (1 - d/D)^{\delta_2}$	$B(\delta_1, \delta_2) (d/D)^{\delta_1} (1 - d/D)^{\delta_2}$	$(\delta_1, \delta_2)^T$	$D$

Table 1: Dose-response models implemented in the MCPMod package. Column (\*) lists for each model the parameters for which guesstimates are required and the order in which they need to be specified in the `models` list, while column (‡) lists the parameters, which fixed and not estimated. For the beta model  $B(\delta_1, \delta_2) = (\delta_1 + \delta_2)^{-\delta_1 - \delta_2} / (\delta_1^{\delta_1} \delta_2^{\delta_2})$  and for the quadratic model  $\delta = \frac{2\beta_2}{3\beta_1}$ . For the quadratic model the standardized model function is given for the concave-shaped form.

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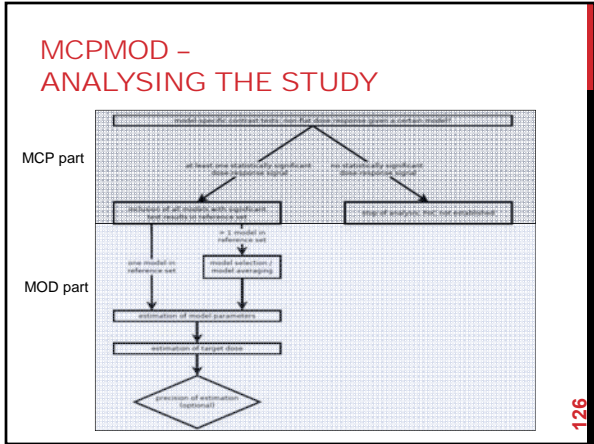
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**EXAMPLE:**

Treatment arm results*					
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5
Doses	0.0	25.0	50.0	100.0	150.0
Means	-0.19	-0.174	-0.21	-0.162	-0.06
n	83	83	86	83	84
sd	0.36	0.36	0.36	0.36	0.36

Computation result - Result information  
There is no additional information on this computation results.

Computation result - Multiple contrast test

	t-Stat	p-Value
Exponential (δ = 77.9216)	2.772	0.0074
Linear	2.4726	0.0165
Logistic (ED <sub>50</sub> = 75, δ = 15)	2.3556	0.0222
EMax (ED <sub>50</sub> = 37.5)	1.6857	0.0958
EMax (ED <sub>50</sub> = 4.0891)	1.0293	0.2709

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**Finding the MED – an illustration**

- Either D2 or D3 could be chosen as the MED in the MCP case
- Modeling is more flexible, but requires additional assumptions

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**TARGET DOSE, EFFECTIVE DOSE**

- **Minimum effective dose (MED or MinED):**
  - ICH-E4: "The smallest dose with a discernible useful effect".
  - Target Dose (TD) : Minimum dose with absolute effect difference of Δ compared to control: 30% increase of ACR20
  - Effective Dose (EDp): Minimum dose achieving 100p% of the maximum treatment effect in the **observed** dose range: 60% of maximum effect (Δ=2) => Δ = 1.2.
- **Difference to EDp in Emax model**

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### OPTION FOR MODEL SELECTION/AVERAGING

- Model selection (MaxT or AIC (the bigger, the better))
- Model average, e.g. based on AIC
- The pragmatic experience is that linear model sometimes are overweighed.
- Suggested to look at all reasonable model fitting to evaluate the robustness of the conclusion.
- In many cases, it lead to similar dose recommendation for phase III.
- Consider empirical evidence (Emax has higher prior weight)
  - Thomas, N., Sweeney, K., and Somayaji, V. (2014)
  - Thomas, N., and Roy, D. (2016)
  - Wu, J., Banerjee, A., Jin, B., Menon, S., Martin, S., Heatherington, A. (2017)

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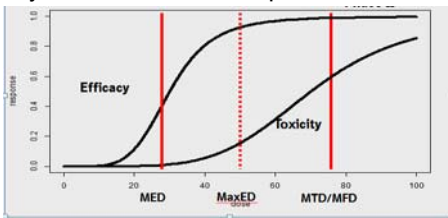
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### HOW SHOULD WE USE ESTIMATED TD/ED

- It defines the lower end of the dose range that can be selected for phase III
- The phase III dose selection should be driven by balance of Benefit/Risk
- Always evaluate risk of "late developed AE"



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Emax Model (chapter 9)  
(Based on Slides from Jim MacDougall)

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## E<sub>MAX</sub> MODEL INTRODUCTION

The E<sub>MAX</sub> model function:

$$R = E_0 + \frac{D^N \times E_{MAX}}{D^N + ED_{50}^N}$$

Note EDp here are different from Effective Dose (ED) defined earlier

Where:

R = Response

D = Dose

E<sub>0</sub> = Baseline Response 4 Parameters

E<sub>MAX</sub> = Maximum Effect

ED<sub>50</sub> = Dose at Half of Maximum Effect

N = Slope factor (Hill Factor)

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## EMAX MODEL

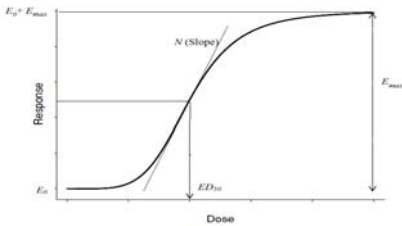


Figure 9.1. E<sub>max</sub> Model dose-response curve.

“Hyperbolic E<sub>MAX</sub>”:  $R = E_0 + \frac{D \times E_{MAX}}{D + ED_{50}}$   
 $N=1$

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## LOGISTIC MODEL

The four-parameter logistic model as described in O’Connell et al. (1993) is given by the following equation

$$R_i = \beta_2 + \frac{(\beta_1 - \beta_2)}{1 + (D_i/\beta_3)^{\beta_4}} + \epsilon_i \quad (9.7)$$

It is equivalent with Emax model by re-parameterization

When  $\beta_4 > 0$

$$\begin{aligned} X &= D^{-1} \\ \beta_2 &= E_0 \\ (\beta_1 - \beta_2) &= E_{max} \\ \beta_3^{-1} &= ED_{50} \\ \beta_4 &= N \end{aligned}$$

When  $\beta_4 < 0$

$$\begin{aligned} \beta_2 &= E_0 \\ (\beta_1 - \beta_2) &= E_{max} \\ \beta_3 &= ED_{50} \\ -\beta_4 &= N \end{aligned}$$

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### **E<sub>MAX</sub> Model Properties**

- The E<sub>MAX</sub> curve follows the “law of diminishing returns”
- The E<sub>MAX</sub> model predicts the maximum effect a drug can have (E<sub>MAX</sub>).
- The E<sub>MAX</sub> predicts baseline effect (E<sub>0</sub>) when no drug is present
- Four parameters
- The model's parameters are readily interpretable

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### **WHY/WHEN USE THE E<sub>MAX</sub> MODEL**

- Useful model for characterizing dose-response
- Common descriptor of dose-response relationships
- Dose response is monotonic and continuous
- A range of different dose levels
- Can be a useful tool in determining the “optimal” dose and the “minimally effective dose”
- Straight-forward to implement: S-plus, SAS Proc NLIN, NONMEM

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### **Parameter Sensitivities: ED<sub>50</sub>**

The E<sub>MAX</sub> model function:

$$R = E_0 + \frac{D^N \times E_{MAX}}{D^N + ED_{50}^N}$$

Where:

R = Response

D = Dose

E<sub>0</sub> = Baseline Response

E<sub>MAX</sub> = Maximum Effect

ED<sub>50</sub> = Dose at Half of Maximum Effect

N = Slope factor (Hill Factor)

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PARAMETER SENSITIVITIES: ED<sub>50</sub>

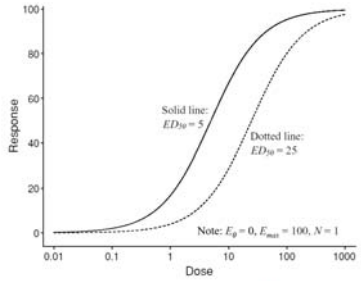


Figure 9.3. E<sub>max</sub> Model dose-response curves with differing ED<sub>50</sub> values.

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Parameter Sensitivities: N(Slope Factor)

The E<sub>MAX</sub> model:

$$R = E_0 \pm \frac{D^N \times E_{MAX}}{D^N + ED_{50}^N}$$

**N = Slope factor (Hill Factor)**

The slope factor determines the steepness of the dose response curve.

As **N** increases, the “dose range” (i.e.  $\frac{ED_{90}}{ED_{10}}$ ) tightens.

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PARAMETER SENSITIVITIES:  
N (SLOPE FACTOR)

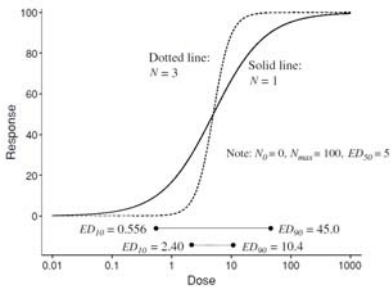


Figure 9.4. E<sub>max</sub> Model dose-response curves with differing N values.

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### $E_{MAX}$ Model: Caveat

- In situations where the study design does not include dose values that produce close to a maximal effect, the resulting parameter estimates may be poorly estimated.
  - Dutta, Matsumoto and Ebling (1996) demonstrated that when the highest dose in the study was less than  $ED_{95}$  the parameter estimates for  $E_{MAX}$ ,  $ED_{50}$ , and  $N$  are poorly estimated with a high coefficient of variation and bias.
  - However, within the range for which the data were available, the fit of the  $E_{MAX}$  model to the data was quite good.

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### DOSE RANGE VS. $N$ (SLOPE FACTOR)

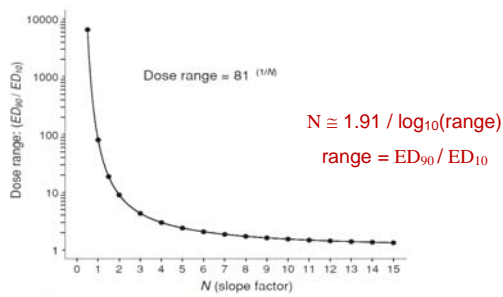


Figure 9.5.  $E_{max}$  Model dose range as a function of  $N$ .

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- To estimate  $ED_{90}$  &  $ED_{95}$  use the formula

$$ED_p = ED_{50} \times \left( \frac{p}{1-p} \right)^{(1/N)}$$

$$ED_{90} = 8.39 \times (9)^{(1/2.2)} = 22.8$$

$$ED_{95} = 8.39 \times (19)^{(1/2.2)} = 32.0$$

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- **NONMEM** (UCSF) software used in PK/PD  
<http://www.globomaxservice.com/products/>
- **SAS**  
Proc NLIN, NLMIXED
- **Spplus**
- Any software for non-linear and non-linear mixed models.

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**SAS**

Proc NLIN is the SAS procedure for Non-Linear models using least squares (or weighted least squares) methods to estimate the parameters

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Optimal Design

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## IMPACT OF ALLOCATION RATIO ON POWER FOR MCPMOD

•For contrast-based method, more allocation to placebo and the dose that achieves the maximum efficacy will lead to higher power

- > Under monotonic assumptions, that means allocating more subjects to placebo and the highest dose.
- > Under betamod or quadratic curves, that means allocating more subjects to placebo and the dose at the peak of response.

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## OPTIMAL DESIGN

Optimal design in dose finding trials usually

•minimize a criterion

- D-optimal: minimize the variance of the model parameters
- TD-optimal: minimize the variance for the estimation of the target dose, i.e. the length of the confidence interval for the target dose is minimized.
- Optimization with respect to both of these criteria above.
- > D-optimal is usually the recommended approach, but the other two can be considered depending on the objective of the optimization.
- > D and TD optimal designs is not to optimize the power. In practice, however, D or TD-optimal designs usually lead to higher allocation ratios to two ends, which in turn leads to higher power comparing to equal allocation.

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## D-OPTIMAL DESIGN FOR A PARAMETER OF A GIVEN EMAX MODEL

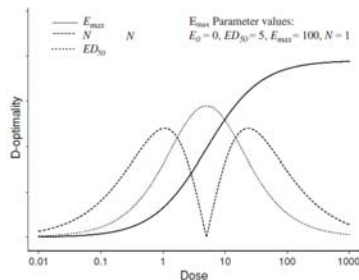


Figure 9.6. D-Optimal design criteria for the  $E_{max}$  model parameters  $ED_{50}$ ,  $E_{max}$ , and  $N$ .

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### D-OPTIMAL DESIGN FOR A MODEL WITH MULTIPLE PARAMETERS

- How to deal with multiple parameters in optimization?
- Operate on the determinant of the information matrix  $M(\xi, \theta)$  and minimize the volume of the confidence ellipsoid for the model parameters
- It focuses on the entire dose response relationship rather than on a single dose, or a single parameter.

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### D-OPTIMAL DESIGN FOR MCPMOD (MULTIPLE MODELS)

- Also called Robust design in some literature.
- Two methods to handle multiple models
  - Maximin Design to safeguard against the worst case scenario
 
$$\text{maximizes } \min\{\text{eff}_1(\xi), \dots, \text{eff}_m(\xi)\}$$
  - Maximize the weighted sum of log efficiency.
 
$$\sum_{j=1}^m \alpha_j \log \text{eff}_j(\xi), \text{ with } \sum_{j=1}^m \alpha_j = 1,$$
- Efficiency is used instead of information matrices
  - variance is model dependent, so some model will dominate by nature
  - Efficiency is value of information matrices relatively to the best design, therefore avoids this problem

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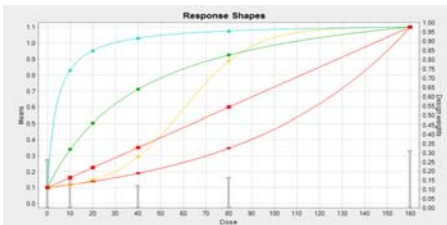
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### OPTIMAL ALLOCATION

- Usually suggest to allocate slightly more patients to placebo
- Usually increase power compare to equal allocation, but in general not “optimal” for power of PoC




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## OPTIMAL ALLOCATION

Assuming  $\delta=0.9$ ,  $sd=1$

Allocation (0, 10, 20, 40, 80, 160mg)	Sample size	Incremental for added arm	2n study needed if PoC is confirmed
1 : 0 : 0 : 0 : 0 : 1	32		Almost for sure
1 : 0 : 0 : 0 : 1 : 1	48	+16	Almost for sure
1 : 0 : 0 : 1 : 1 : 1	60	+12	Likely
1 : 0 : 1 : 1 : 1 : 1	70	+10	Less likely
1 : 1 : 1 : 1 : 1 : 1	78	+8	Not likely
2 : 1 : 1 : 1 : 1 : 2 (optimal allocation ratio)	56		Not likely

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