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

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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

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

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

DOSE-FINDING IN ONCOLOGY

Cancer patients in Phase I

Not ethical for placebo control

Dose limiting toxicity (DLT)

P[toxicity at MTD] = Γ

Where Γ is the target probability of toxicity

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

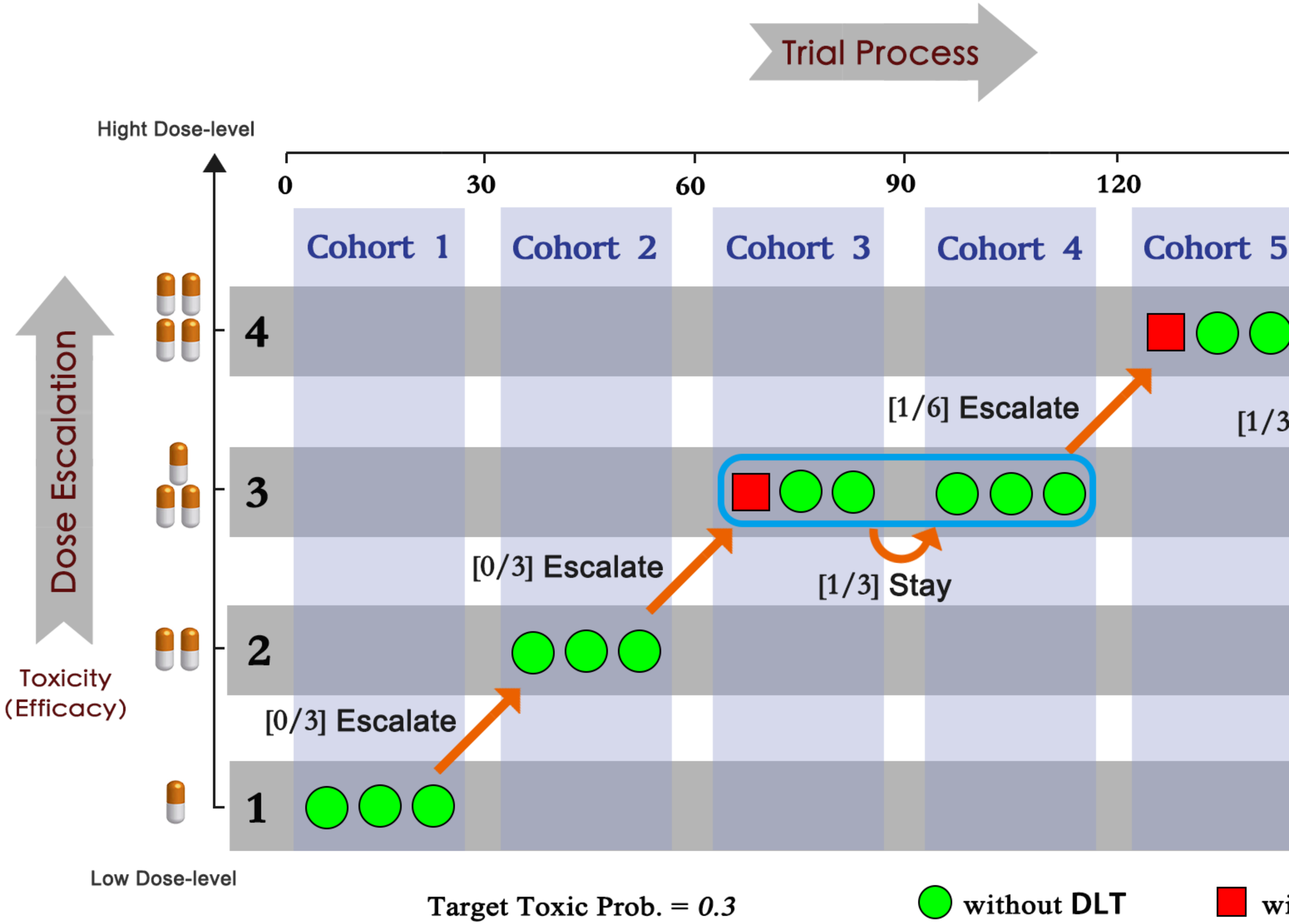
- no toxicity -> 3 on next higher dose
- one toxicity -> add 3 on the same dose
- two or more toxicity -> MTD is exceeded

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.


Trial Process
Hight Dose-level
0
30
60
90
120
Cohort 1
Cohort 2
Cohort 3
Cohort 4
Cohort 5
Dose Escalation
4
3
2
1
[1/6] Escalate
[0/3] Escalate
[1/3] Stay
[0/3] Escalate
Toxicity
(Efficacy)
Low Dose-level
Target Toxic Prob. = 0.3
without DLT

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

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

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 δ is positive

Assuming variance = 1

N is calculated given α and β

PROOF OF CONCEPT

Hypothesis testing

Primary endpoint is clinical efficacy

Pre-specified two-sided alpha could be $>= 0.05$

Power may be greater than 80%

Go/No Go decision

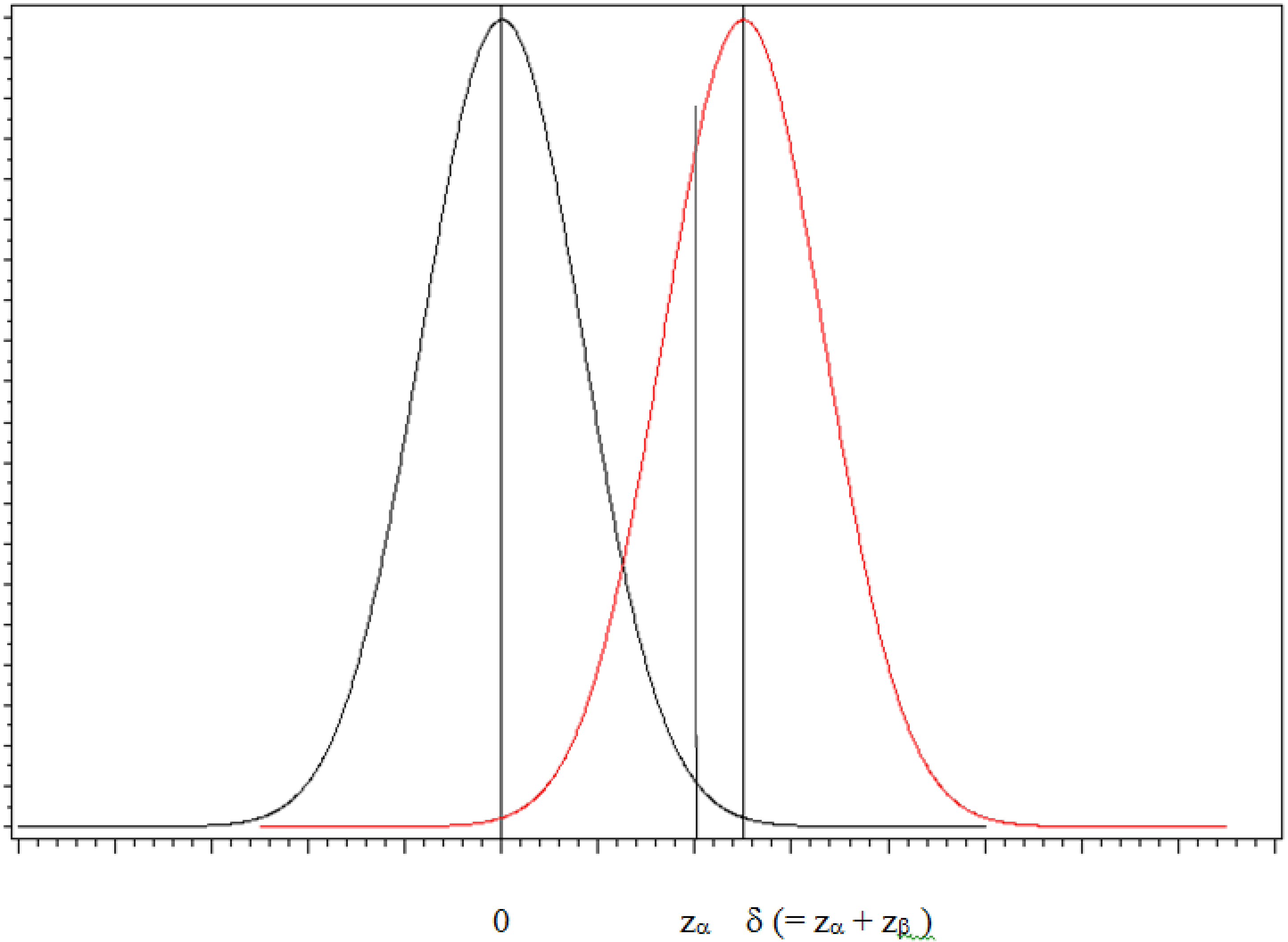
PROPOSE A TOOL TO HELP WITH COMMUNICATIONS

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


0
z_α
δ (= $z_\alpha + z_\beta$)

STATISTICAL HYPOTHESIS

H_0: $\mu_T \leq \mu_P$ vs H_1: $\mu_T > \mu_P$

is tested at Type I error α

0 $\quad$ **z_α** $\quad$ **δ (= $z_\alpha + z_\beta$)**

The distance between z_α and δ reflect the absolute value of z_β

Hence $\delta = z_\alpha + z_\beta$

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 α;
- If $z_\alpha < \hat{\delta} < z_\alpha + z_\beta$, then a "Go" decision is made, then the Type I error is controlled under α, however, the clinically meaningful

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.

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

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?

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?

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

CONCERNS IN DOSE RANGING STUDIES

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

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

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

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

RISKS OF INCONCLUSIVENESS

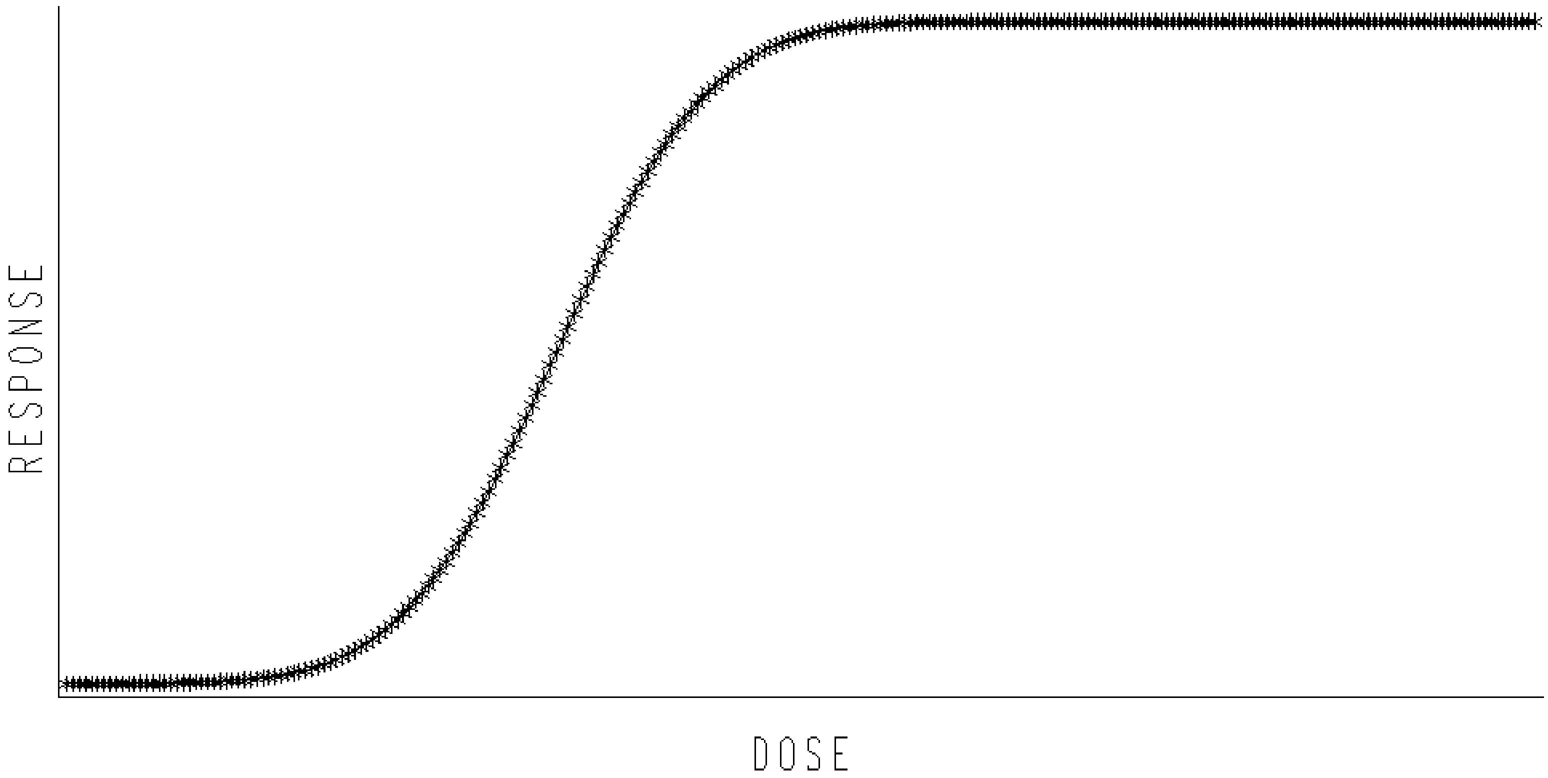
After results are ready, there is very little a statistician can do

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

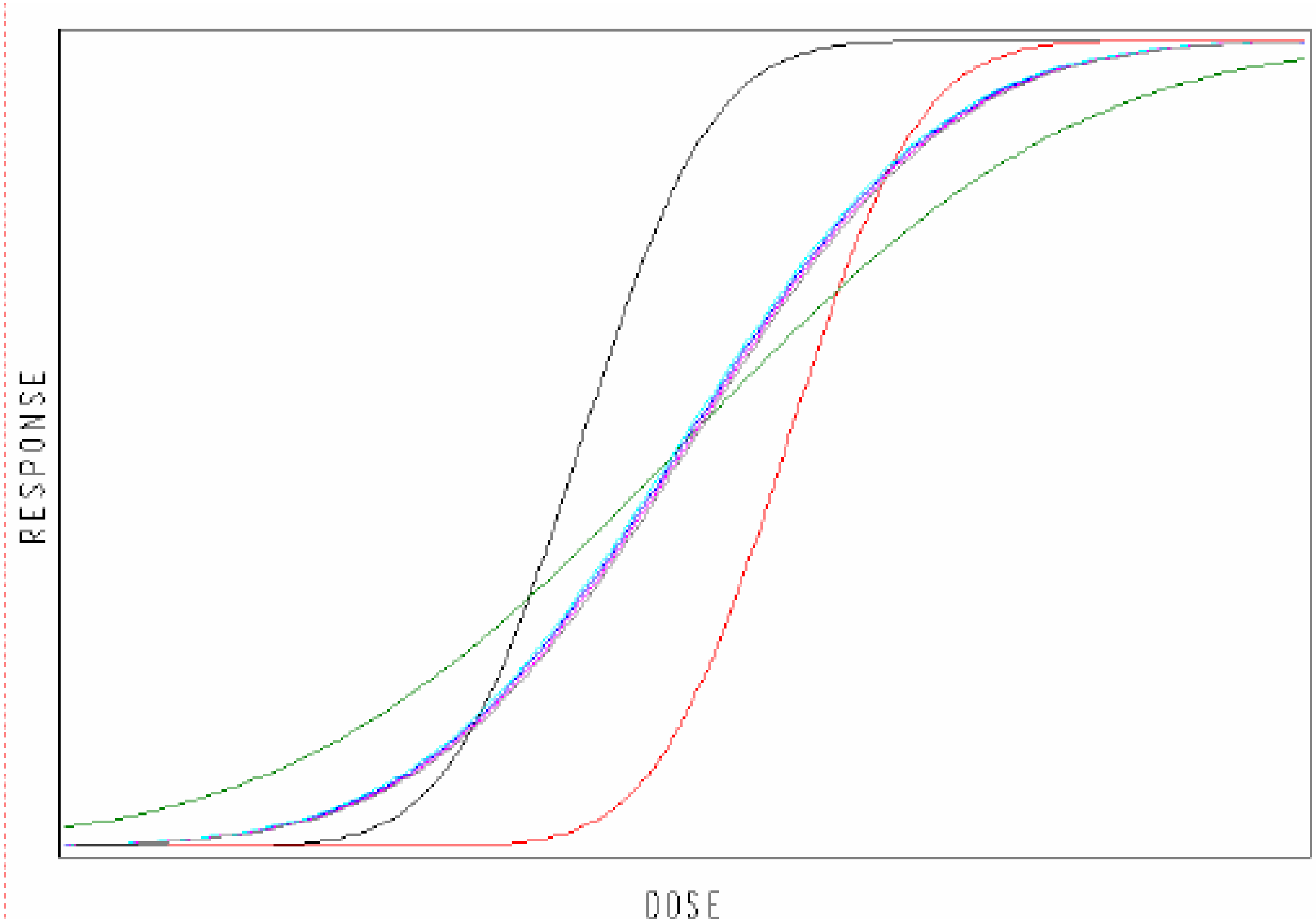
Clearly communicate the Type I and II risks

Define Go/No Go criteria

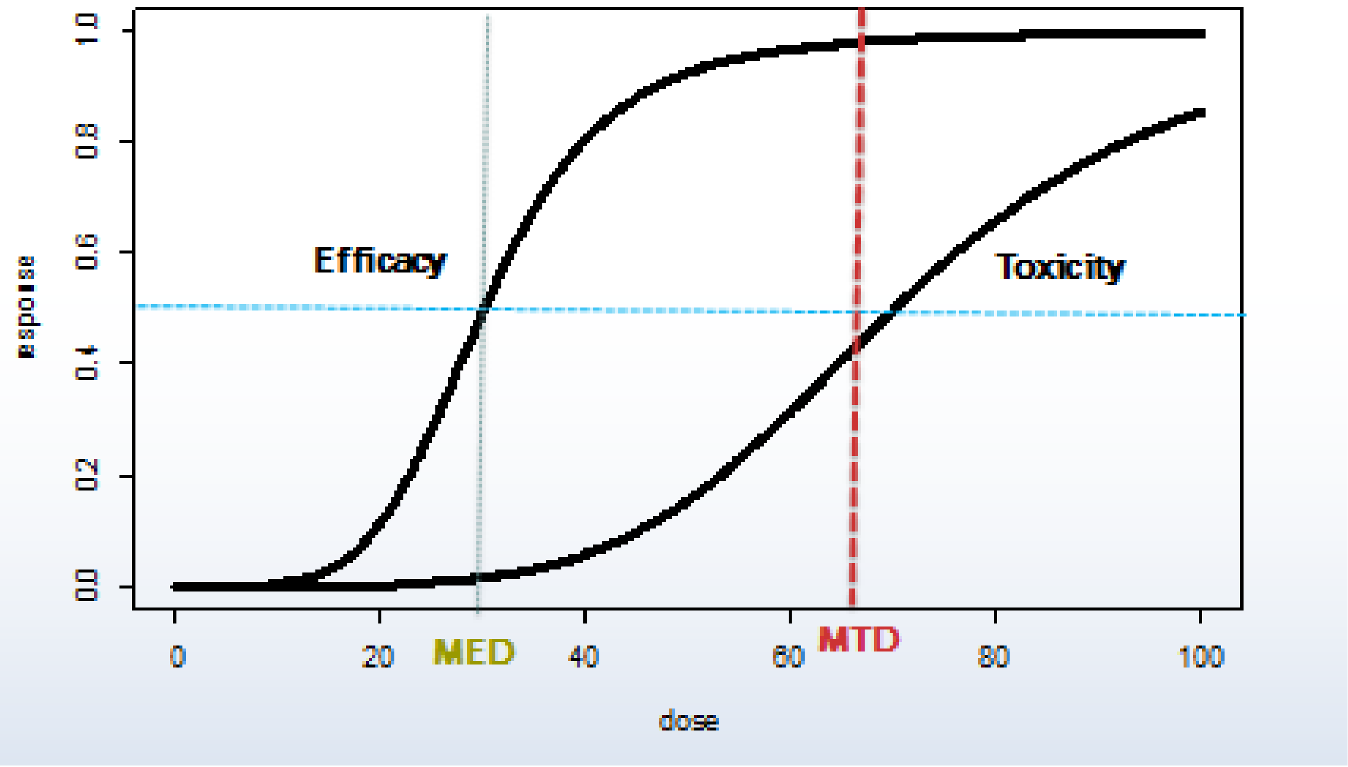
FIGURE 1 A THEORETICAL DOSE–RESPONSE CURVE

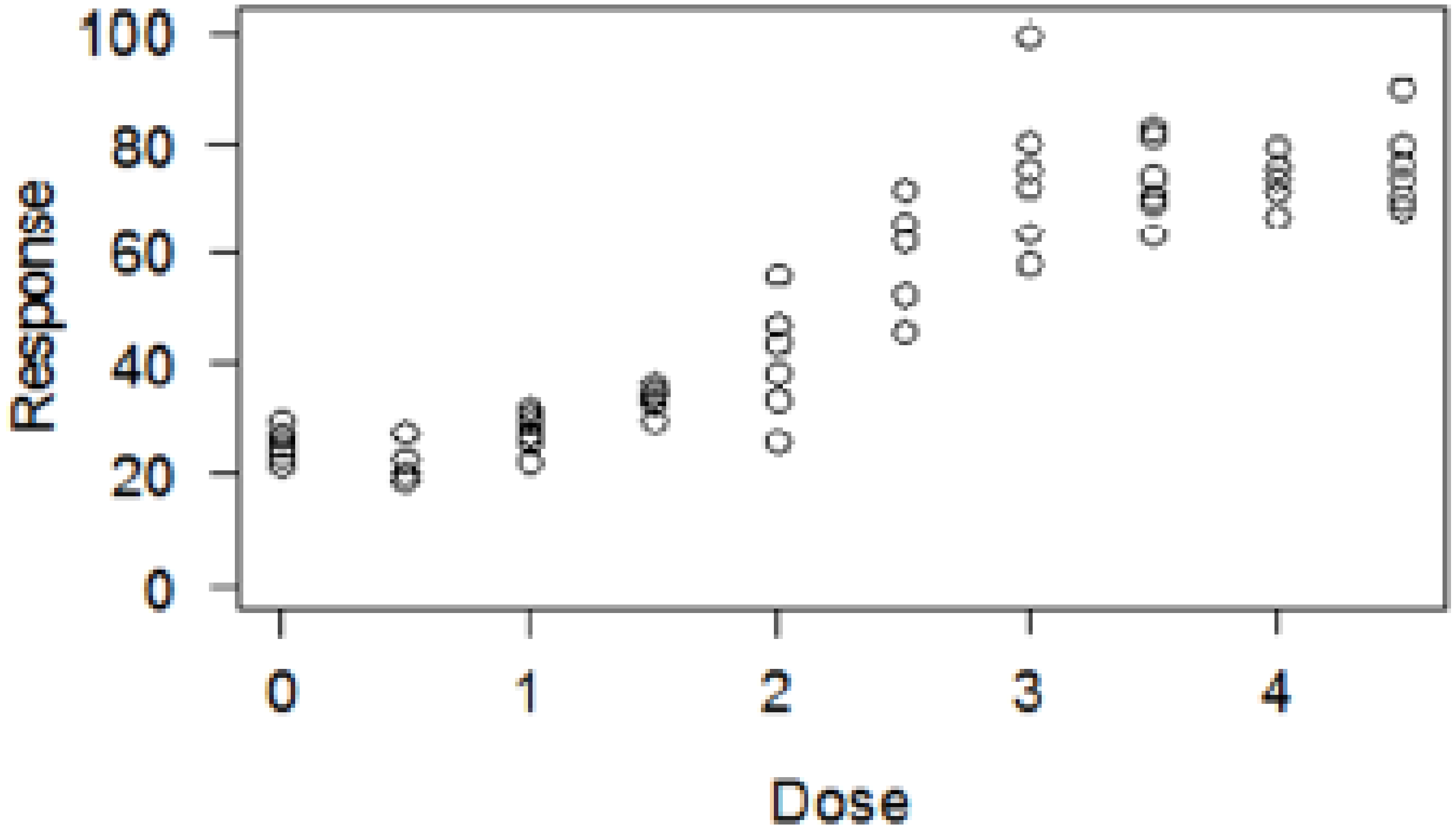


INDIVIDUAL DOSE RESPONSE AND POPULATION DOSE RESPONSE



EFFICACY AND TOXICITY DOSE RESPONSE CURVES



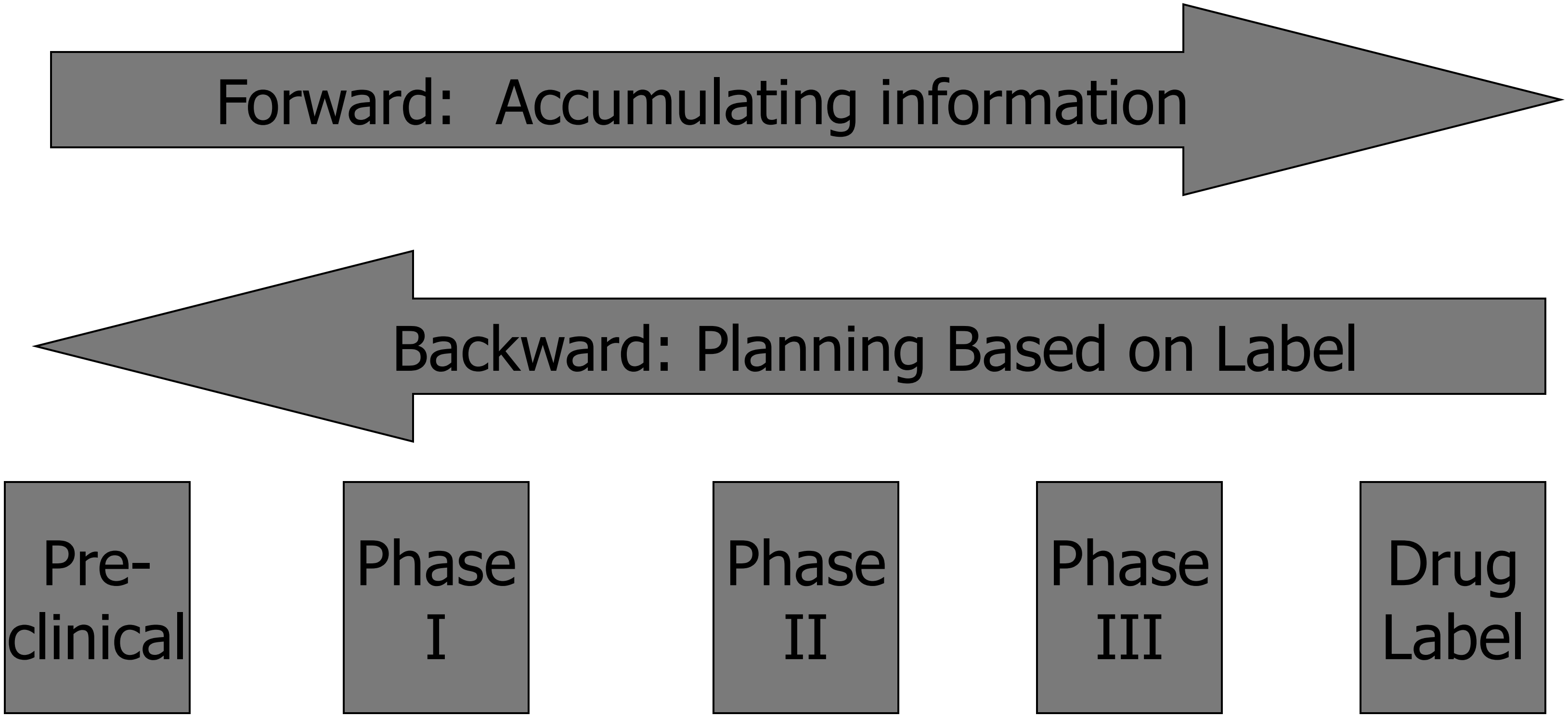


100
80
60
40
20
0
Response
0
1
2
3
4
Dose

DRUG LABEL (PACKAGE INSERT)

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

PLANNING PROCESS



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**

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**

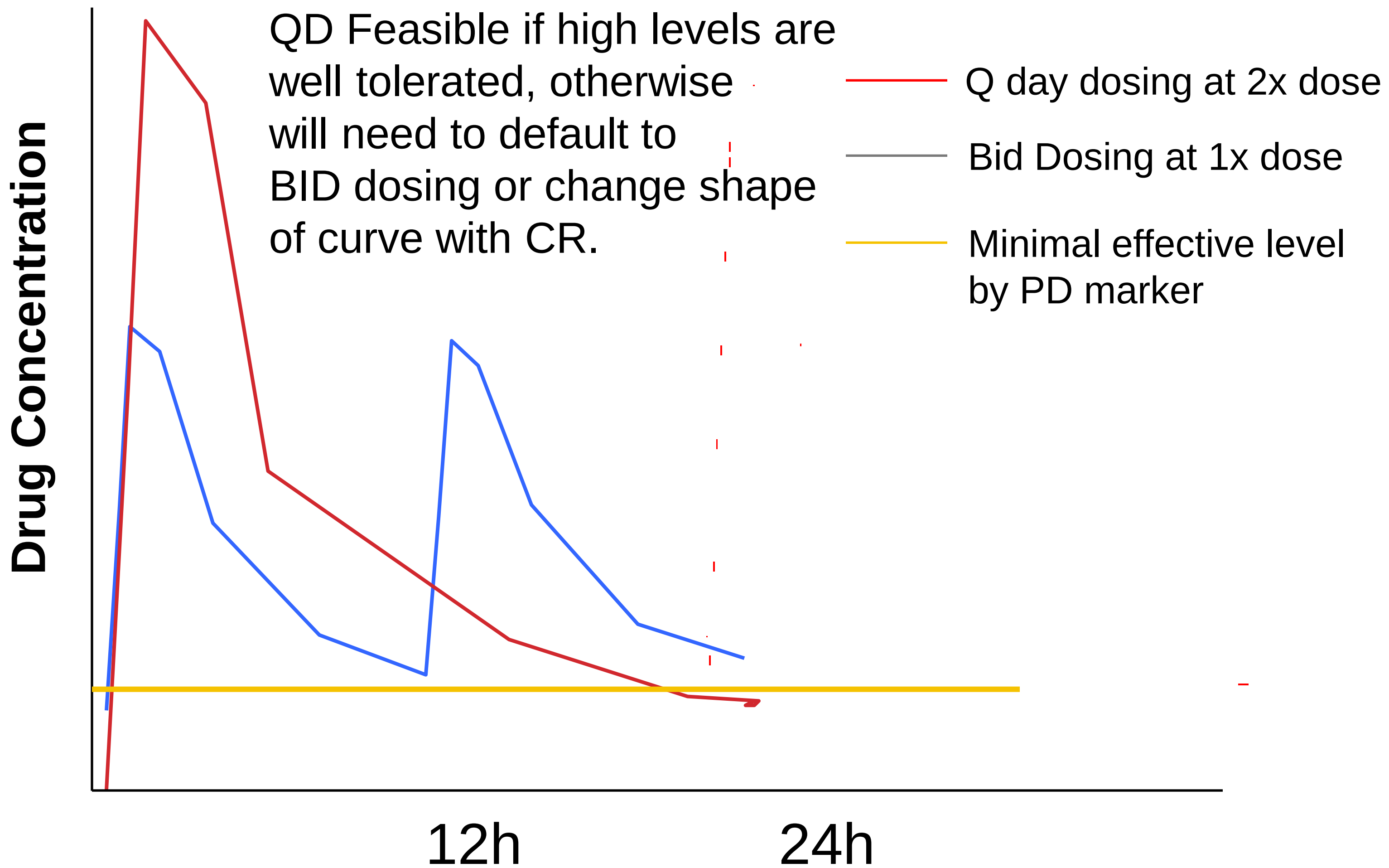
PHARMACOKINETICS (PK), PHARMACODYNAMICS (PD)

- **PK, PD, PK/PD**
  - PK: body act on drug
  - PD: drug act on body
- **Concentration response uses PK, but should we consider PD?**

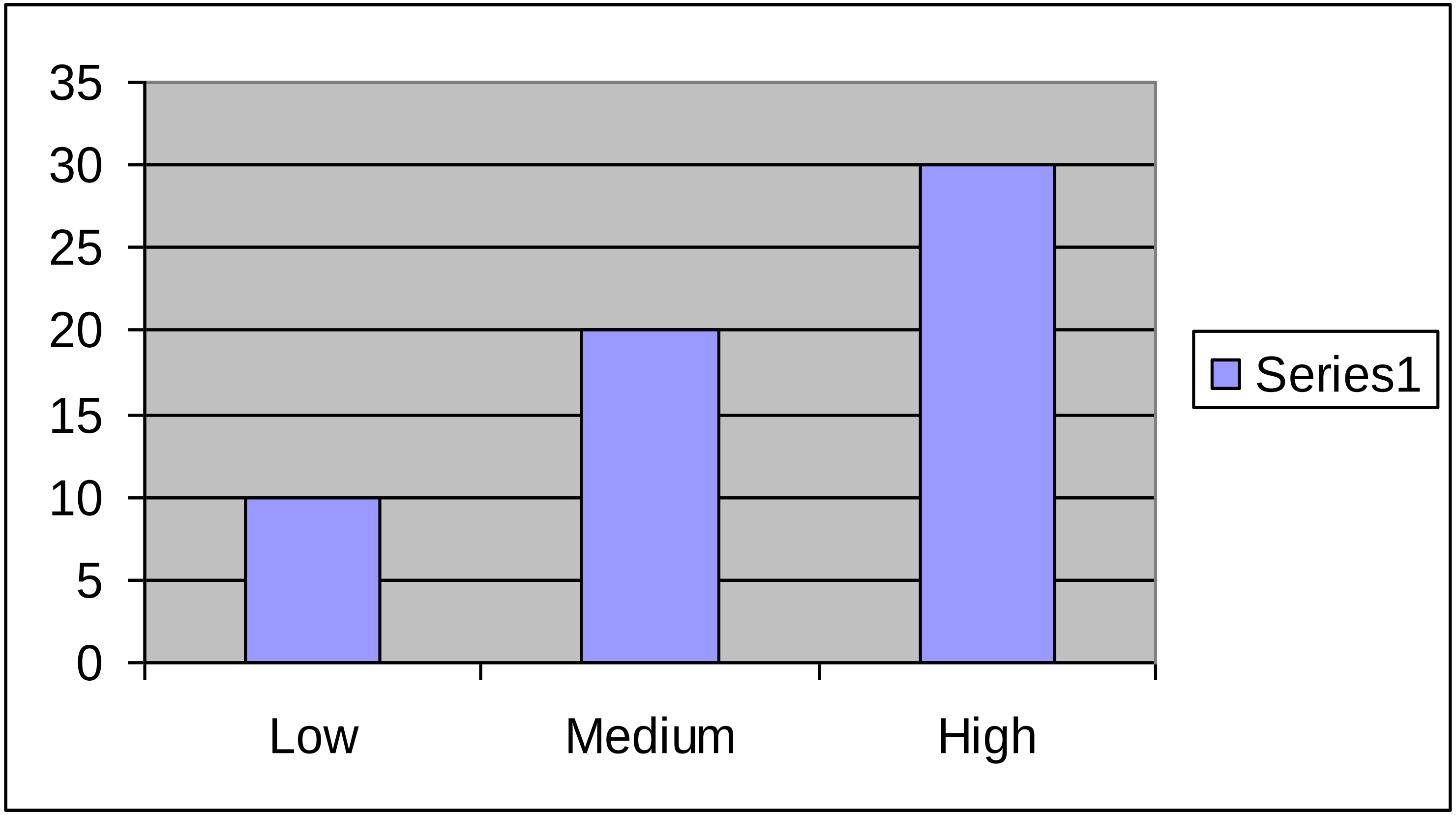
DETERMINING DOSING FREQUENCY

- 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?

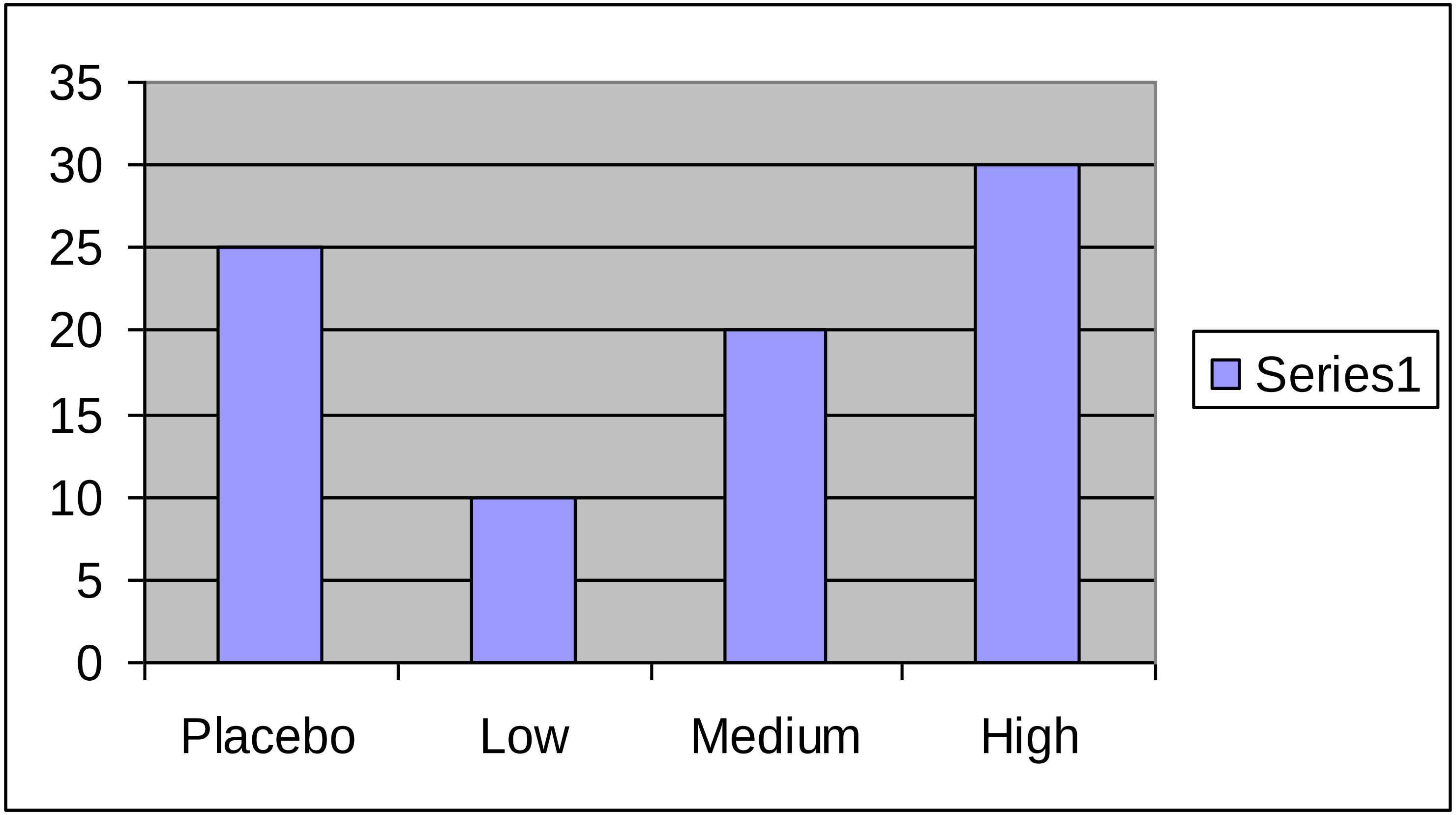
DETERMINING DOSING FREQUENCY



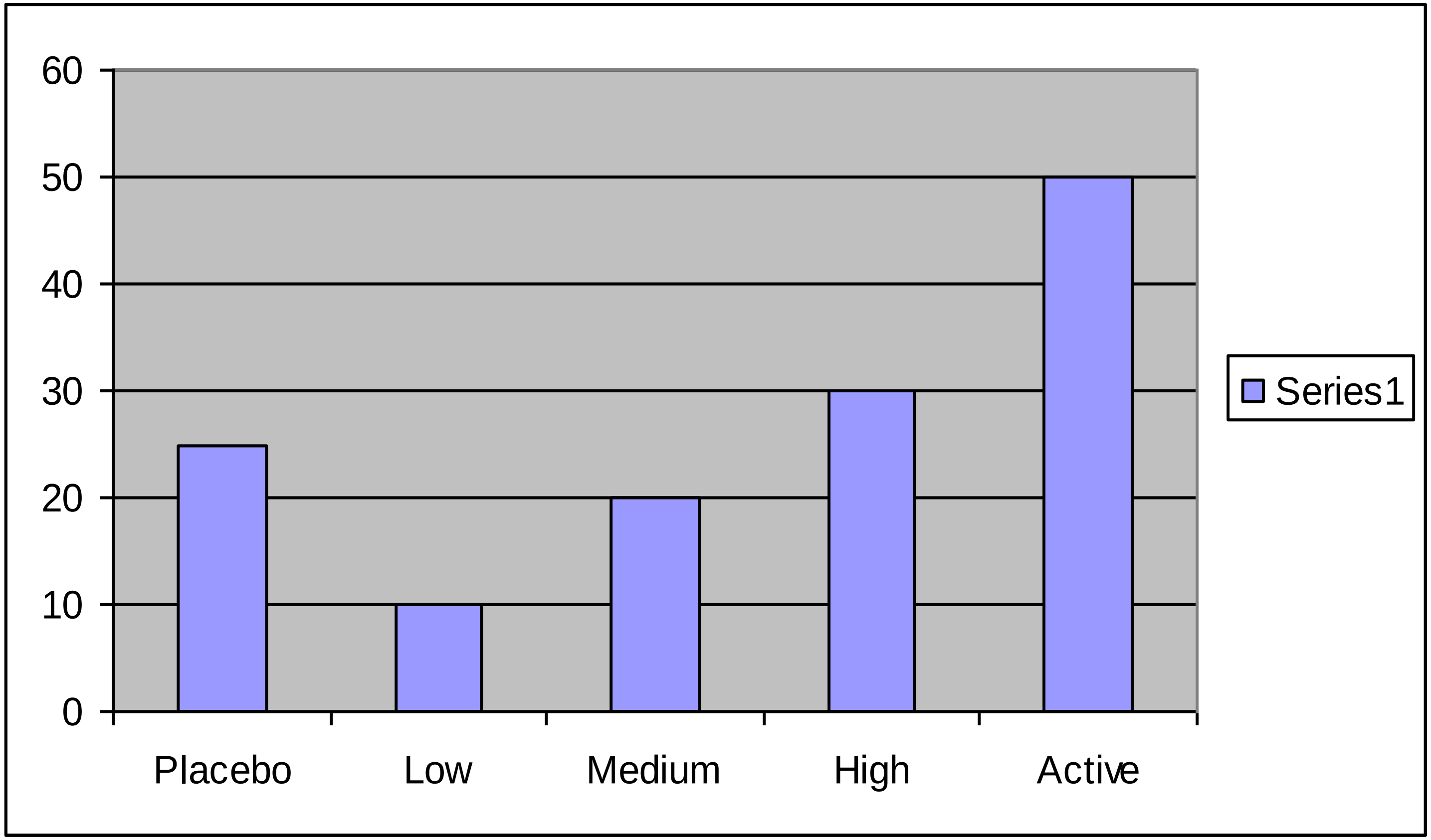
IS THERE A DOSE RESPONSE?



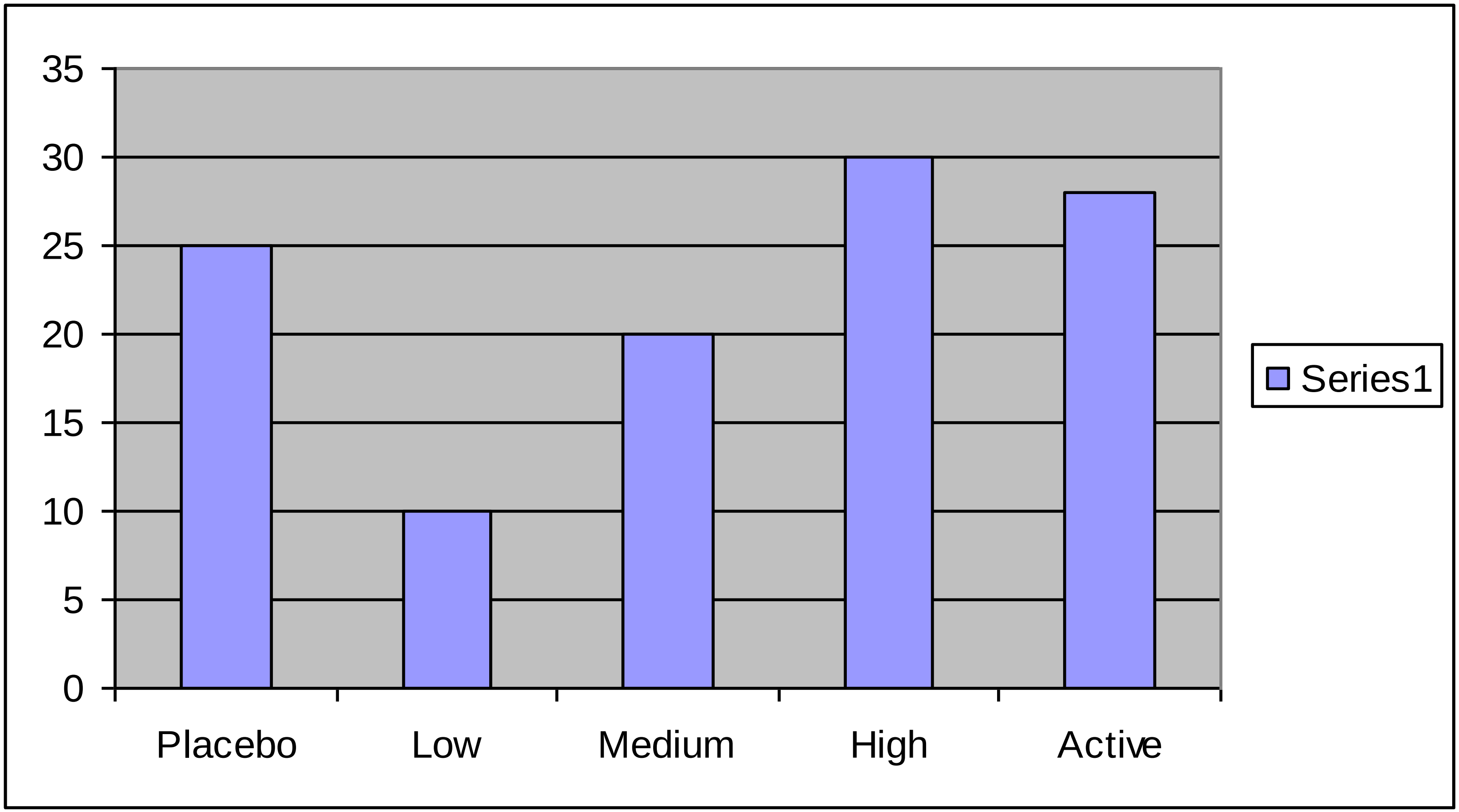
IMPORTANCE OF PLACEBO RESPONSE



ACTIVE CONTROL



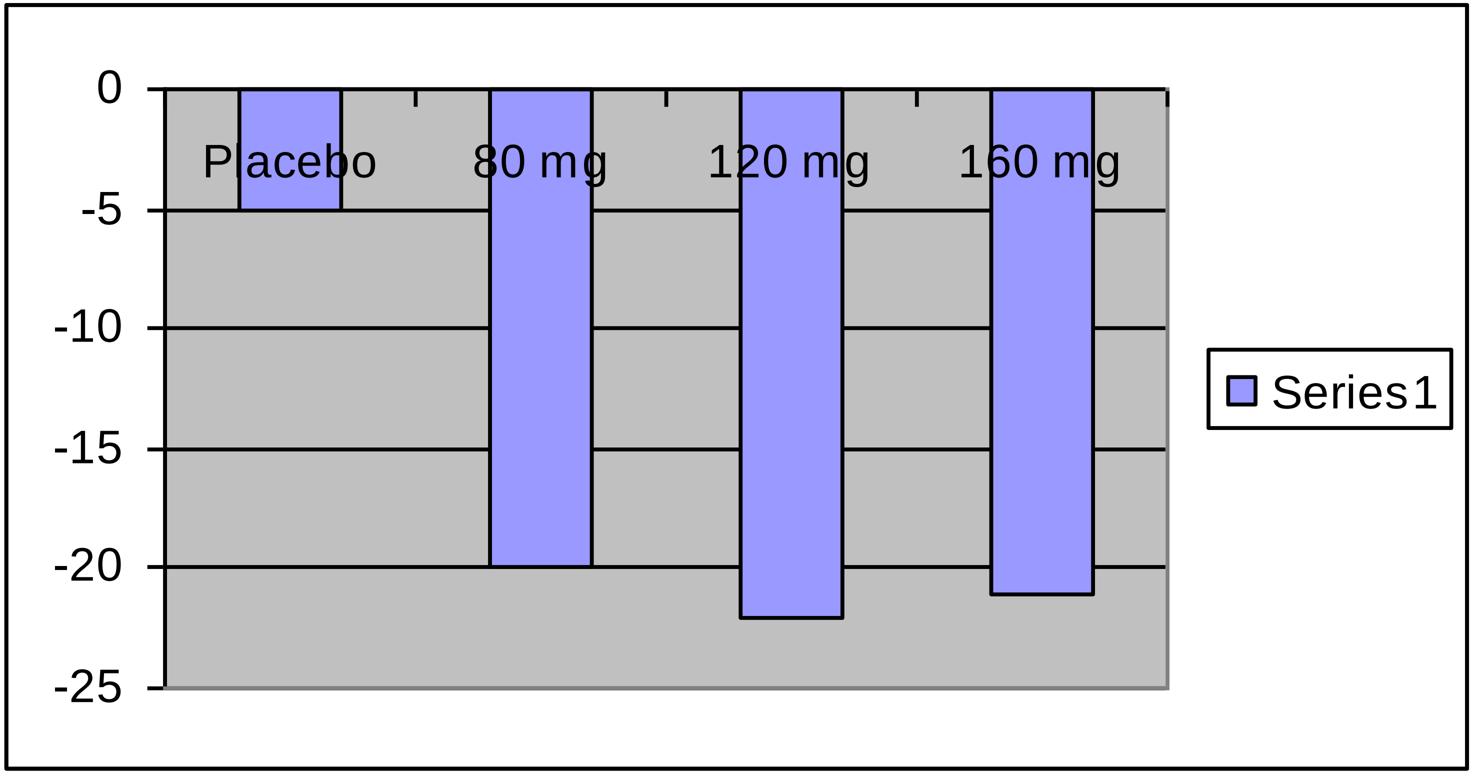
ACTIVE CONTROL



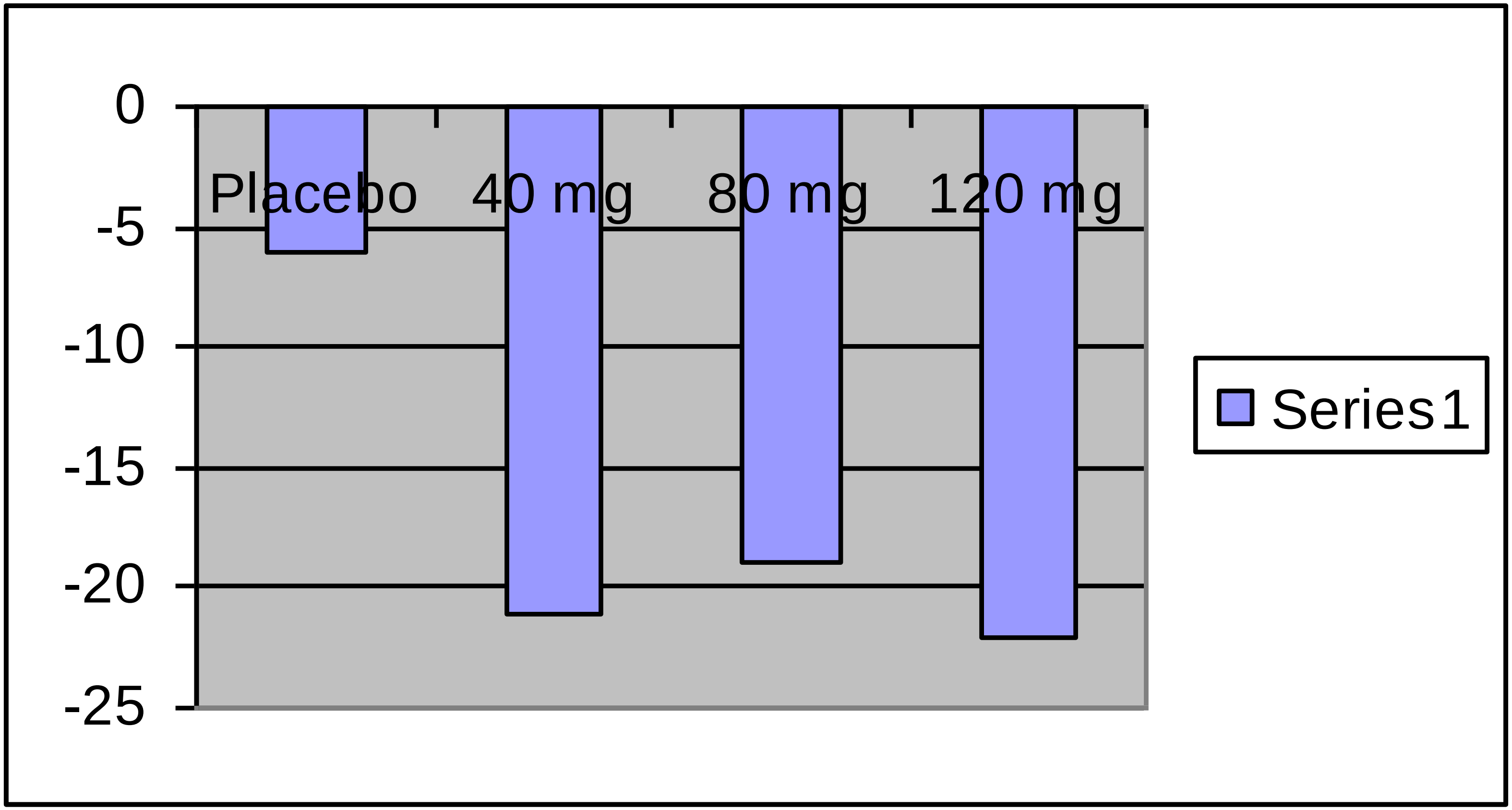
ACTIVE CONTROL

- **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”?

DRUG A
STUDY 1 - WHAT'S NEXT?



DRUG A
STUDY 2 - WHAT'S NEXT?



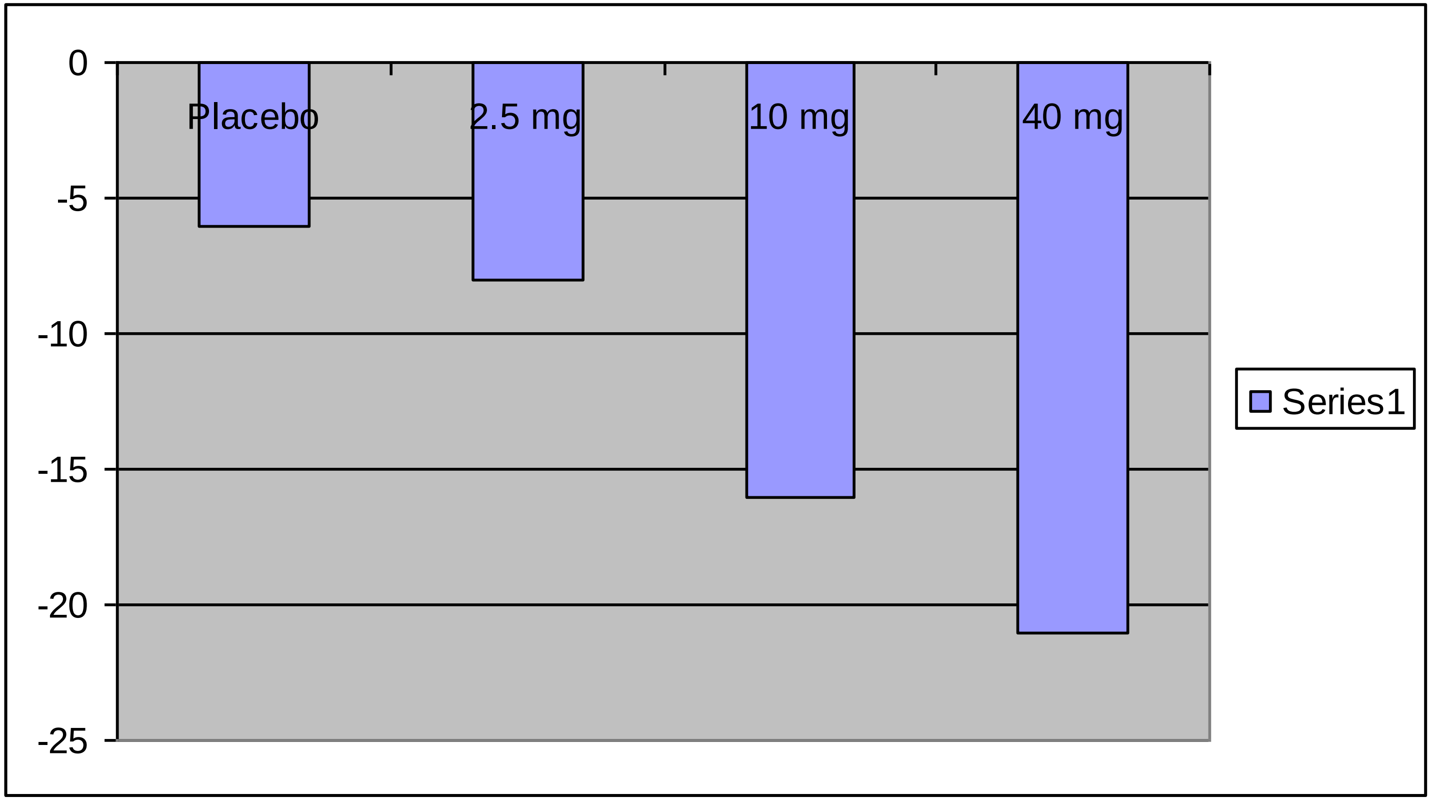
DRUG A

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

DRUG A - STUDY 3



DRUG A

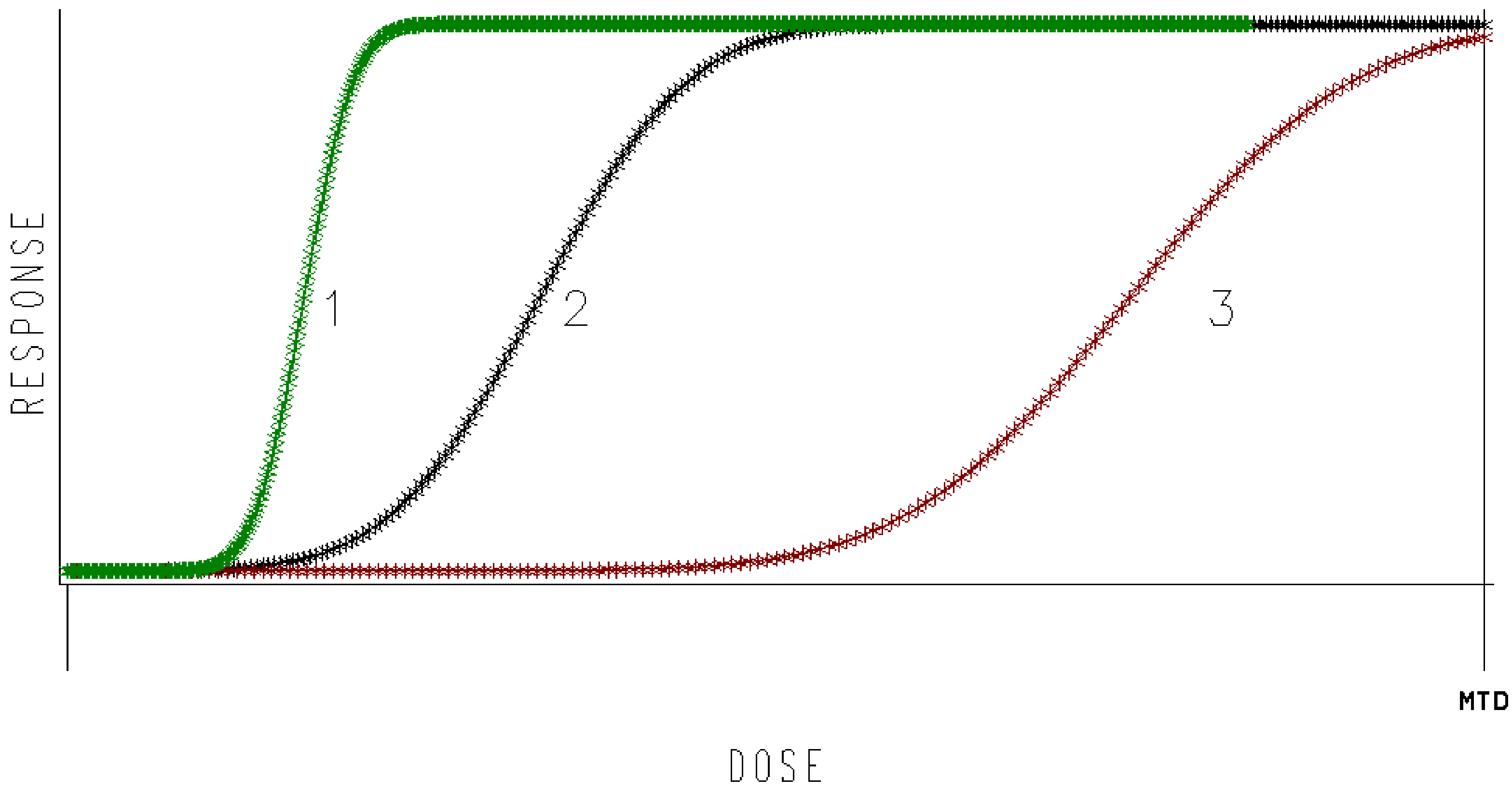
Redesigned Phase III studies with 20 mg and 40 mg

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

FIGURE 4   SEVERAL POSSIBLE DOSE–RESPONSE CURVES



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.

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**

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)

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

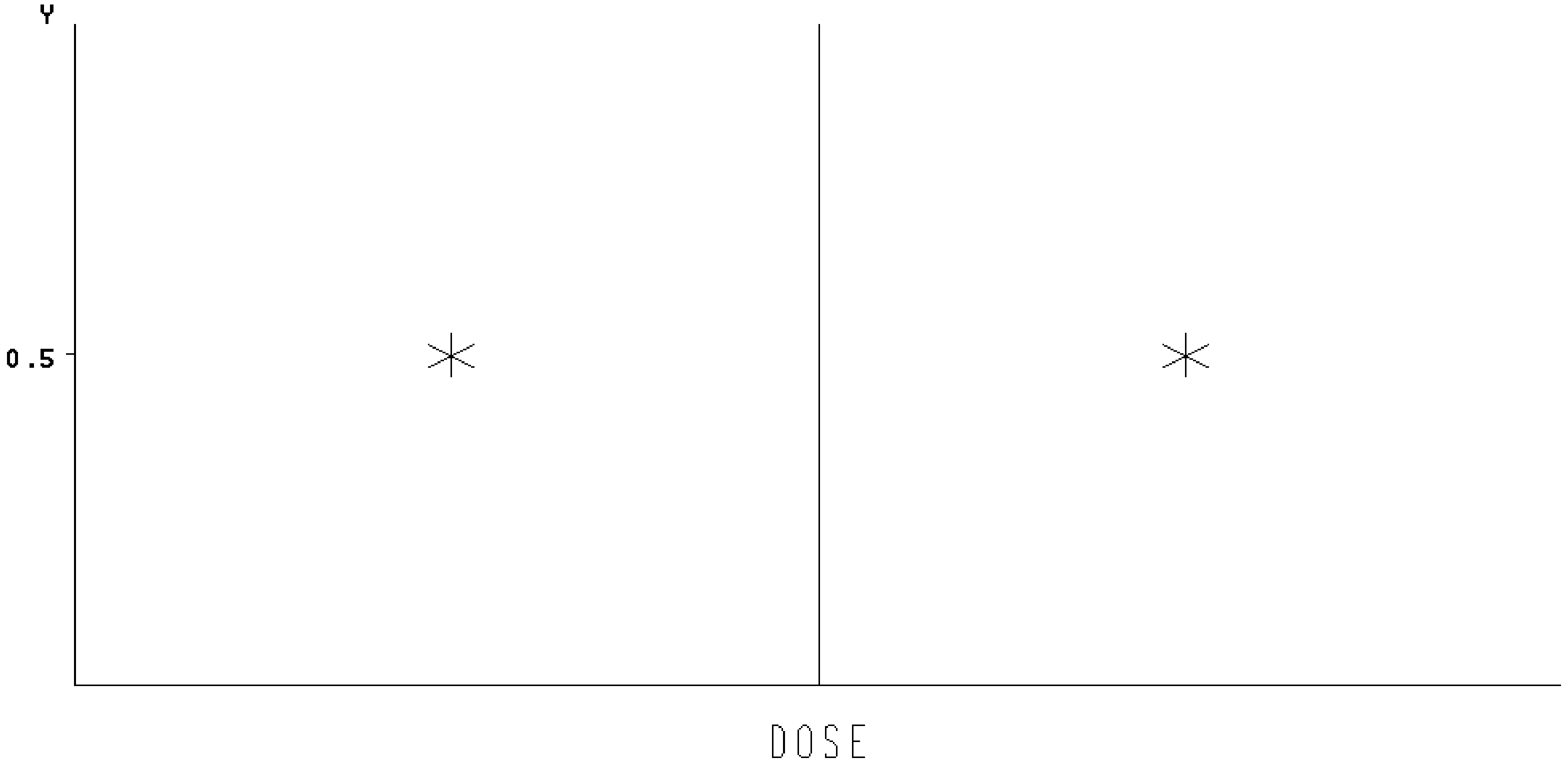
- Multiple center designs
- Formulation considerations
- Placebo and maximally tolerable dose (MTD)
- Incorporate active control?
- Concerns in interpreting titration dose

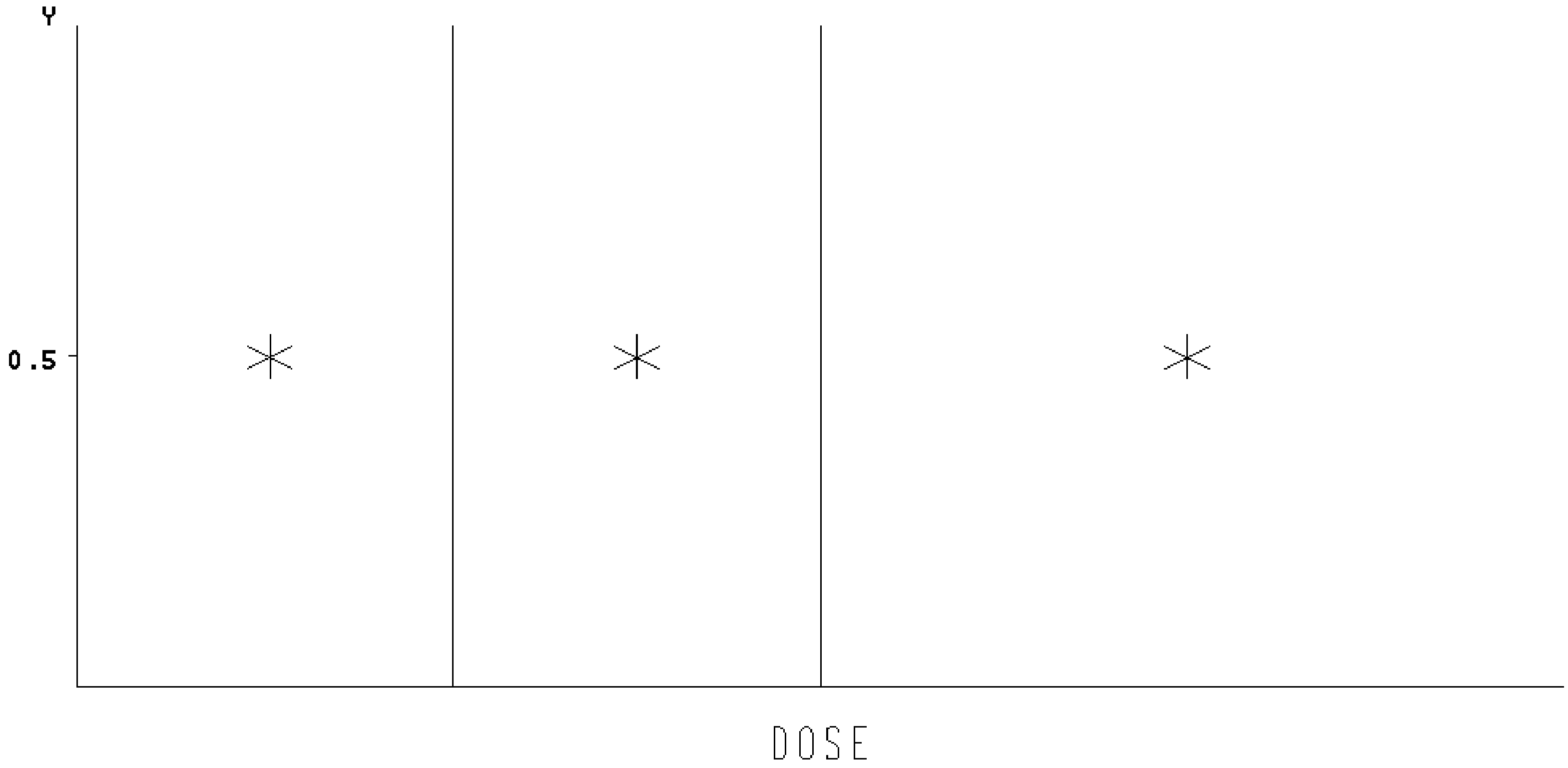
TREATMENT BY CENTER INTERACTION

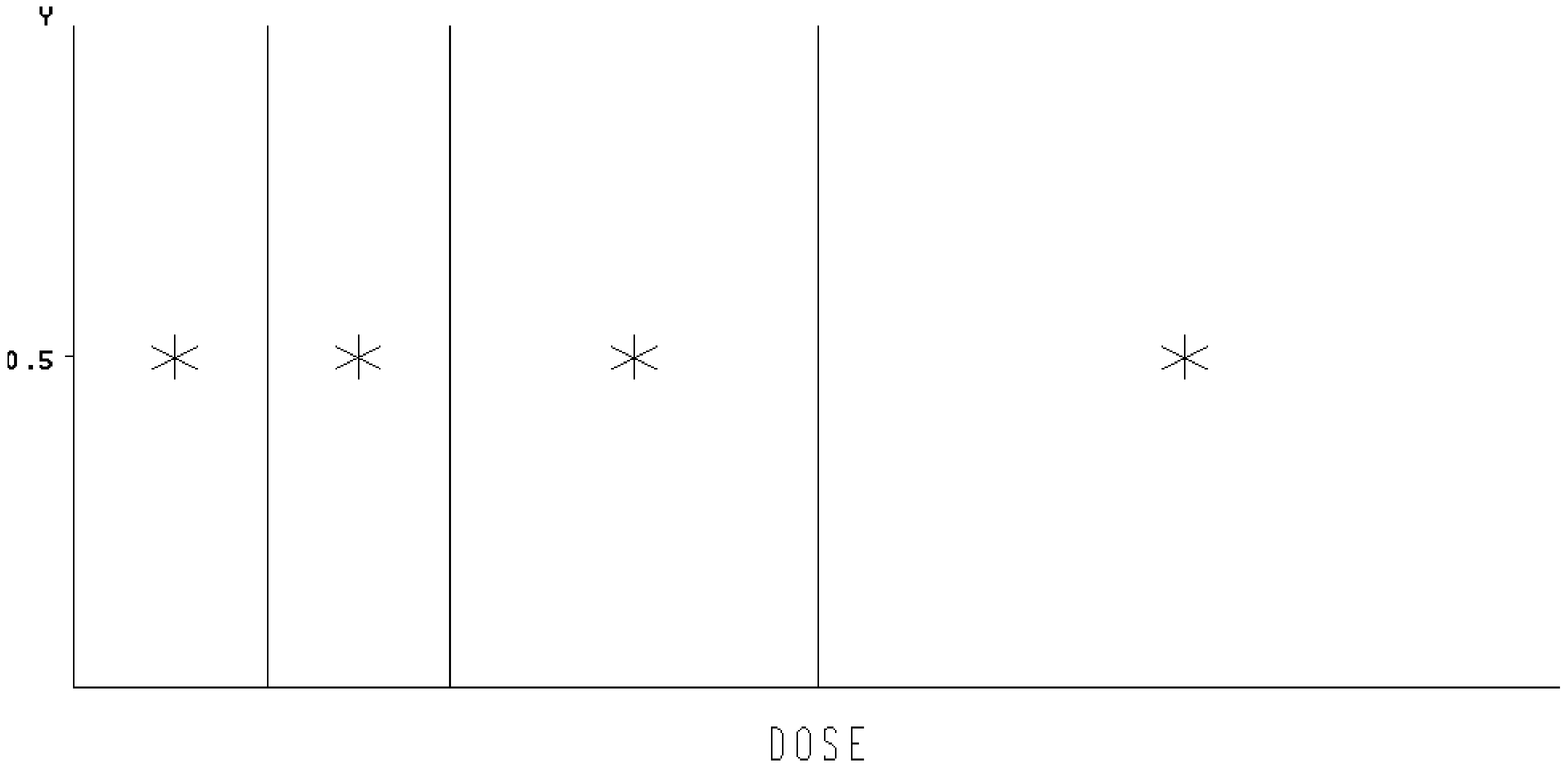
	Placebo	Low	Medium	High
Center 1	6	7	6	8
Center 2	1	1	0	1
Center 3	4	2	3	2

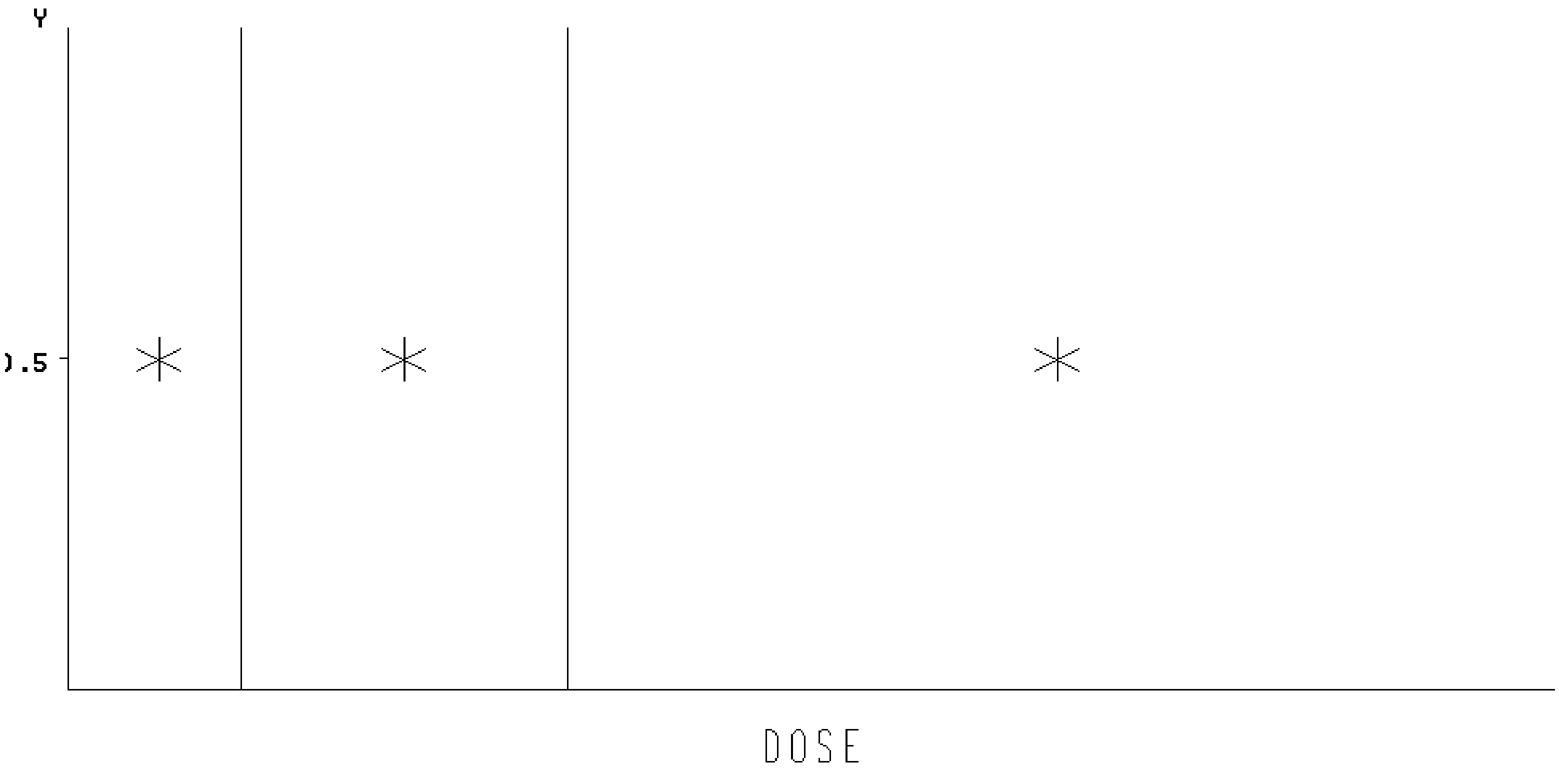
LIMITED NUMBER OF FIXED DOSES

- 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


Y
0.5
DOSE


Y
0.5
DOSE


Y
0.5
DOSE


Y
0.5
DOSE

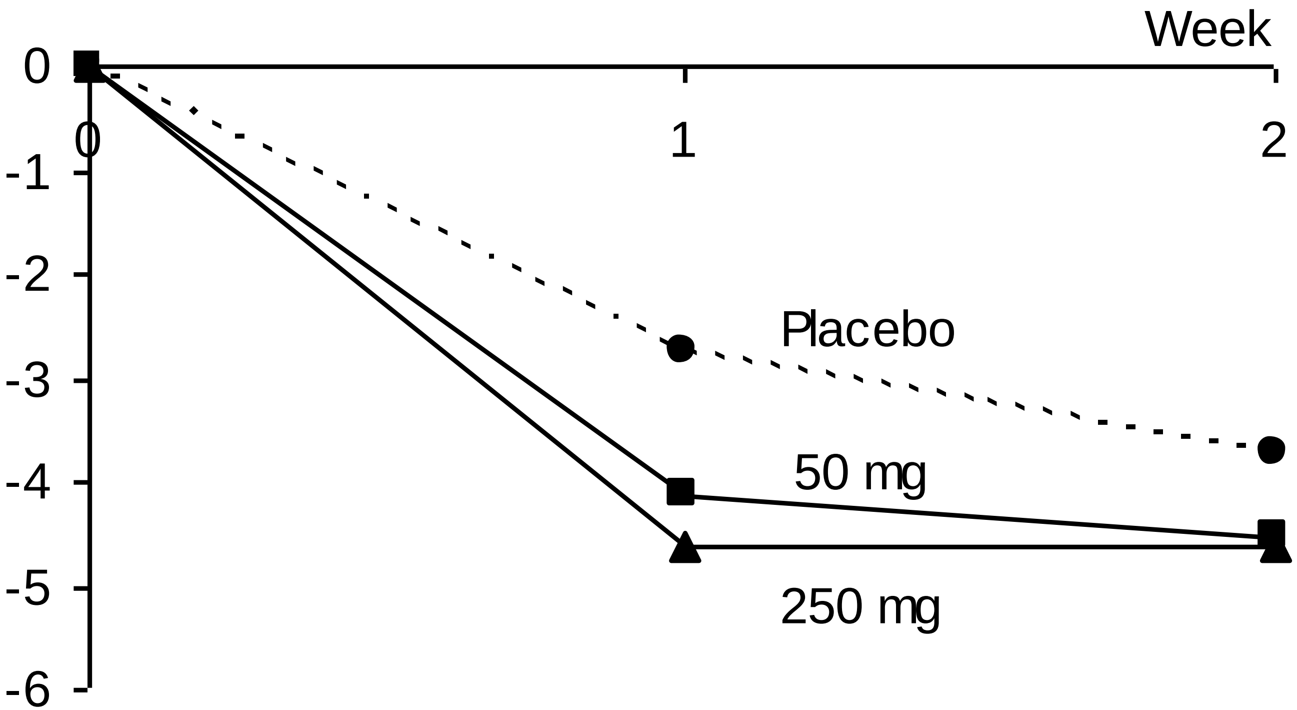
BINARY DOSE SPACING

- **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 ≥ 2**
- **Non-parametric, model independent**
- **Applies to titration design, sequential design, active control, early or late Phase**

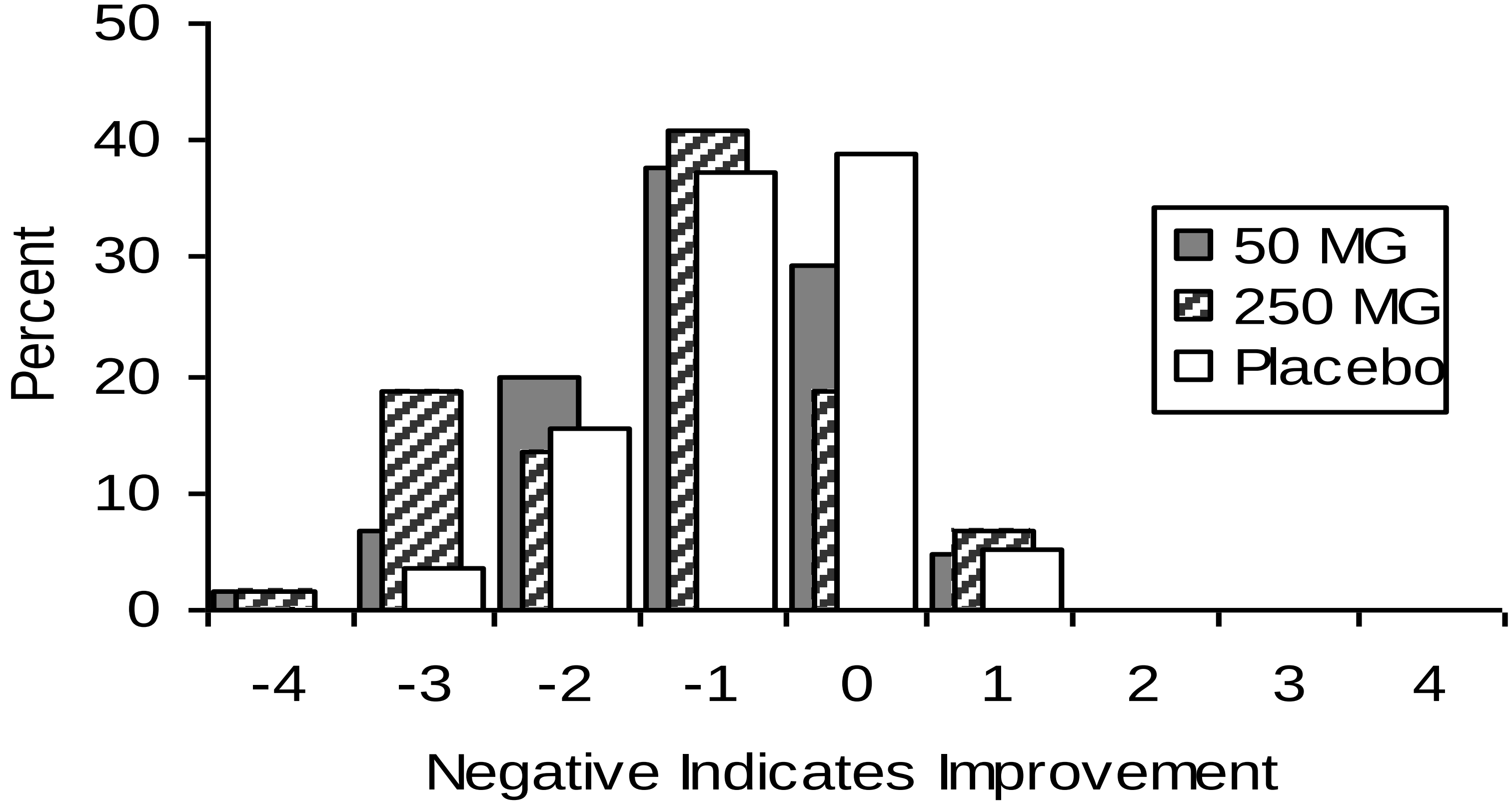
BINARY DOSE SPACING

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

DRUG B: EXPLORATORY STUDY – PRIMARY ENDPOINT



DRUG B: EXPLORATORY STUDY – SECONDARY ENDPOINT



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

DRUG B: DOSE RANGING STUDY DESIGN

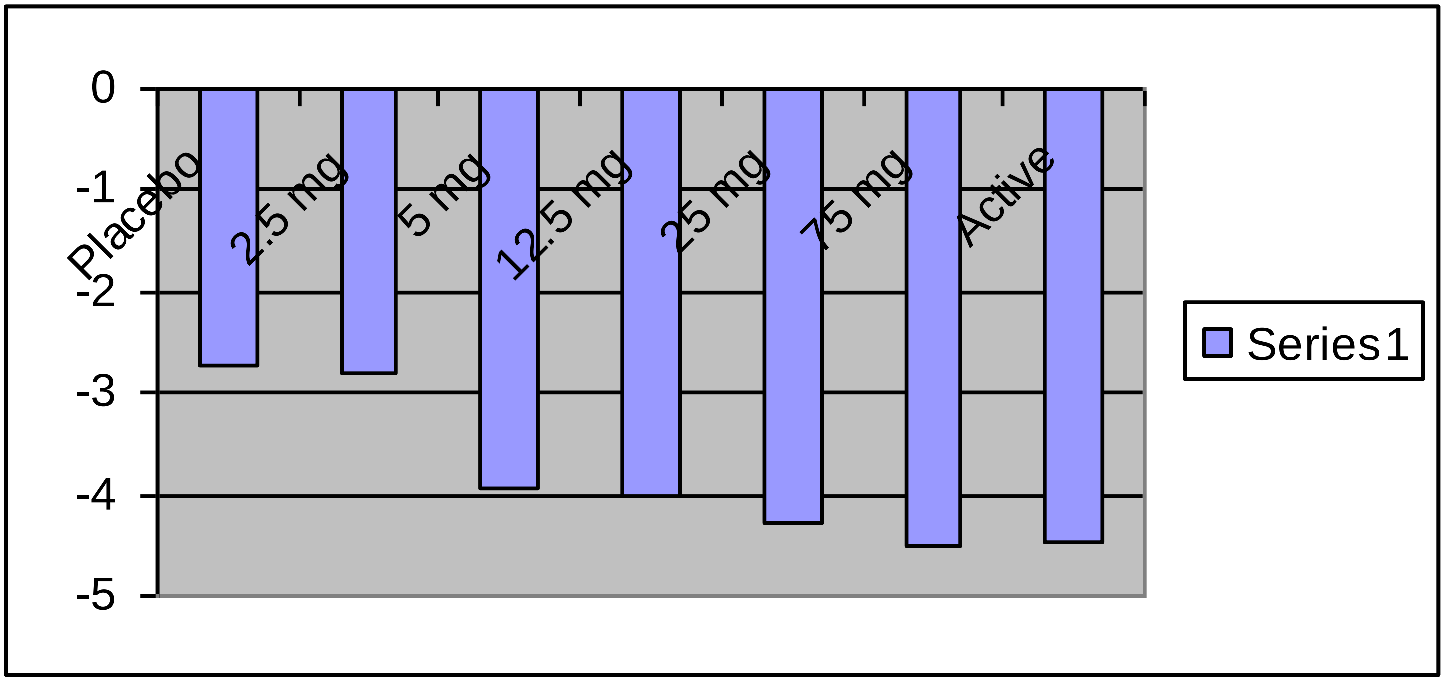
Length of study restricted by toxicity coverage

Placebo controlled

Including an active control

Proposed 5 test doses – 2.5 mg, 5 mg, 12.5 mg, 25 mg and 75 mg

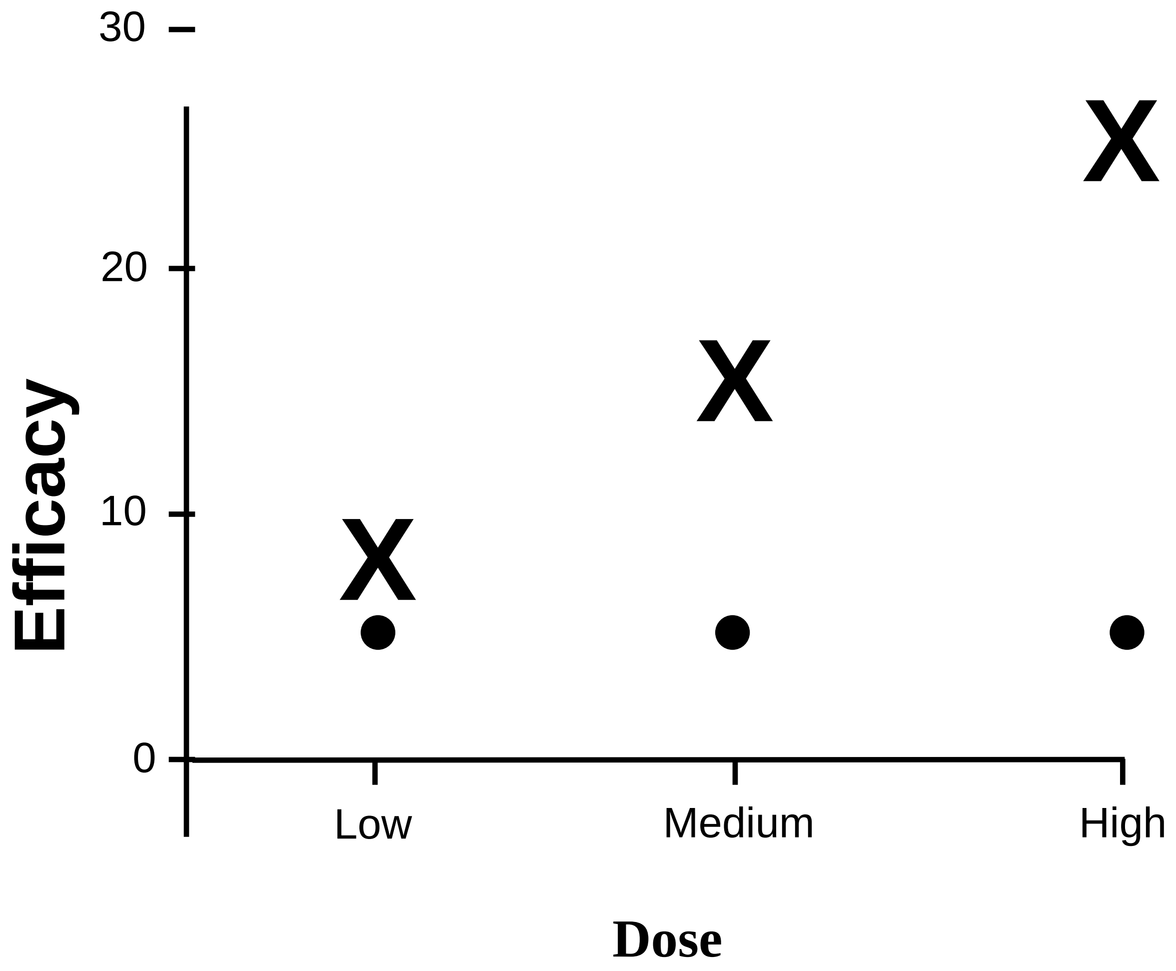
DRUG B
STUDY RESULTS



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

MULTIPLE ENDPOINTS



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)

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

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?

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

MULTIPLE COMPARISONS

Consider a dose response study with high and low dose against placebo

2 comparisons each dose vs placebo

Bonferroni is to divide α by 2

Gate-keeping

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

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

MULTIPLE COMPARISONS

Experimentwise error (EWE)

Familywise error (FWE)

Comparisonwise error (CWE)

Pairwise error (PWE)

MULTIPLE COMPARISON ADJUSTMENT

Bonferroni procedure

Product Inequality

Pre-determined step down (Gate keeping)

Sample determined step down

Sample determined step up

BONFERRONI PROCEDURE

If there are k comparisons, then each comparison is tested at α/k level

In dose response studies with k dose groups against placebo, each dose is compared with placebo

For these k comparisons, each is tested at α/k

USING PRODUCT INEQUALITY

Assuming independence among comparisons

For k comparisons, each is tested at $1-(1-\alpha)^{1/k}$

Again, in dose response studies with k doses and placebo, each dose against placebo is tested at $1-(1-\alpha)^{1/k}$

DUNNETT'S PROCEDURE

Compare unordered doses with control

Assuming continuous data with normal distribution

Dunnett provides a critical value for all k comparisons

If the dose with largest t is significant at α under the joint distribution of all k comparisons, then that dose is diff from placebo

Step down to the second largest t, compare with joint distribution of k-1 comparisons

…

DUNNETT'S PROCEDURE

The dose with the second largest t will be compared with Dunnett's critical value of the other k-1 groups

Continue until the dose with smallest t

This is a sample determined step down

Can be viewed as a partition testing

HOLM'S STEP DOWN

Divide α by number of remaining tests (k)

If the dose with the smallest p-value is less than α/k, then claim that dose is different from placebo

Compare the dose with second smallest p-value with $\alpha/(k-1)$

Continue this procedure until the dose with largest p-value

HOCHBERG'S STEP UP

Compare the largest p-value with α, if significant, then claim all doses are different from placebo

If not, then compare the next largest p-value with $\alpha/2$. If significant, then claim all k-1 doses are different from placebo (except for the dose with largest p)

HOCHBERG'S STEP UP

If not significant, then compare the 3rd largest p-value with $\alpha/3$. If significant, then claim k-2 doses are different from placebo (except for the doses with larger p-values).

Continue until all p-values are compared

PRE-DETERMINED STEP DOWN (GATE KEEPING)

Test high dose = placebo at α

If significant, then test medium dose = placebo at α

If not, stop

Continue to low dose …

Most powerful if dose response is monotonic

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

QIQI DENG

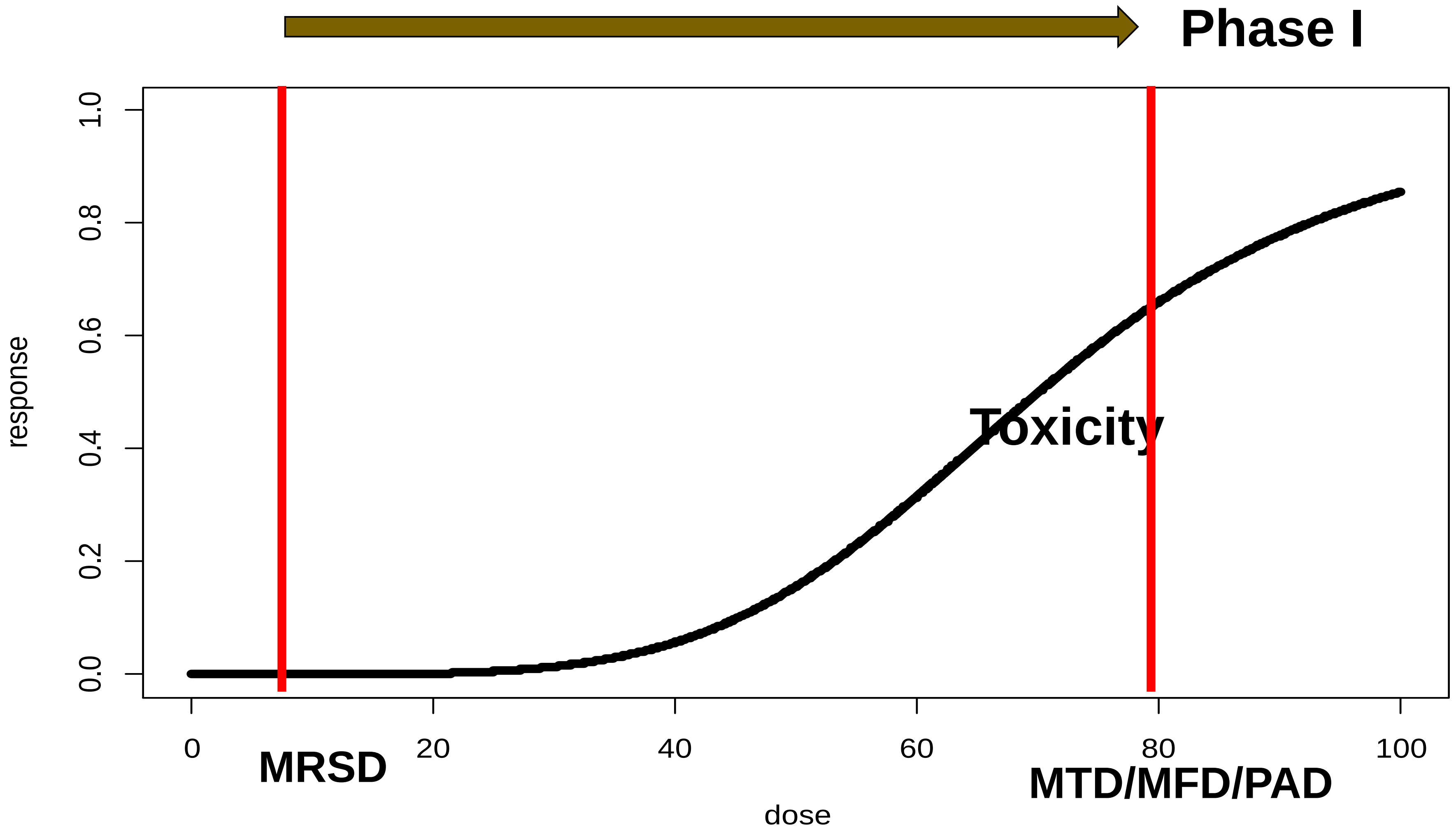
BOEHRINGER-INGELHEIM

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.

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

OBJECTIVE FOR PHASE I DOSE FINDING



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)**

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

DOSE SELECTION FOR FIH

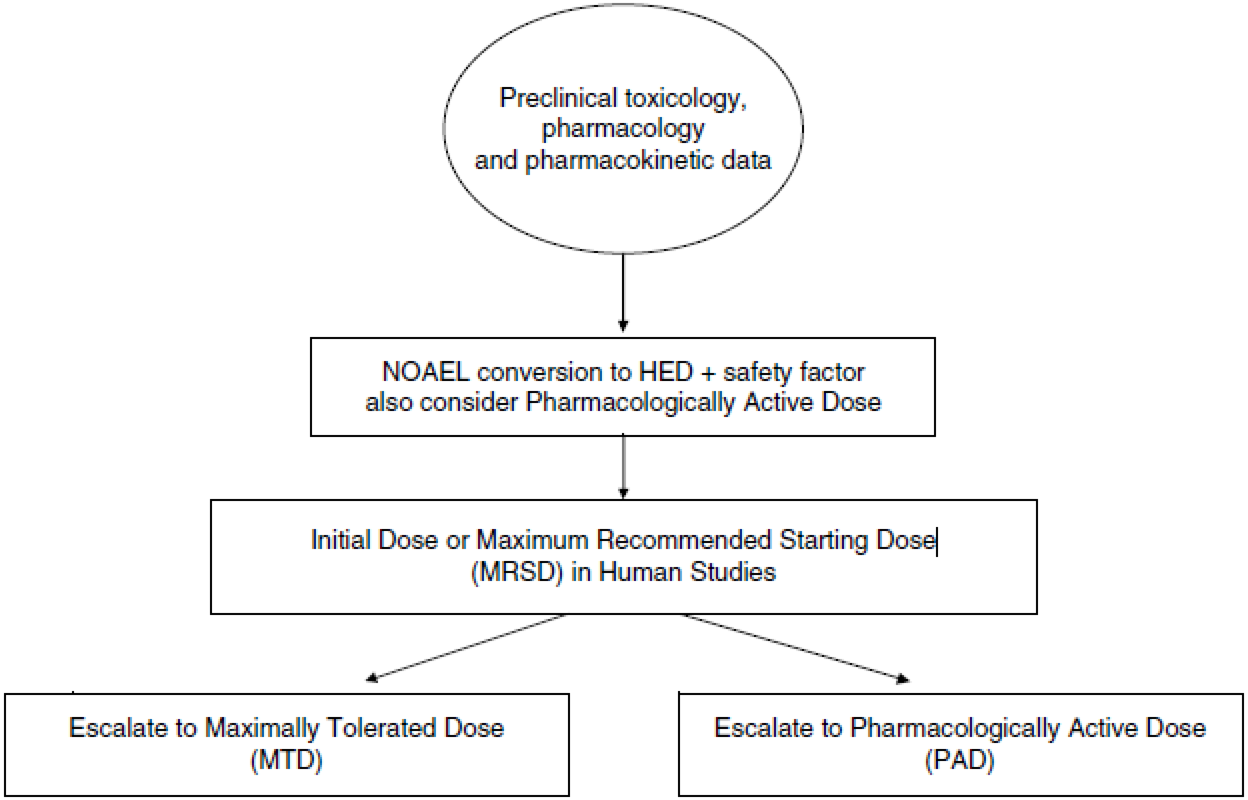


Figure 3.3. Overview of dose selection for FIH studies.

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.**

PD MARKER OR CLINICAL ENDPOINT

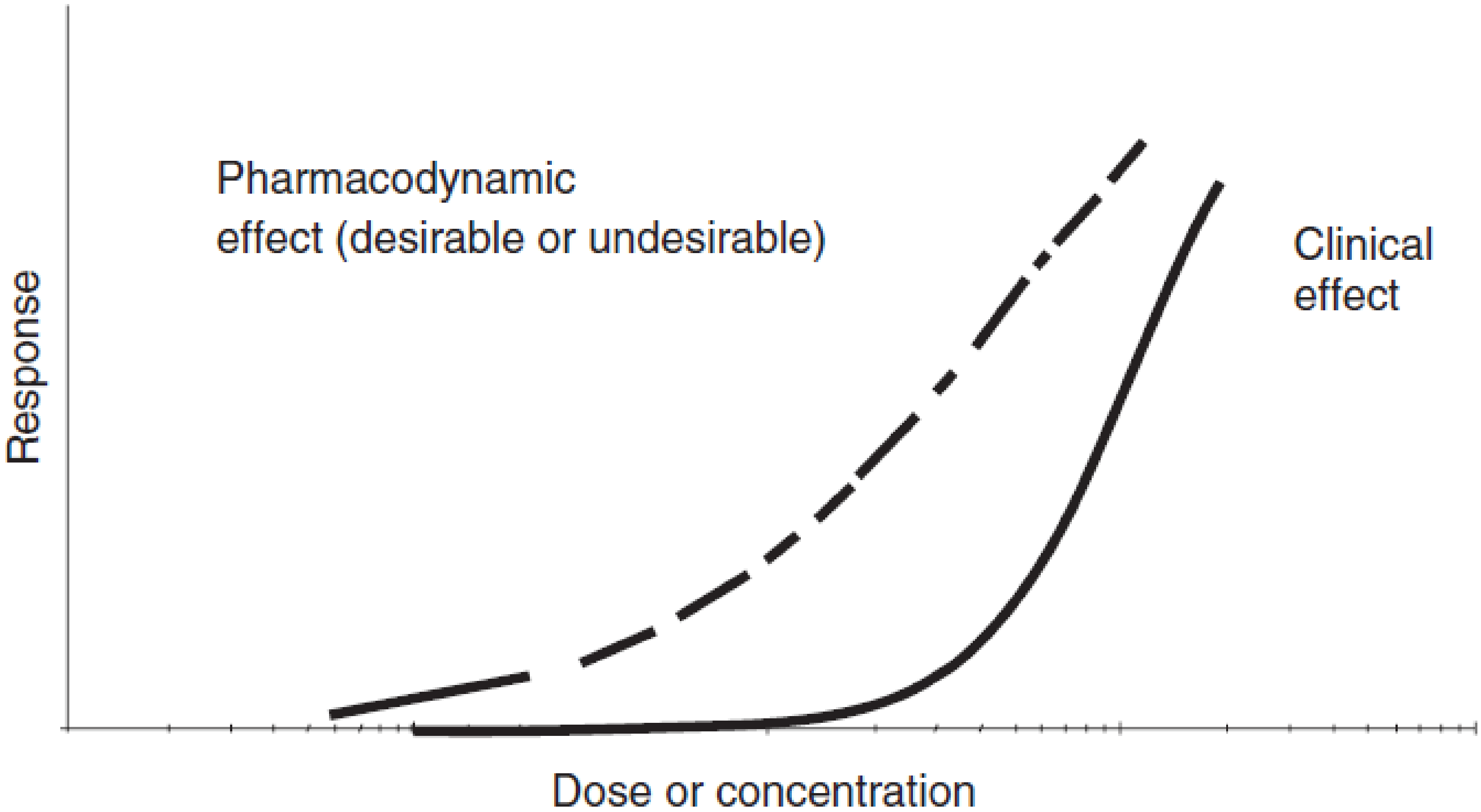


Figure 3.4. PD effect vs. clinical efficacy dose– or exposure–response relationships.

PHASE I DESIGN
IN HEALTHY VOLUNTEER

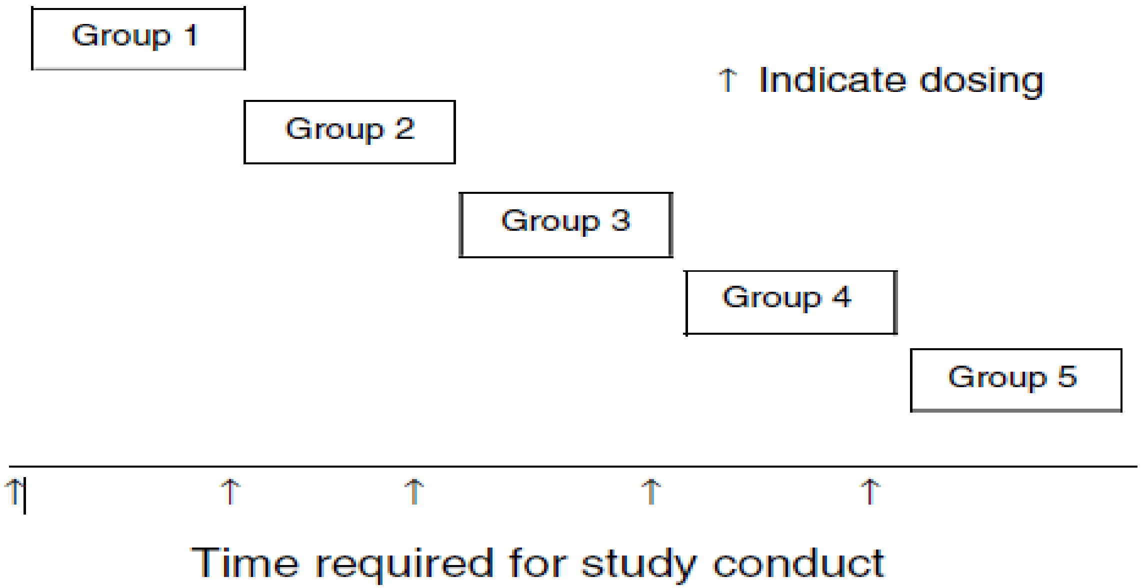


Figure 3.2. Parallel-group, placebo-controlled, randomized, double-blind ascending dose Phase I study design.

SRD: Single rising study

MRD: Multiple rising study

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 >=Grade 3, or treatment related hematological toxicity >= Grade 4.

- **=> RP2D are often close to MTD (γ), where**

$$Prob\{DLT|Dose = \gamma\} = \theta$$

SELECTION OF DOSE FOR ONCOLOGY

- **Too low a starting dose or slow escalation is a concern**
- **Murine LD_{10}: Dose with approximately 10% mortality mice**
- **1/10 or 2/10 of murine equivalent of LD_{10} (milligrams per m^2) 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)

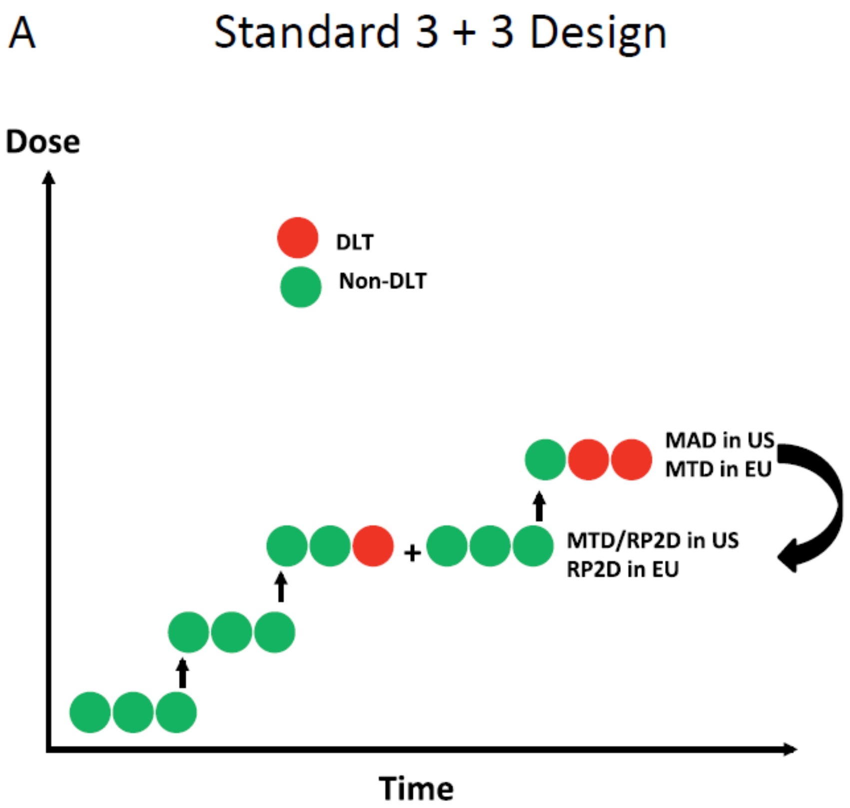
PHASE I DESIGN FOR ONCOLOGY

- **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)

ILLUSTRATION OF 3+3 DESIGN



Phase 1 Trial Design: Is 3 + 3 the Best?

Aaron R. Hansen, MBBS, Donna M. Graham, MBBCh, Gregory R. Pond, PhD, and Lillian L. Siu, MD

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

BLRM (BAYESIAN LOGISTIC REGRESSION MODEL)

Two-parameter model, dose as continuous variable

$$\mathbf{logit}\big(\boldsymbol{p}(\boldsymbol{d})\big) = \mathbf{log}\boldsymbol{\alpha} + \boldsymbol{\beta}\mathbf{log}(\frac{\boldsymbol{d}}{\boldsymbol{d}^*})$$

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

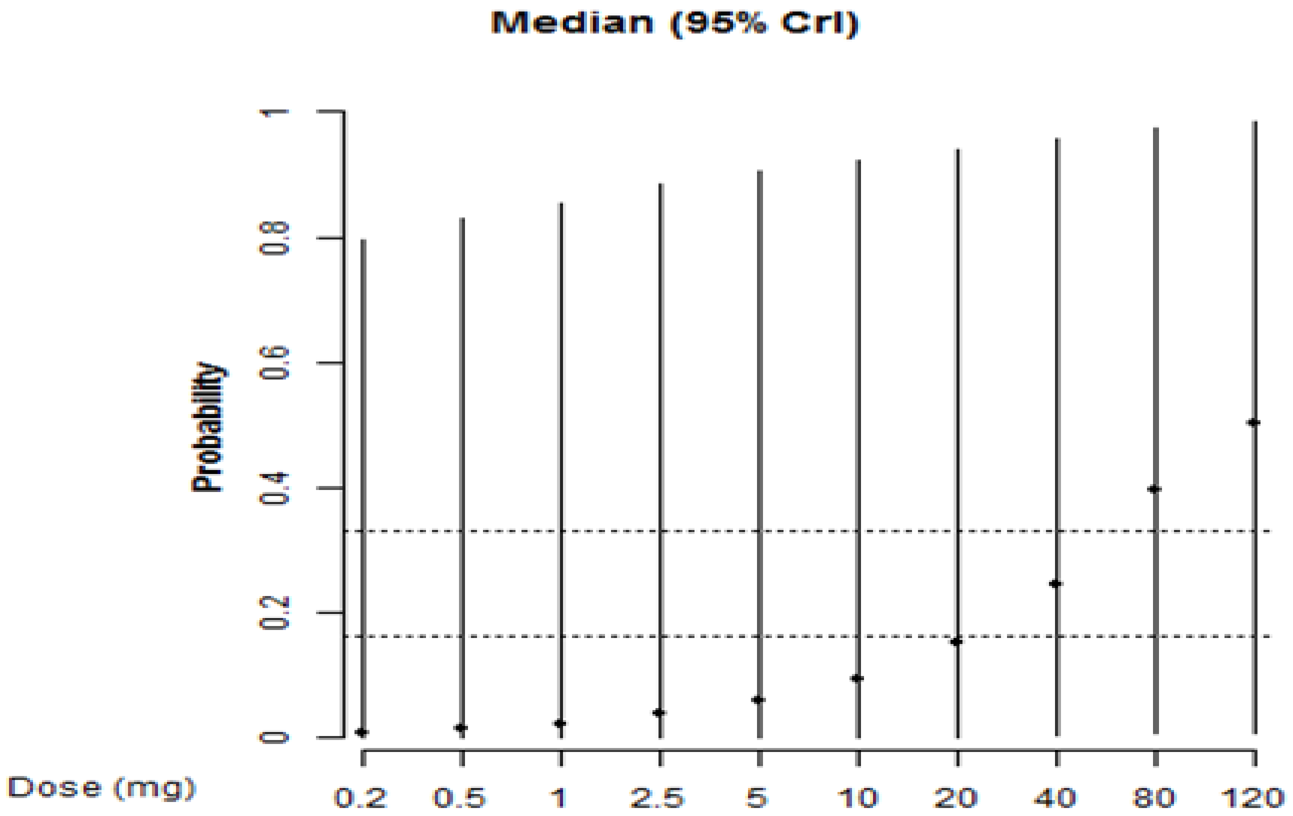
d^*: **reference dose**

α: **intercept, odds of a DLT at d***

β: **slope, steepness of curve**

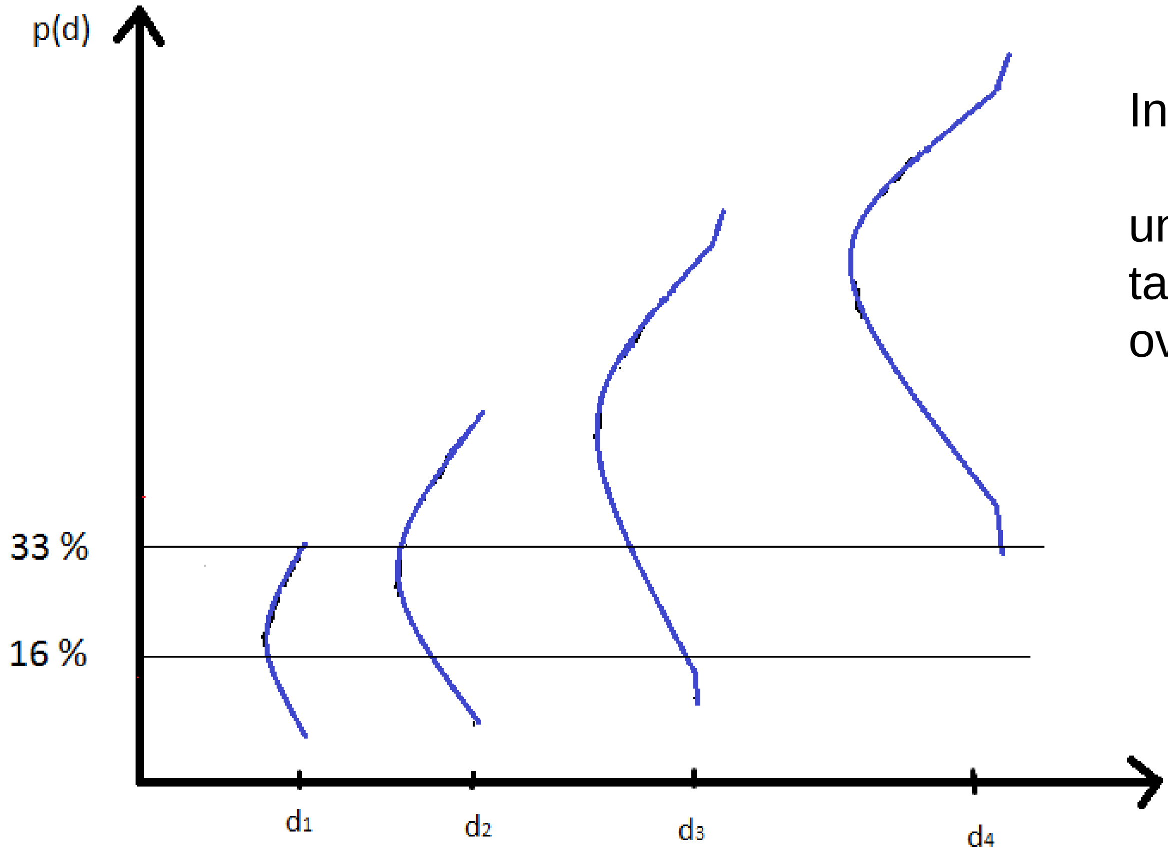
Neuenschwander et al (2008), Statist.Med. 27: 2420-2439

PLOTS



Median (95% CrI)
Probability
0
0.2
0.4
0.6
0.8
1
Dose (mg)
0.2
0.5
1
2.5
5
10
20
40
80
120

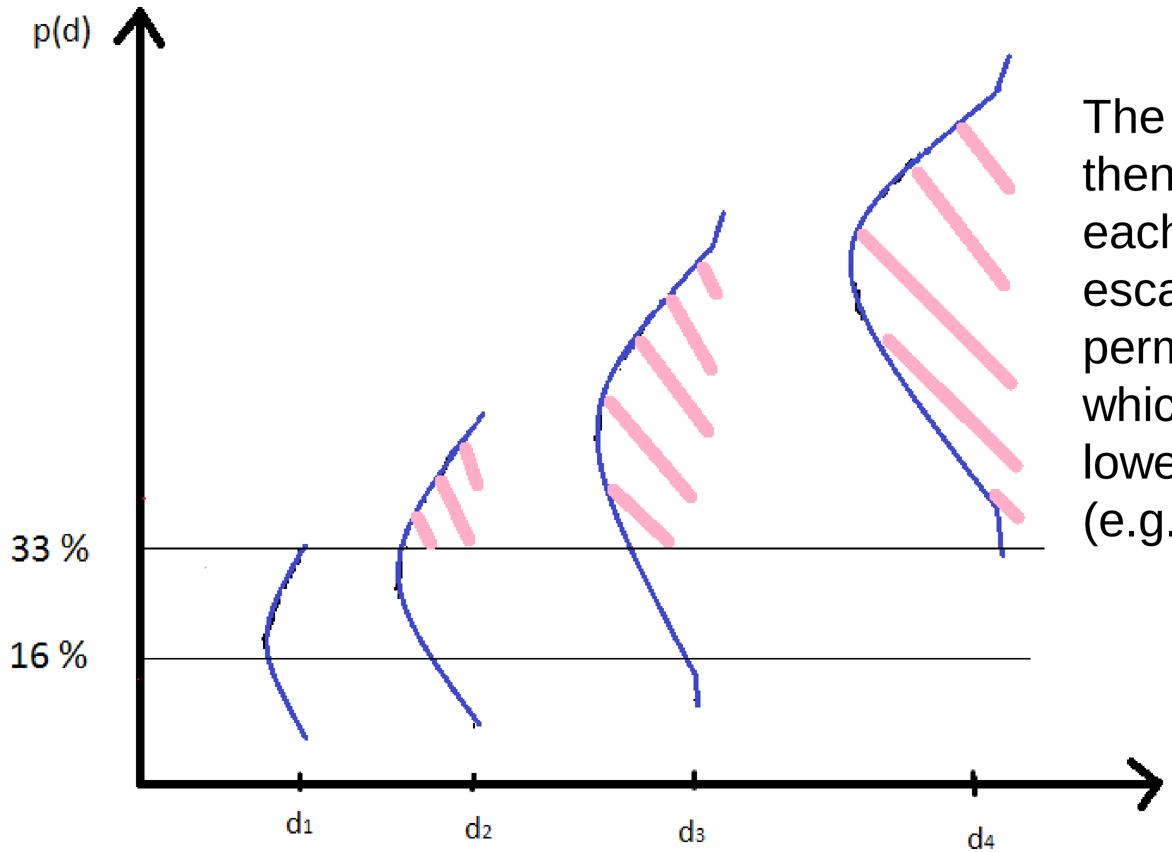
ESCALATION: INTERVALS OF INTEREST



Intervals of interest:

underdose : <16%
target dose: [16%-33%)
overdose : ≥ 33%

ESCALATION WITH OVERDOSE CONTROL (EWOC)



The overdose risk will then be calculated for each dose and escalation will be permitted to all doses for which this probability is lower than a boundary (e.g. 25%)

ESCALATION

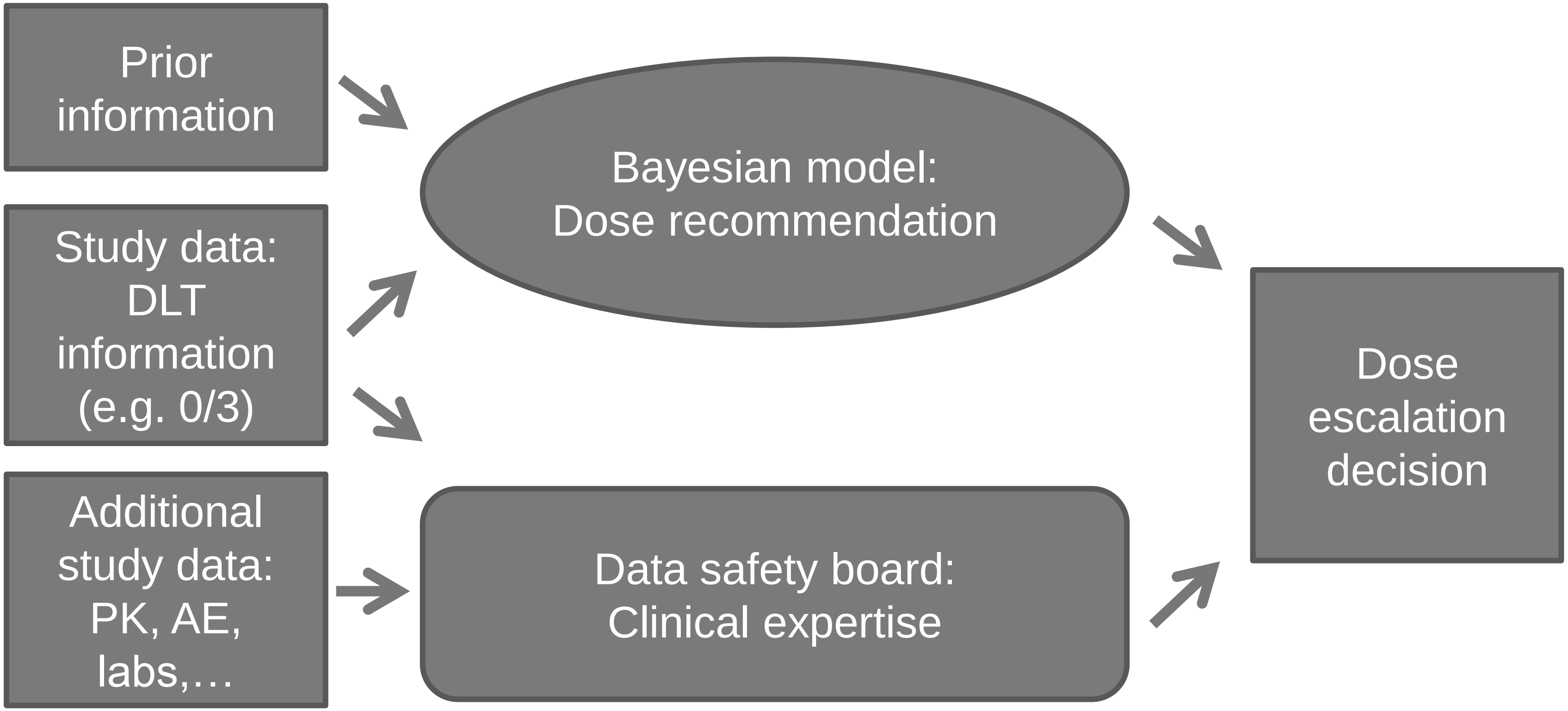
Overdose control: Probability for overdosing should be less than 25%

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

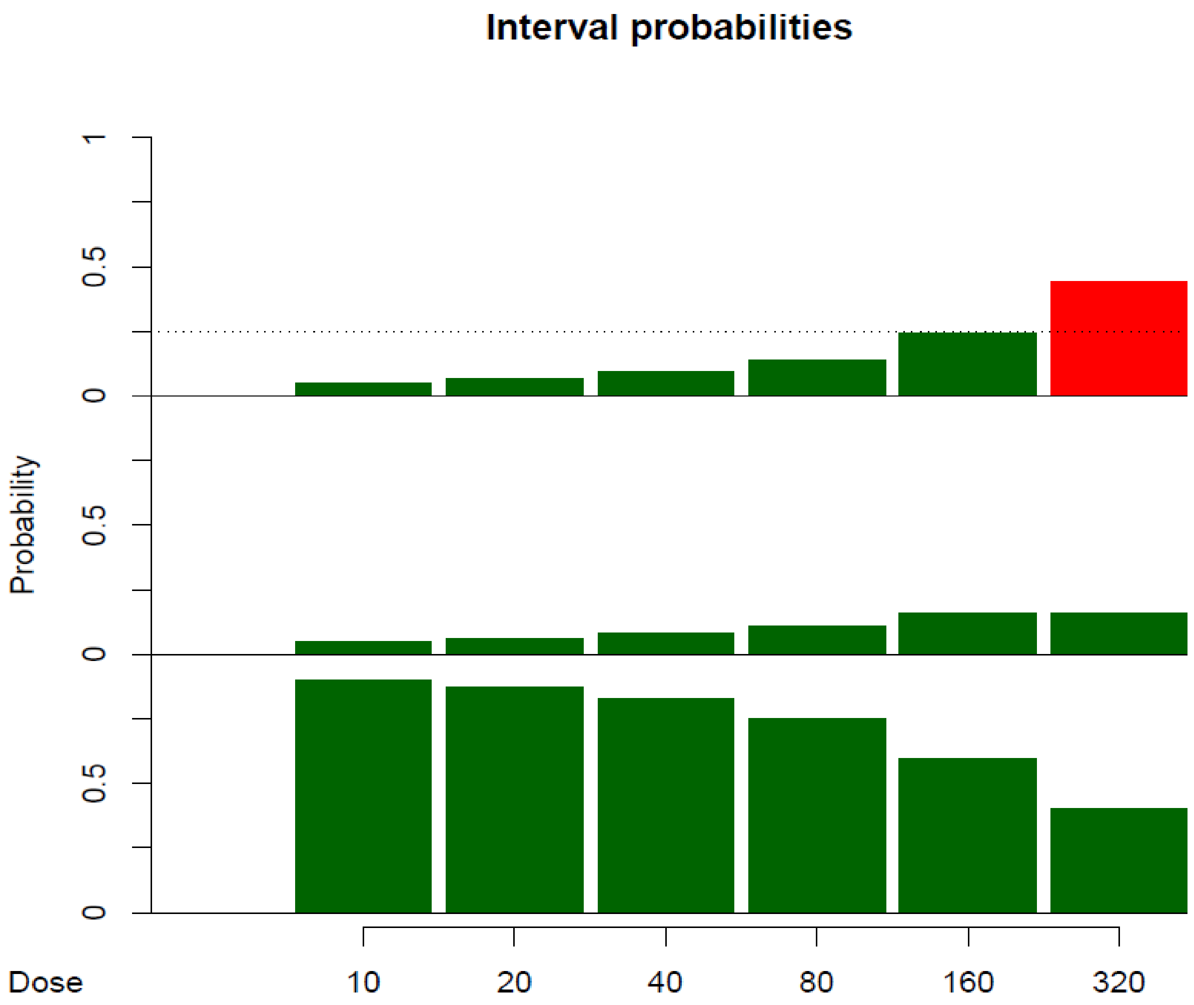
- In-between dose levels are possible

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

DECISION – COMBINATION OF CLINICAL AND STATISTICAL EXPERTISE



ESCALATION



Probability of overtoxicity

Probability of target toxicity

Probability of undertoxicity

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

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

Protective:	No interaction:	Synergism:
The toxic effect of the drug combination is **less** than that obtained if the drugs act independently in the body.	The toxic effect of the drug combination is **equal** to that obtained if the drugs act independently in the body.	The toxic effect of the drug combination is **greater** than that obtained if the drugs act independently in the body.

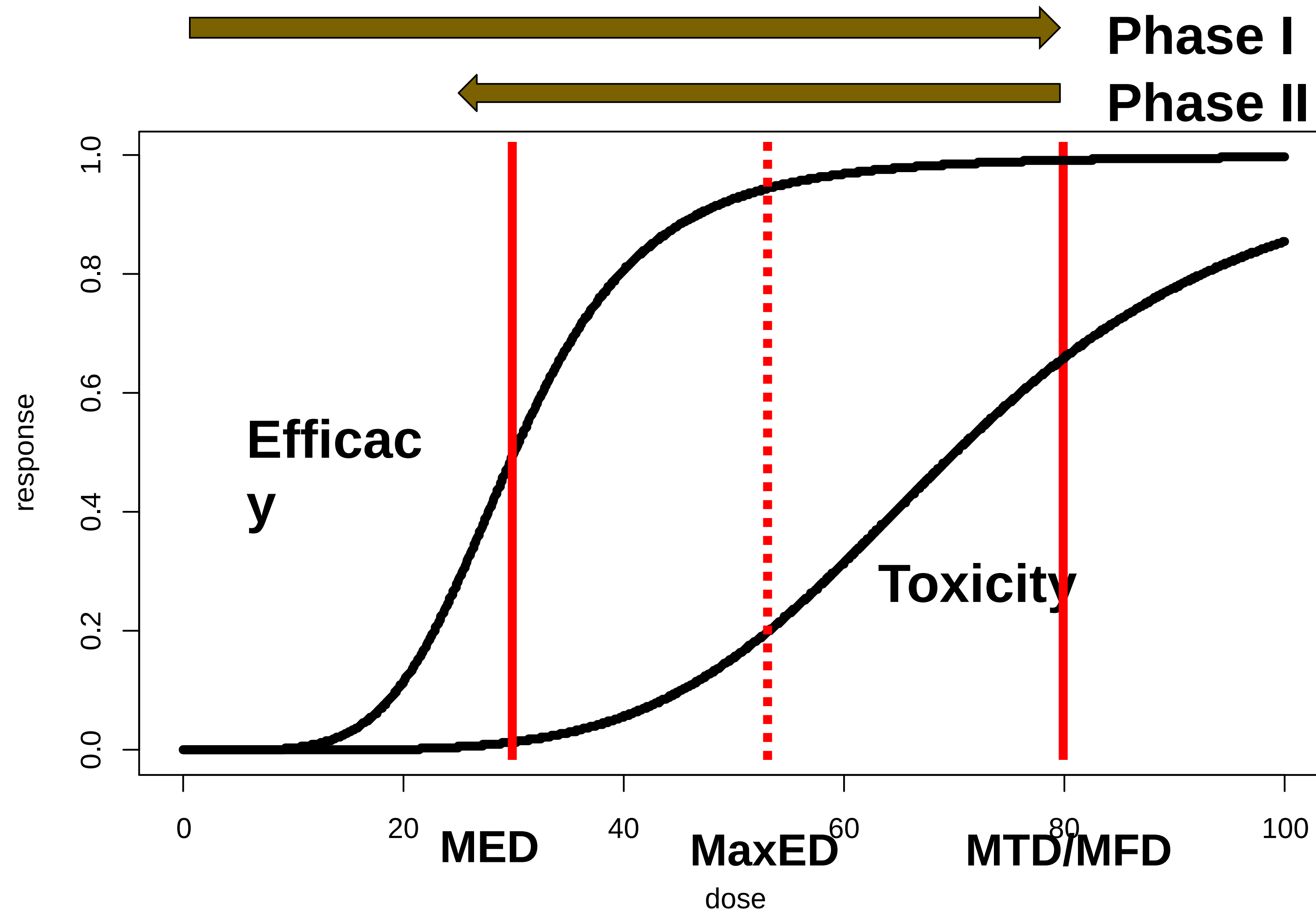
SOFTWARE

- **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

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

OVERVIEW OF DOSE FINDING PROCESS (NON-ONCOLOGY)



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)

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

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 $H_1: -3\mu_P + \mu_L + \mu_M + \mu_H > 0$

FOUNDATION OF CONTRAST TEST

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

$$H_0 : \mu_0 = \mu_1 = ... = \mu_k \tag{14.4}$$

or

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

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:

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

POWER OF A CONTRAST TEST IN A DOSE-FINDING STUDY

For normal distributed data

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

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

And power of the test is

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

Where c_i is the contrast coefficient, f_i is the sample size fraction for the ith group, n is the total sample size($n*f_i=n_i$)

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

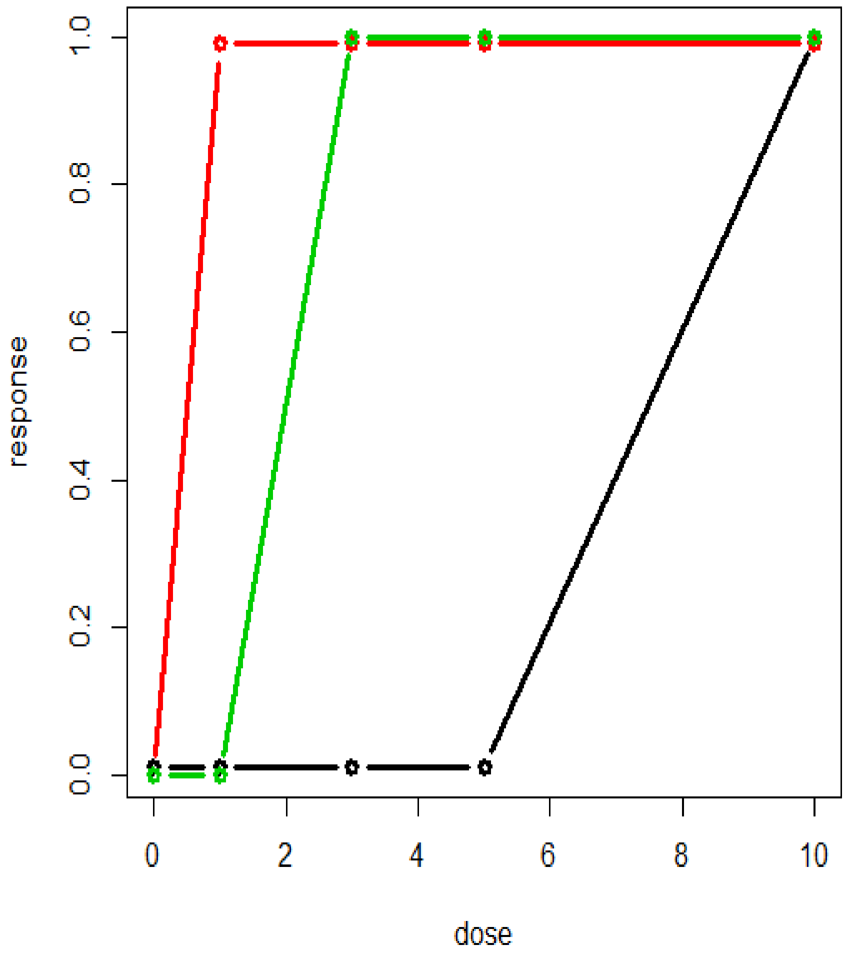
CONTRAST TEST #1: OPTIMAL CONTRAST FOR A SINGLE MODEL

- For given set of means of all treatment groups (μ_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.

$$c_i \propto n_i(\mu^0_{mi} - \bar{\mu}),\ i = 1, \ldots, k, \tag{3}$$

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

EXAMPLE



1. **Mean =(0,0,0,0,1), equal allocation:**

   (-0.22, -0.22, -0.22, -0.22, 0.89)

2. **Mean =(0,1,1,1,1), equal allocation:**

   (-0.89, 0.22, 0.22, 0.22, 0.22)

3. **Mean =(0,0,1,1,1), equal allocation**

   (-0.55, -0.55, 0.37, 0.37, 0.37)

4. **Mean =(0,0,0,0,1), allocation ratio=(2,1,1,1,2):**

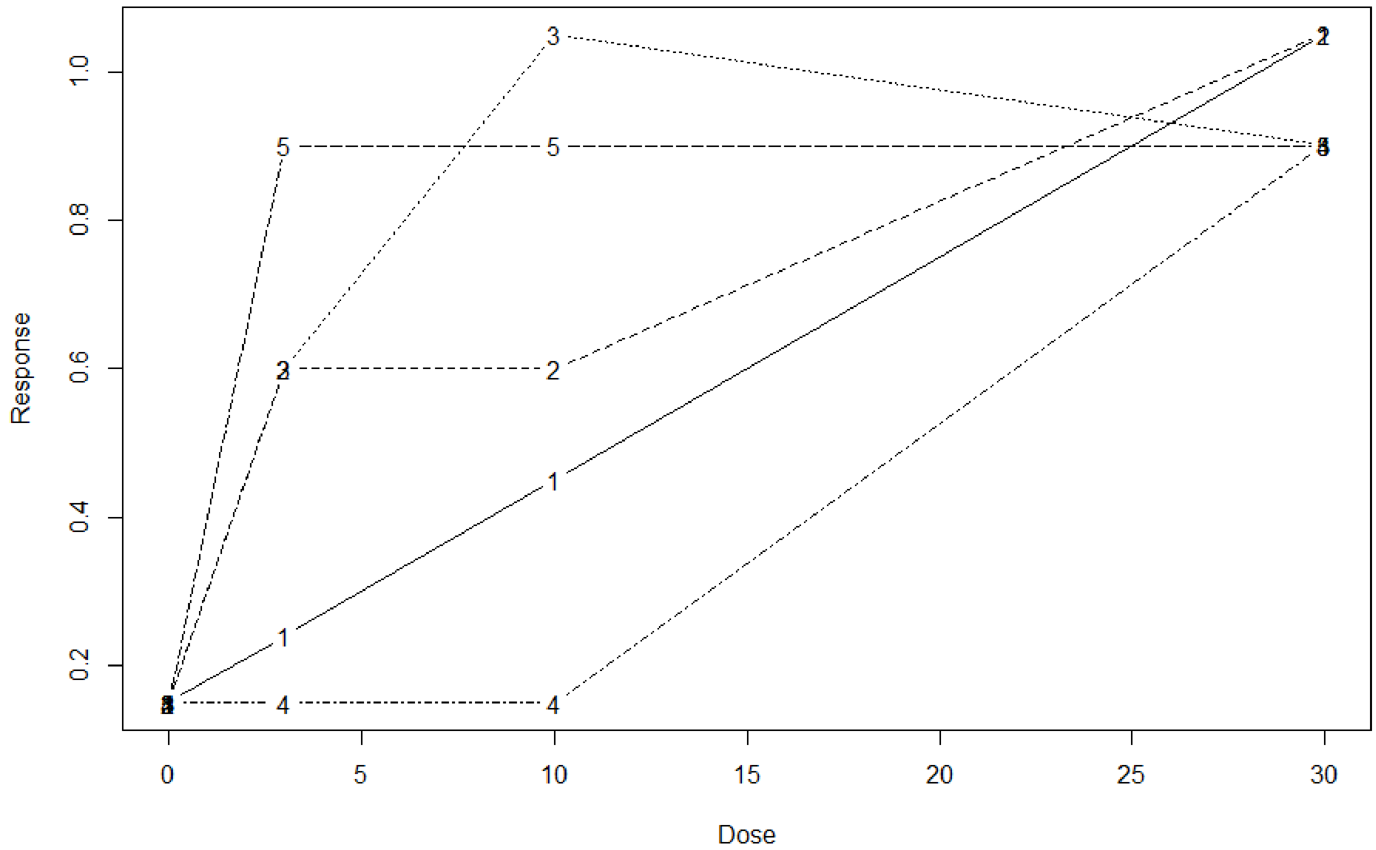
   (-0.35, -0.18, -0.18, -0.18, 0.88)

CONTRAST TEST #2: ORDINAL LINEAR CONTRAST TEST (OLCT)

•**Non-parametric, the contrast is based on ranks of different treatment groups**

	Coefficients						
Number of Doses plus Placebo	Placebo	Lowest Dose	Doses increase from left to right				Highest Dose
Two Doses	-1	0					1
Three Doses	-3	-1	1				3
Four Doses	-2	-1	0	1			2
Five Doses	-5	-3	-1	1	3		5
Six Doses	-3	-2	-1	0	1	2	3

•**In general, not optimal for a specific model. However, it is robust to most of the monotonic dose-response curves**



Deng and Ting (2016): Sample size allocation in a dose-ranging Trial combined with PoC

PERFORMANCE OF DIFFERENT CONTRAST

	Method	Linear	Step	Quadratic	Convex	Concave
1:1:1:1	A: High vs PBO (-1,0,0,1)	.88	.88	.78	.78	.78
	B: OLCT (-3, -1, 1, 3)	.89	.85	.85	.75	.75
	C: High vs Median/Low/PBO (-1,-1,-1,3)	.90	.77	.39	.89	.33
	D: High/Median vs Low/PBO (-1,-1,1,1)	.81	.68	.85	.57	.57
	E: High/Median/Low vs PBO (-3,1,1,1)	.56	.77	.86	.33	.89
2:1:1:2	A: High vs PBO (-1,0,0,1)	.94	.94	.86	.86	.86
	B: OLCT (-3, -1, 1, 3)	.93	.90	.90	.81	.81
	C: High vs Median/Low/PBO (-1,-1,-1,3)	.93	.81	.42	.92	.35
	D: High/Median vs Low/PBO (-1,-1,1,1)	.77	.64	.82	.53	.53
	E: High/Median/Low vs PBO (-3,1,1,1)	.60	.81	.89	.35	.92

CONTRAST TEST #3: MULTIPLICITY-ADJUSTED NON-PARAMETRIC CONTRAST TESTS

- **Multiple non-parametric test which is good for different candidate model (although not optimal)**
- **Dunnett test is a special form of such test, using pairwise contrast.**
- **Multiplicity from multiple contrast tests are adjusted by multivariate normal/t distribution. PoC is established if $T_{max} \geq q_{1-\alpha}$, where $q_{1-\alpha}$ is the critical values so that** $P(T_{max} \geq q_{1-\alpha}) = 1 - P(T_1 \leq q, \ldots, T_M \leq q) = \alpha$

SOME EXAMPLE OF TEST

- Dunnett Contrast:

$$C_{Dunnett} := \begin{pmatrix} -1 & 1 & 0 & 0 & 0 \\ -1 & 0 & 1 & 0 & 0 \\ -1 & 0 & 0 & 1 & 0 \\ -1 & 0 & 0 & 0 & 1 \end{pmatrix}$$

- Williams contrast:

$$C_{Williams} := \begin{pmatrix} -1 & 0.25 & 0.25 & 0.25 & 0.25 \\ -1 & 0 & 0.33 & 0.33 & 0.33 \\ -1 & 0 & 0 & 0.5 & 0.5 \\ -1 & 0 & 0 & 0 & 1 \end{pmatrix}$$

- Marcus contrast

$$C_{Marcus} := \begin{pmatrix} -1 & 0.25 & 0.25 & 0.25 & 0.25 \\ -1 & 0 & 0.33 & 0.33 & 0.33 \\ -1 & 0 & 0 & 0.5 & 0.5 \\ -1 & 0 & 0 & 0 & 1 \\ -0.5 & -0.5 & 0.33 & 0.33 & 0.33 \\ -0.5 & -0.5 & 0 & 0.5 & 0.5 \\ -0.5 & -0.5 & 0 & 0 & 1 \\ -0.33 & -0.33 & -0.33 & 0.5 & 0.5 \\ -0.33 & -0.33 & -0.33 & 0 & 1 \\ -0.25 & -0.25 & -0.25 & -0.25 & 1 \end{pmatrix}$$

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

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.**

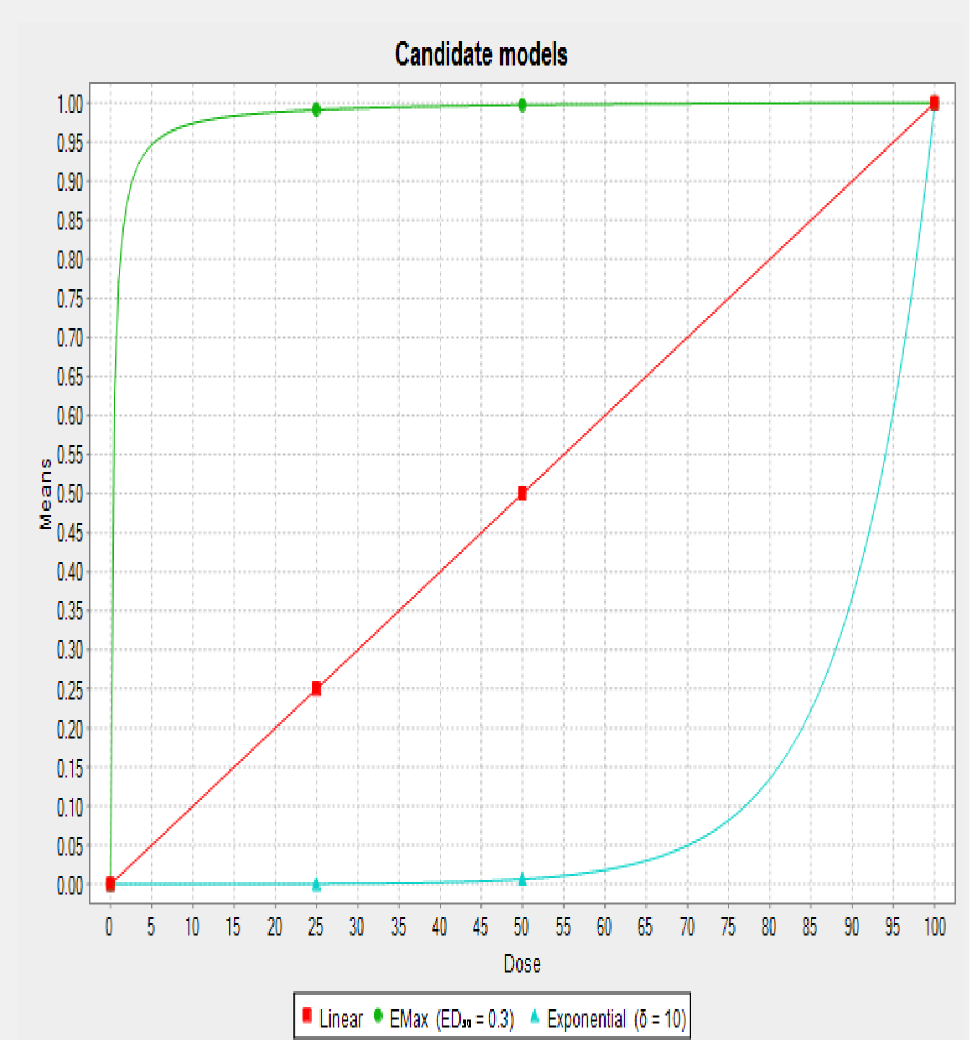
The final detection of a significant dose-response signal (i.e., demonstrating PoC), is based on the maximum contrast test statistic

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

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

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

DETERMINE THE OPTIMAL WEIGHT FOR TEST OF NON-FLAT RESPONSE



Four doses: 0, 25, 50, 100 for illustration

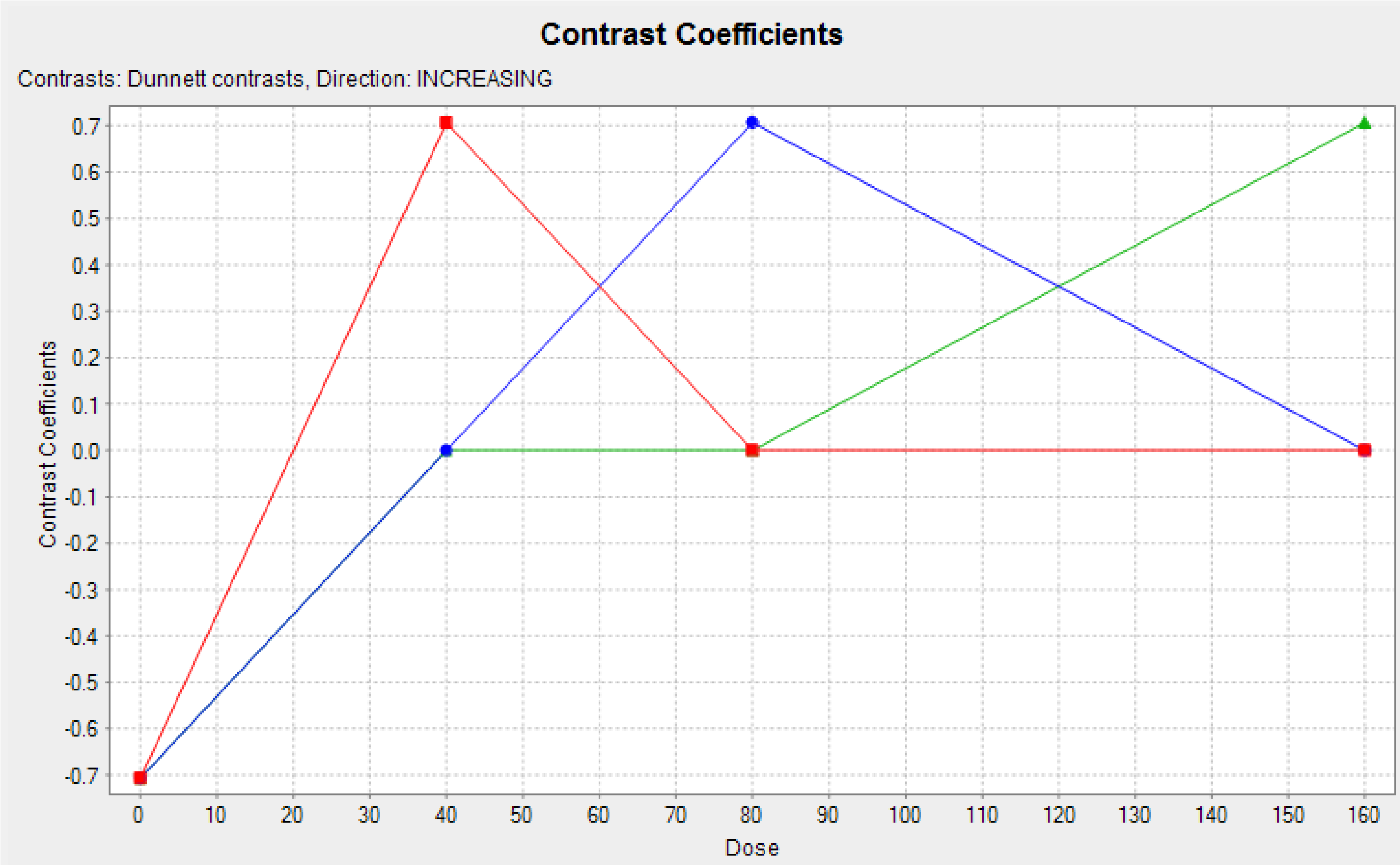
Green (emax): (-3, 1, 1, 1)

Red (linear): (-3, -1, 1, 3)

Blue (exponential): (-1, -1, -1, 3)

<u>MCP step</u>: apply the 3 contrast tests, and claim success if at least one test is significant

DOSE RESPONSE SHAPES WHERE PAIR-WISE COMPARISON IS OPTIMAL



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

EXAMPLE (CONTINUED)

What is the sample size for

- **MCPMod**
- **OLCT**
- **Highest dose vs PBO**
- **Dunnett**
- **Williams contrast**
- **Marcus contrast**

EXAMPLE (CONTINUED)

Methods	Sample Size Per Arm	Total Sample Size	% increase compared to MCP-Mod
Pairwise Comparison with Bonferroni adjustment	78	390	77%
Dunnett test	66	330	50%
ANCOVA F test	58	290	32%
Highest dose against Placebo&	55	275	25%
OLCT[&]	47	240	9%
MCP-Mod[$]	44	220	0%

& Subject to Monotonic assumption

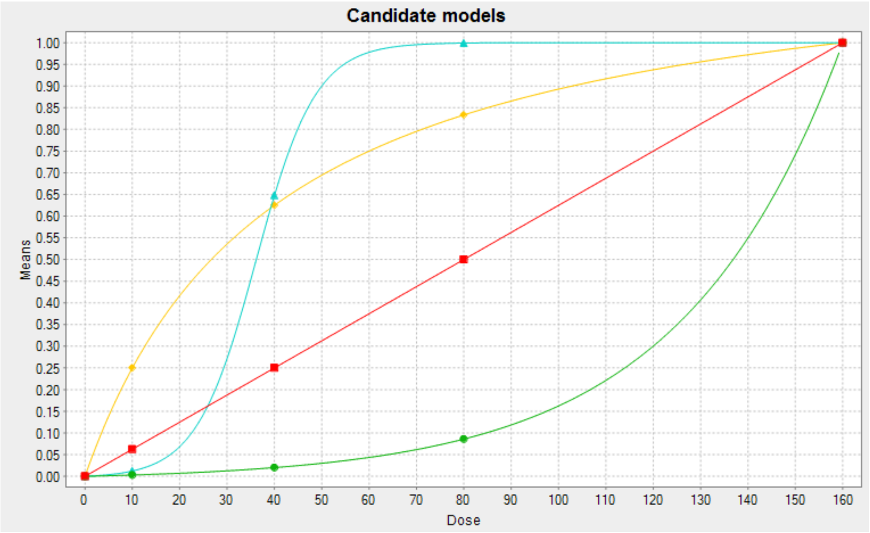
$ When true model is included in candidate set.

"LOWER DOSES DOESN'T WORK"

"Don't use low doses, since they are not going to work"

Not quite…

- This is main objective of phase II to find it out
- With the same number of arms, power doesn't necessarily decrease when using lower dose under MCPMod. Many times, power may even increase.



- Delta=1, sd=1.5, alpha=2.5%
- 30 patient per arm

- Pair-wise comparison (Dunnett):
  - 40, 80, 160 mg: power=67%
  - 10, 80, 160 mg: power=66%

- MCPMod
  - 40, 80, 160 mg: power=77%
  - 10, 80, 160 mg: power=85%

Generalized MCP-MOD (non-normal endpoint)

- Transform the data to normally distributed

- Binary data: logit
- Count data: log

Study Design

- Getting S matrix using candidate models information
- Determination of optimal contrasts for each candidate model shape by

  $$C_m \propto \; S^{-1}\left(\boldsymbol{\mu}_m - \frac{\boldsymbol{\mu}_m{}' S^{-1}\mathbf{1}}{\mathbf{1}' S^{-1}\mathbf{1}}\right)$$

- Sample Size Assessment and Power Calculation

Analysis

- Transform the data into dose-response parameters estimates $\hat{\boldsymbol{\mu}}$ and the corresponding $\hat{\boldsymbol{S}}$
- Recalculate optimal contrasts and the critical value for the test based on $\hat{\boldsymbol{S}}$
- Doing similar tests with

  $T_m = \frac{\boldsymbol{c}_m{}'\hat{\boldsymbol{\mu}}}{(\boldsymbol{C}'\hat{\boldsymbol{S}}\boldsymbol{C})_{m,m}{}^{1/2}}$, where $\boldsymbol{C} = [\boldsymbol{c}_1, \ldots, \boldsymbol{c}_M]$

SOFTWARE -- MCPMOD

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

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 ;
```

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.

MODELING AND ESTIMATION (CHAPTER 9, 10)

MODELS AVAILABLE IN MCPMOD

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

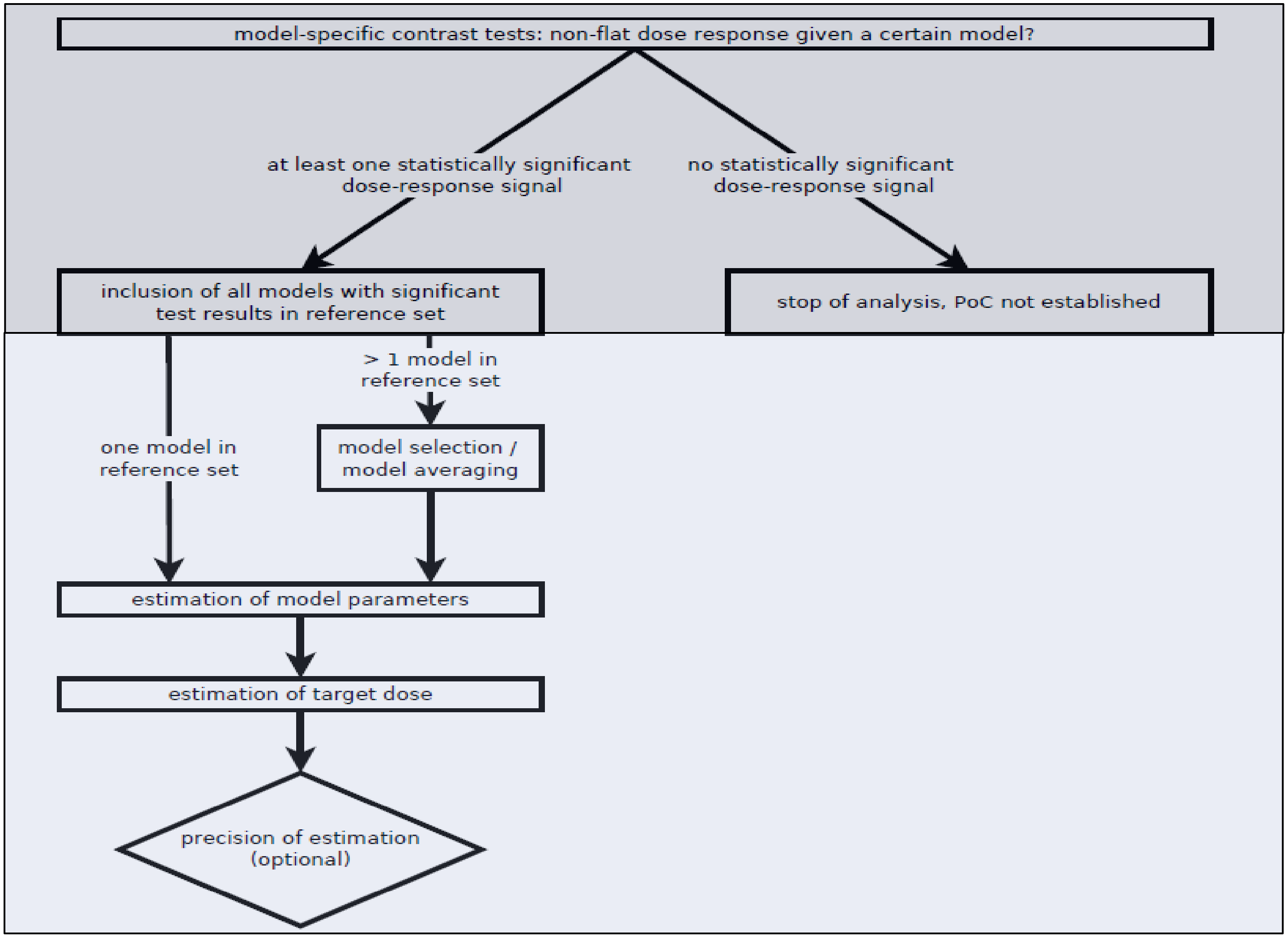
Name	$f(d,\boldsymbol{\theta})$	$f^0(d,\boldsymbol{\theta}^*)$	(*)	($\sharp$)
`linear`	$E_0 + \delta d$	d		
`linlog`	$E_0 + \delta \log(d+c)$	$\log(d+c)$		c
`quadratic`	$E_0 + \beta_1 d + \beta_2 d^2$	$d + \delta d^2$ if $\beta_2 < 0$	δ	
`emax`	$E_0 + E_{\max} d/(ED_{50} + d)$	$d/(ED_{50} + d)$	ED_{50}	
`logistic`	$E_0 + E_{\max}/\left\{1 + \exp\left[\left(ED_{50} - d\right)/\delta\right]\right\}$	$1/\left\{1 + \exp\left[\left(ED_{50} - d\right)/\delta\right]\right\}$	$(ED_{50}, \delta)^\top$	
`exponential`	$E_0 + E_1(\exp(d/\delta) - 1)$	$\exp(d/\delta) - 1$	δ	
`sigEmax`	$E_0 + E_{\max} d^h/(ED_{50}^h + d^h)$	$d^h/(ED_{50}^h + d^h)$	$(ED_{50}, h)^\top$	
`betaMod`	$E_0 + E_{\max} B(\delta_1,\delta_2)(d/D)^{\delta_1}(1-d/D)^{\delta_2}$	$B(\delta_1,\delta_2)(d/D)^{\delta_1}(1-d/D)^{\delta_2}$	$(\delta_1, \delta_2)^\top$	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 ($\sharp$) 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 $\delta = \frac{\beta_2}{|\beta_1|}$. For the quadratic model the standardized model function is given for the concave-shaped form.

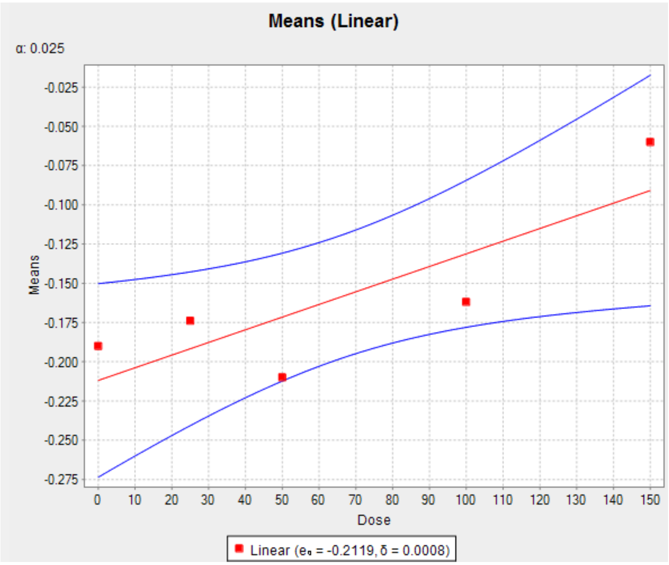
MCPMOD –
ANALYSING THE STUDY

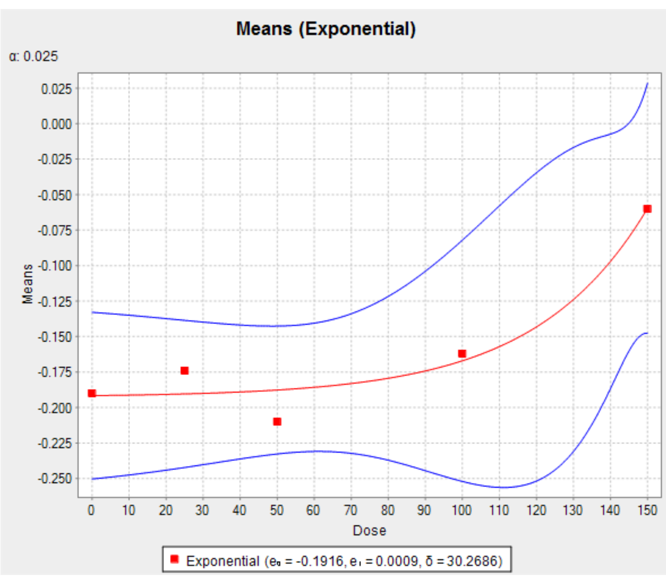
MCP part

MOD part



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	85	86	85	84
sd	0.36	0.36	0.36	0.36	0.36

Computation result - Result information

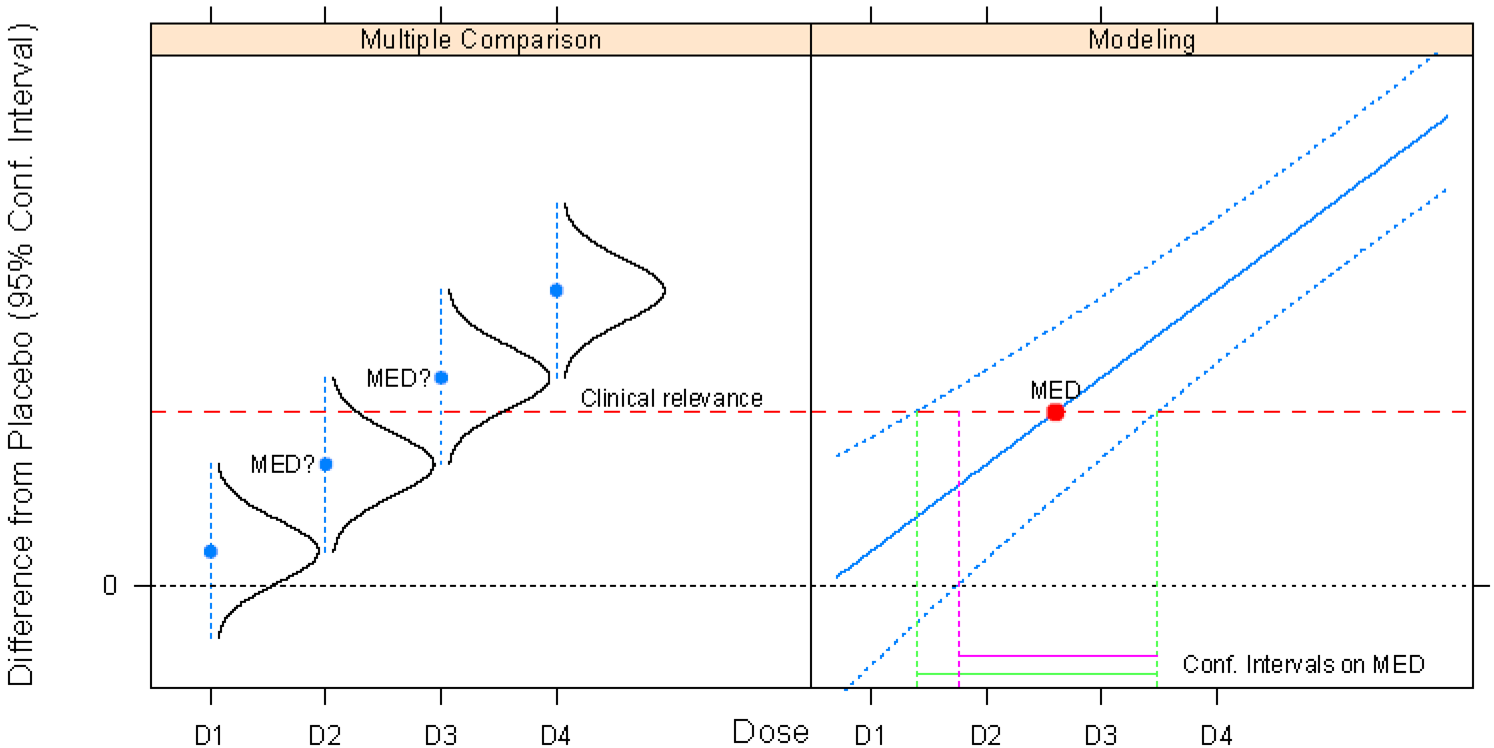
There is no additional information on this computation results.

Computation result - Multiple contrast test

Computation result - Multiple contrast test

	t-Stat	p-Value
Exponential (δ = 77.9216)	2.772	0.0074
Linear	2.4726	0.0165
Logistic (ED_{50} = 75, δ = 15)	2.3556	0.0222
EMax (ED_{50} = 37.5)	1.6857	0.0958
EMax (ED_{50} = 4.0861)	1.0293	0.2709

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

TARGET DOSE, EFFECTIVE DOSE

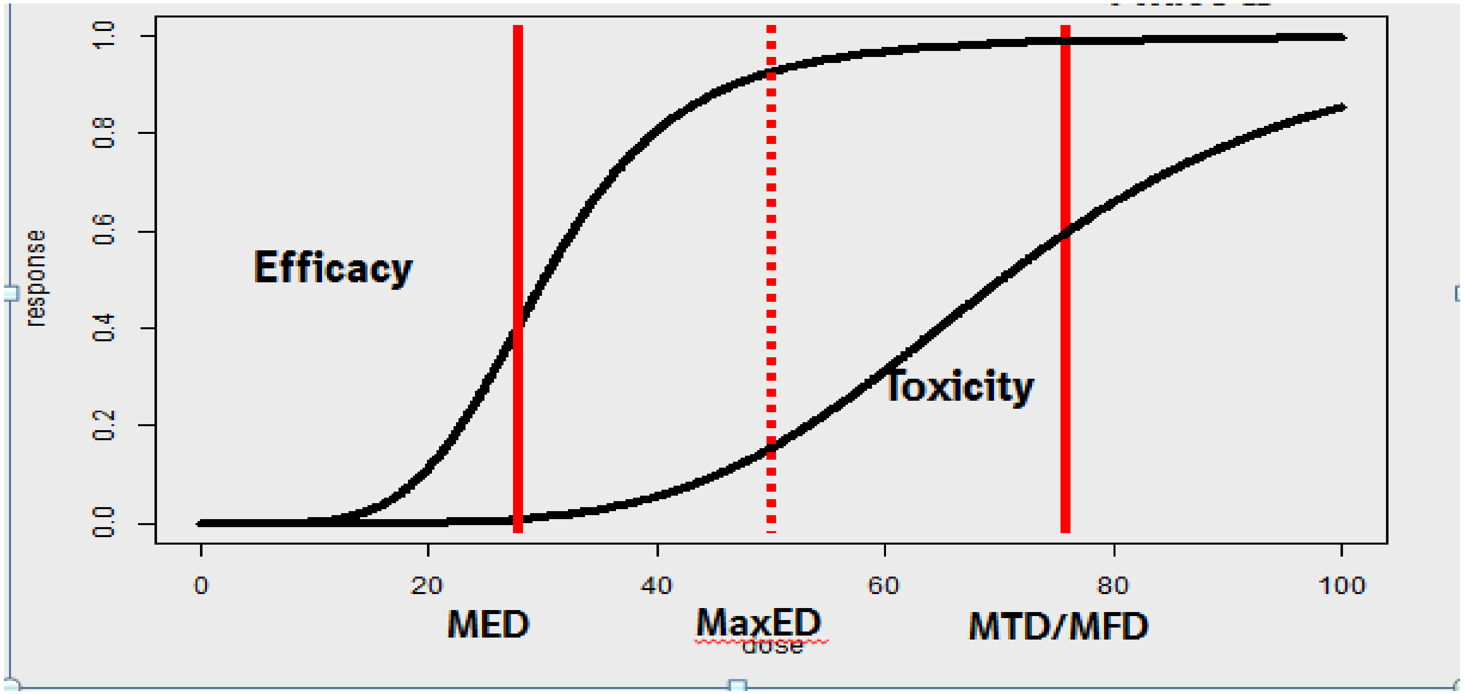
- **Minimum effective dose (MED or MinED):**
  - ICH-E4: “The smallest dose with a discernible useful effect”.
  - Target Dose (TD) : Minimum dose with absolute effect difference of Δ compared to control: 30% increase of ACR20
  - Effective Dose (EDp): Minimum dose achieving 100p% of the maximum treatment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

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)

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"



Emax Model (chapter 9)

(Based on Slides from Jim MacDougall)

E_{MAX} MODEL INTRODUCTION

The E_{MAX} 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

4 Parameters

E_0 = Baseline Response

E_{MAX} = Maximum Effect

ED_{50} = Dose at Half of Maximum Effect

N = Slope factor (Hill Factor)

EMAX MODEL

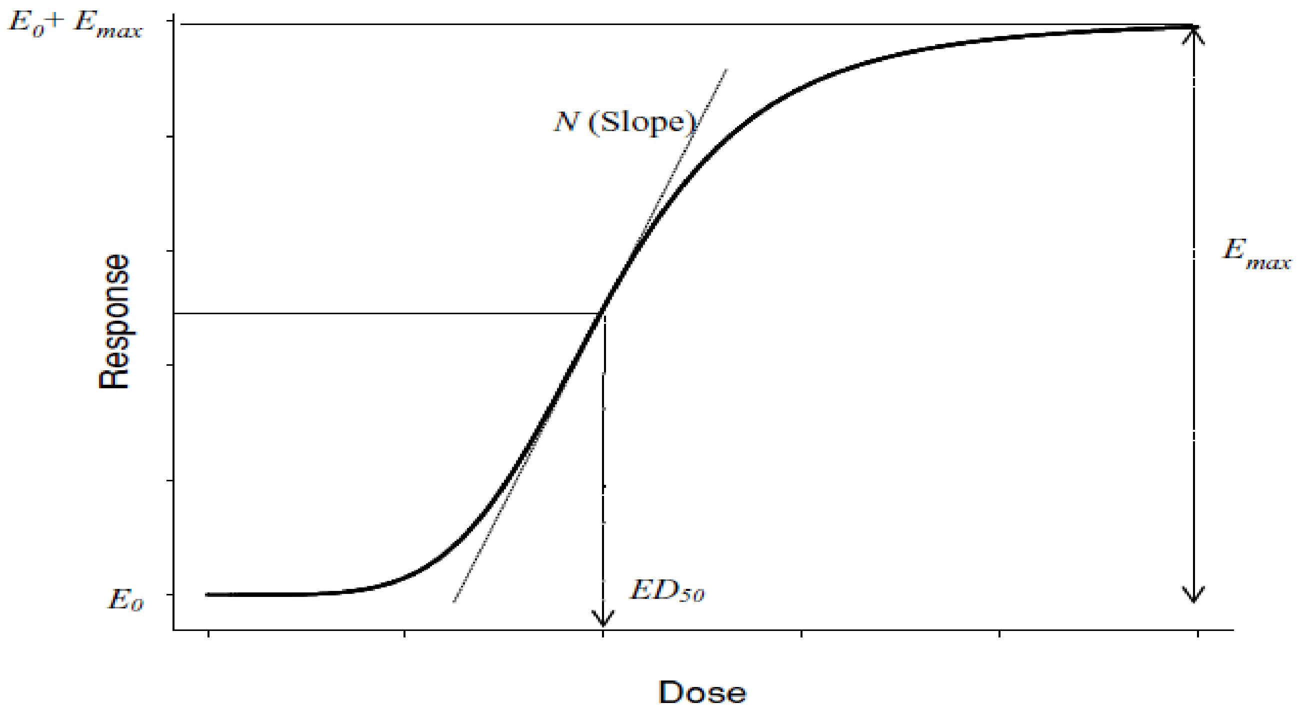


Figure 9.1. $E_{\max}$ Model dose–response curve.

"Hyperbolic E_{MAX}":
N=1

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

LOGISTIC MODEL

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

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

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 $\beta_4 < 0$

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

E_{MAX} Model Properties

- The E_{MAX} curve follows the “law of diminishing returns”
- The E_{MAX} model predicts the maximum effect a drug can have (E_{MAX}).
- The E_{MAX} predicts baseline effect (E_0) when no drug is present
- Four parameters
- The model’s parameters are readily interpretable

WHY/WHEN USE THE EMAX 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

Parameter Sensitivities: ED_{50}

The E_{MAX} model function:

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

Where:

R = Response

D = Dose

E_0 = Baseline Response

E_{MAX} = Maximum Effect

ED_{50} = Dose at Half of Maximum Effect

N = Slope factor (Hill Factor)

PARAMETER SENSITIVITIES: ED_{50}

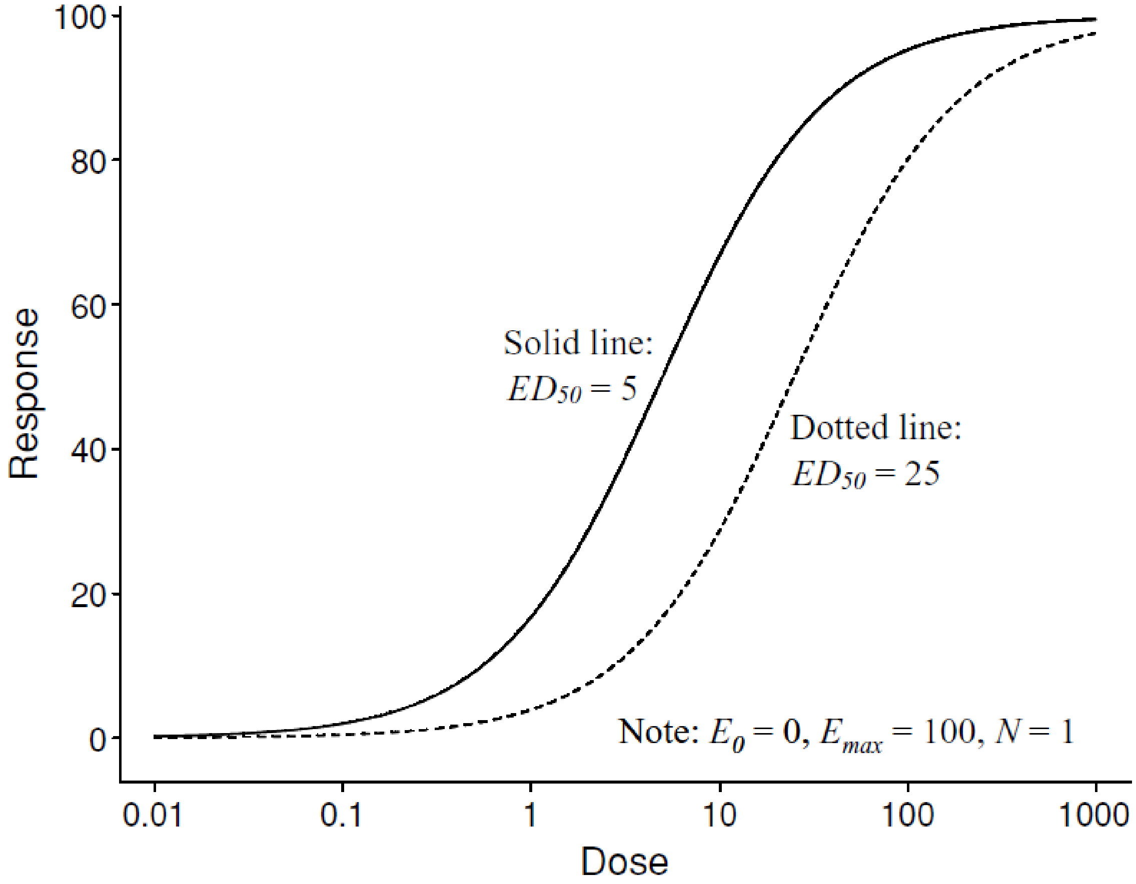


Figure 9.3. $E_{\max}$ Model dose–response curves with differing ED_{50} values.

Parameter Sensitivities: N(Slope Factor)

The E_{MAX} 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.

PARAMETER SENSITIVITIES:
N (SLOPE FACTOR)

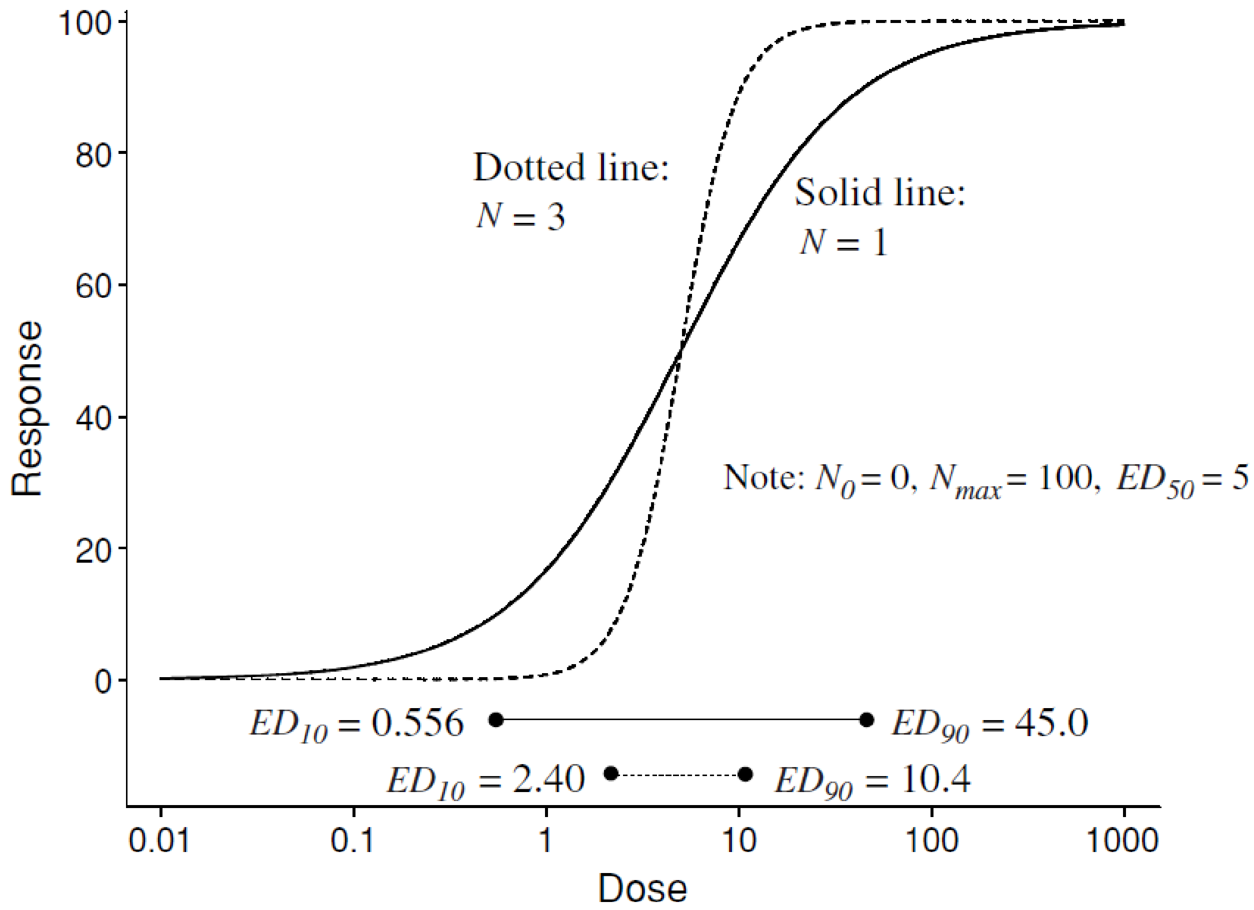


Figure 9.4. E_{max} Model dose–response curves with differing N values.

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.

DOSE RANGE VS. N (SLOPE FACTOR)

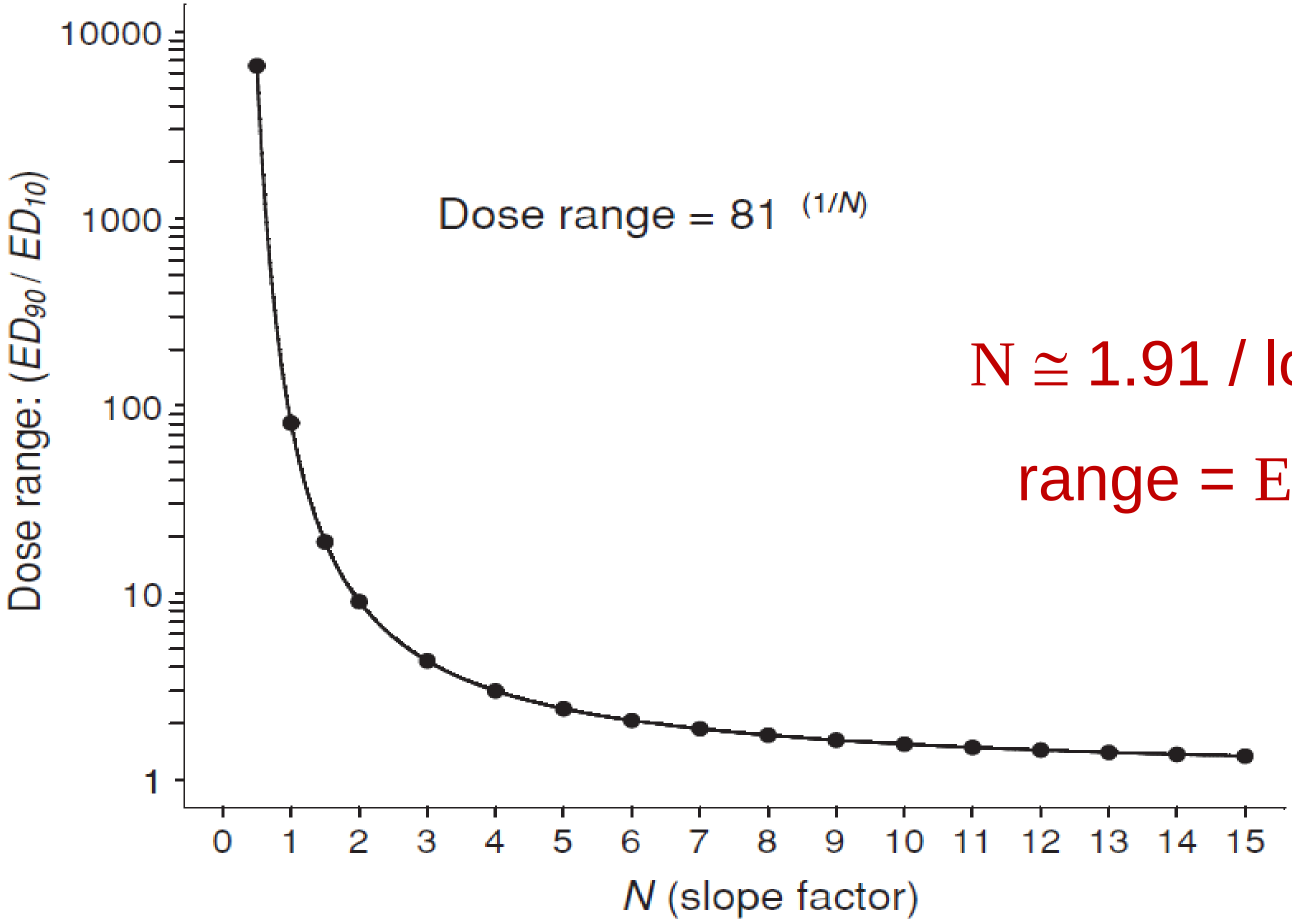


Figure 9.5. $E_{\max}$ Model dose range as a function of N.

$N \cong 1.91 / \log_{10}(\text{range})$

$\text{range} = ED_{90} / ED_{10}$

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

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

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

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

- NONMEM (UCSF) software used in PK/PD

  http://www.globomaxservice.com/products/

- SAS

Proc NLIN, NLMIXED

- Splus

- Any software for non-linear and non-linear mixed models.

SAS

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

Optimal Design

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.

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.

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

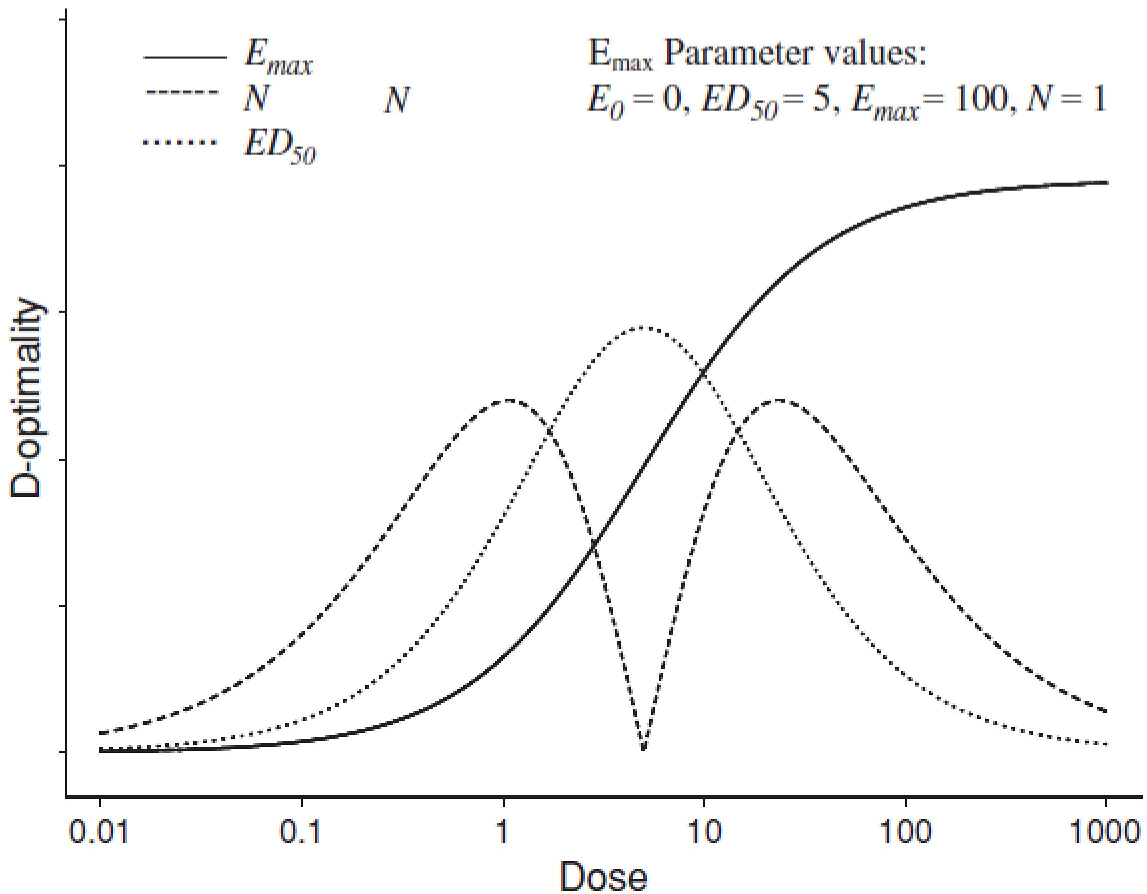


Figure 9.6. D-Optimal design criteria for the E_{max} model parameters ED_{50}, E_{max}, and N.

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 $M(\xi, \vartheta)$ 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.**

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

$$\text{maximizes } \min\{\text{eff}_1(\xi), \ldots, \text{eff}_m(\xi)\}$$

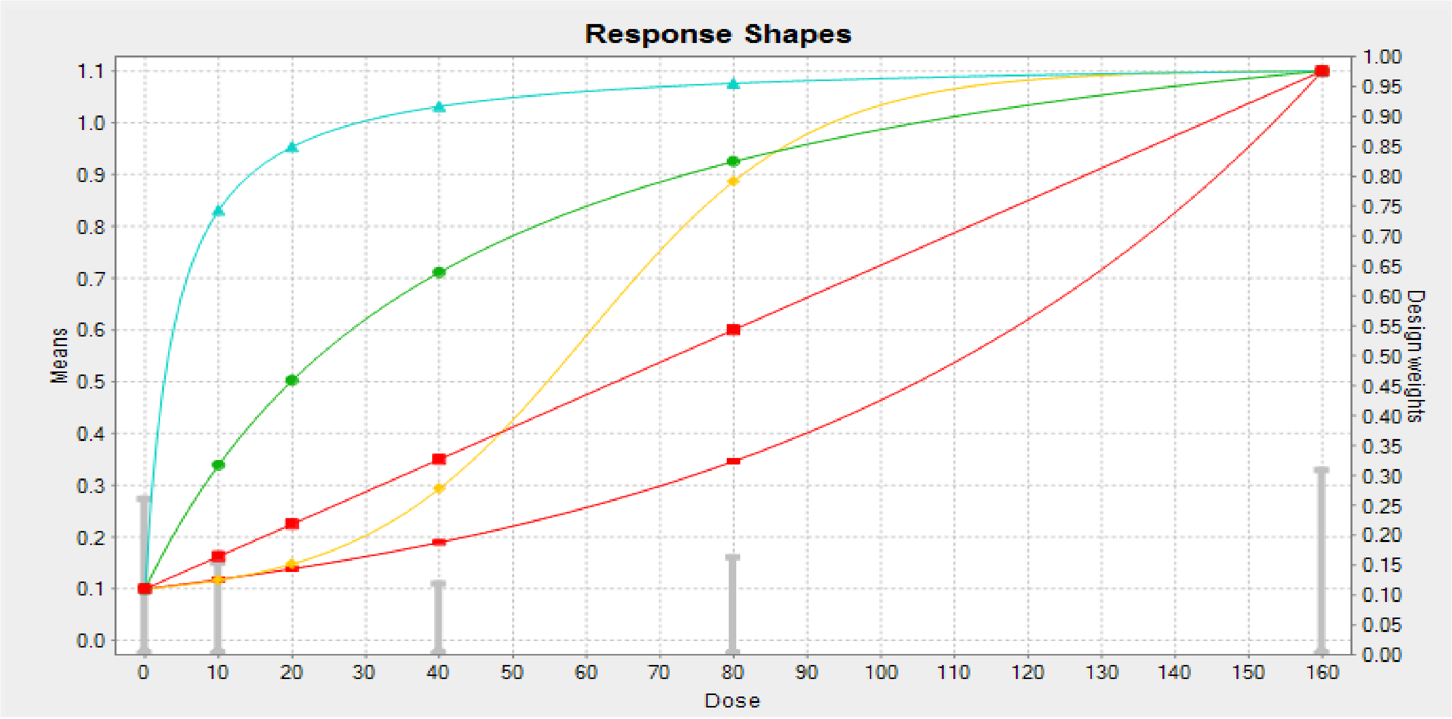
  - Maximize the weighted sum of log efficiency.

$$\sum_{j=1}^{m} \alpha_j \log \text{eff}_j(\xi), \quad \text{with} \sum_{j=1}^{m} \alpha_j = 1,$$

- **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

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



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