



U.S. Food and Drug Administration

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# Clinical Trial Designs

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# Disclaimer

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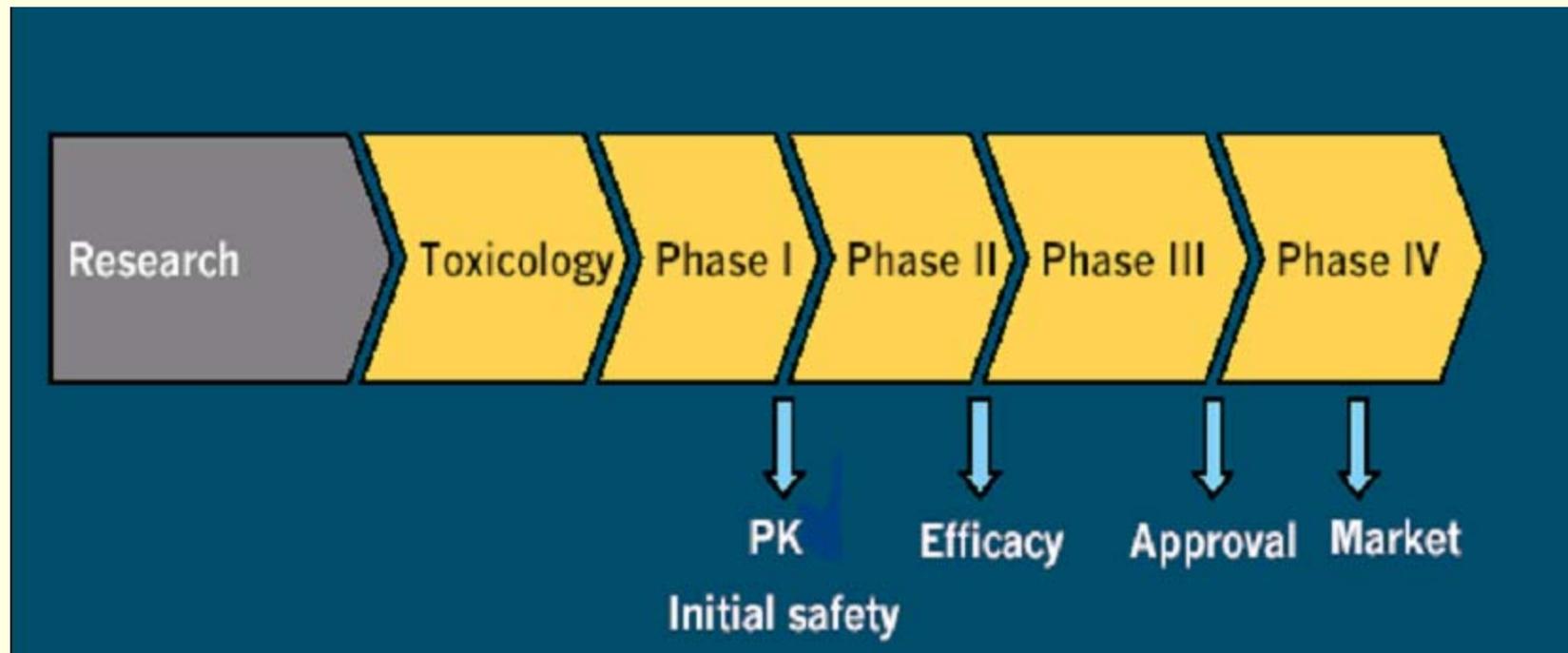
# Outline

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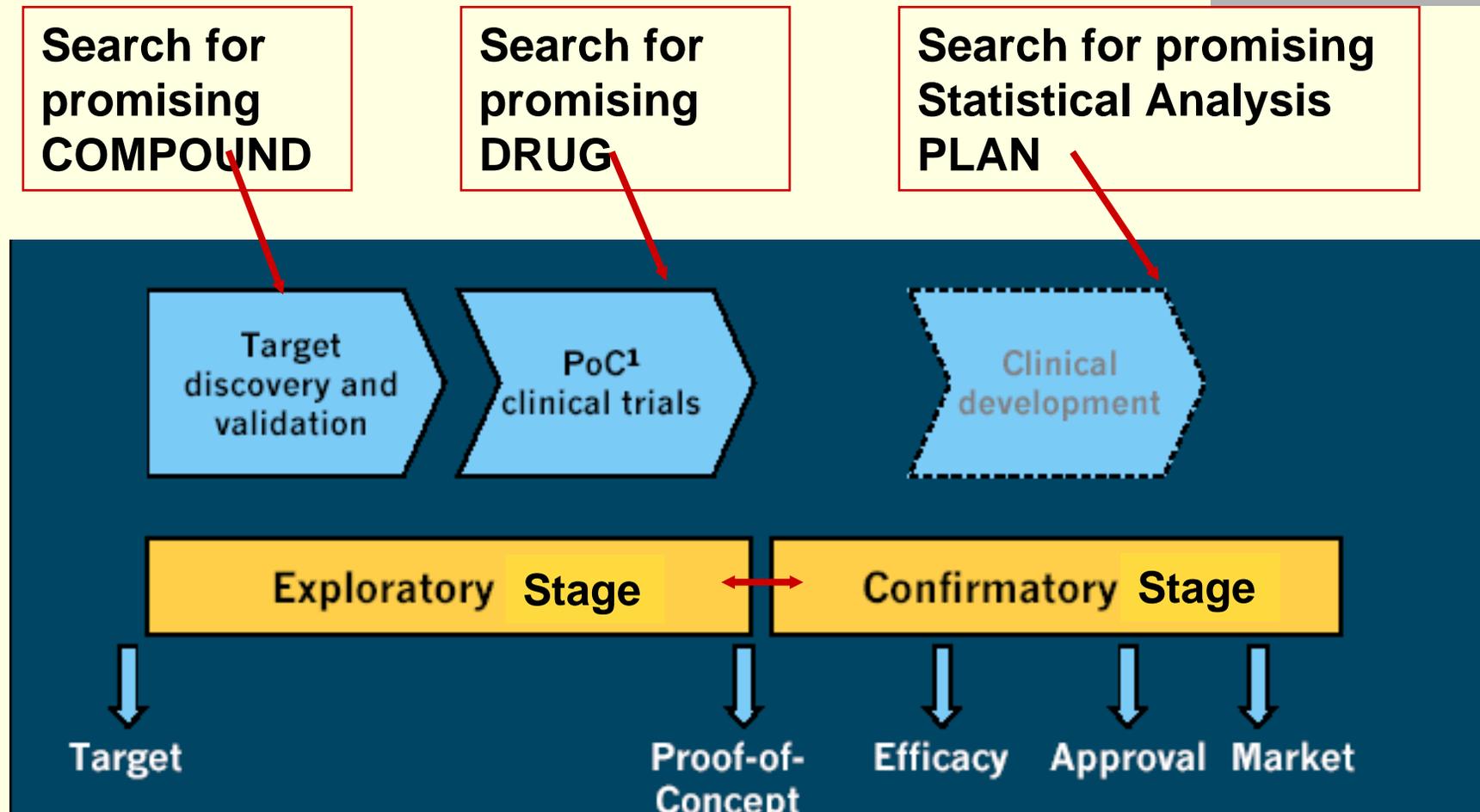
- Overview of drug development
- Key Elements of Study Designs
- Exploratory studies
- Adequate and Well-Controlled Studies
- Some Regulatory Guidance

# Traditional paradigm

## Drug Research & Development



# Emerging Trend for Drug R&D



# Key Elements of Study Design (1)

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- What question(s) does (do) the study want to address?
- What is the experimental unit?
- What measures clinical benefit and/or clinical risk?
- What dose regimens to study ?

# Key Elements of Study Design (2)

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

# Key Elements of Study Design (3)

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

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# Multiple Objectives in Exploratory Clinical Trials

# Aims in Early Phase or Early Stage

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

# Types of Exploratory Studies

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

- ◆ Dose-Response  
Dose-Ranging  
Exposure-response

Target dose(s) estimation

# Dose Regimen of Interest

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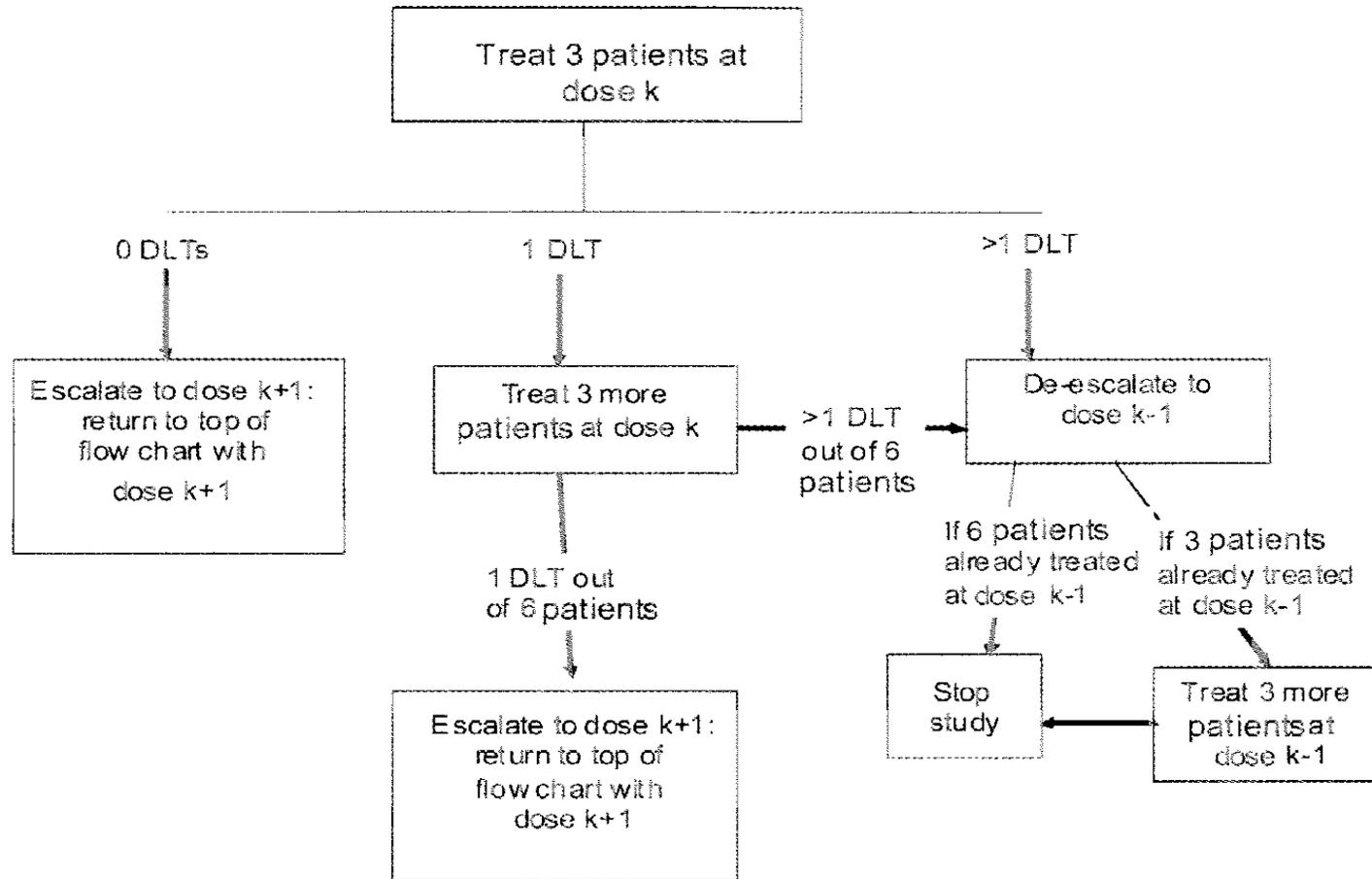
Phase I – primary interest is **Tolerability**

- Maximum Tolerated Dose (MTD)

Phase II – primary interests: **POC**, **Dose Selection**

- Minimum Effective Dose (MED)
- Maximum Safe Dose (MSD)
- Maximum Utility Dose (MUD) based on current info
- Minimally acceptable dose (MAD): the lowest dose that has a utility of at least, say, 70%

**Box 1** A standard “3 + 3” dose escalation design starting at dose k. The maximum tolerated dose (MTD) is usually defined as the highest dose at which 0 or 1 dose-limiting toxicities (DLTs) are observed in six patients (although some “3 + 3” rules call the highest dose with two or fewer dose-limiting toxicities in six patients the MTD). If de-escalation occurs at the first dose level, then the study is discontinued.



# Continual Reassessment Method

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

**TITE CRM**

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

Allow staggered entry → shorten study duration

MTD, e.g., dose level achieved a DLT closest to  $\lambda\%$

## Point est. vs. Interval est.

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

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

# Continual Reassessment Method Often PI-Initiated in oncology

22 patients studied at 4 dose levels (30-45 mg/m<sup>2</sup>), JCO 2004

27 patients studied at 5 dose levels (4 mg/m<sup>2</sup> to 20 mg/m<sup>2</sup>/wk)  
JCO 2004

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

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

**Using the continual reassessment method: Lessons  
Learned from an EORTC phase I dose finding study**

# CRM and its Modifications

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

# Phase 1 Trial CRM Method

Patient population: Androgen Independent Prostate Cancer

Proposed Dose Levels 30, 35, 40 ,45

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

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

Table 2. Cohort Sequence With First-Cycle DLT

Cohort No.	Dose Level (mg/m <sup>2</sup> )	First-Cycle DLTs	
		Proportion	%
1	30	0/6	0
2	45	3/4	75
3	35	5/6	83
4	30	3/6	50

Abbreviation: DLT, dose-limiting toxicity.

# To determine MTD

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

# Early Assessment of Drug Activity

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Dose ranging, dose response studies

What is an appropriate dose range?

Will there be dose-response?

*Plenty of learning and exploration*

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

Preliminary assessment of drug activity

Internal decision making for further development

Fixed, Adaptive vs Model-based Design

# Study Designs

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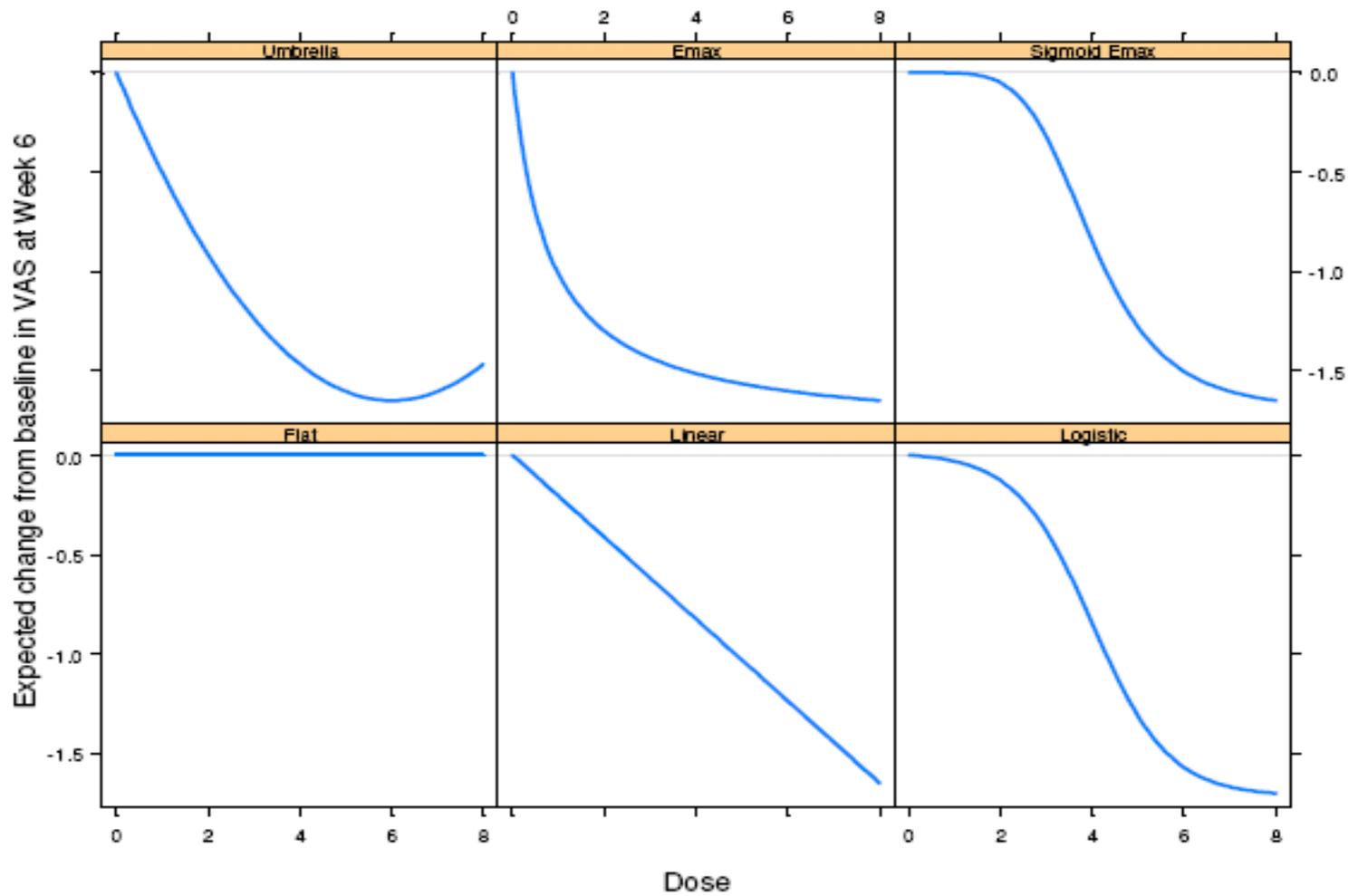
- ◆ **Balanced Design**
- ◆ **Adaptive Frequentist**
- ◆ **Optimal Design**
- ◆ **Adaptive Bayesian**

# POC and Dose-Response

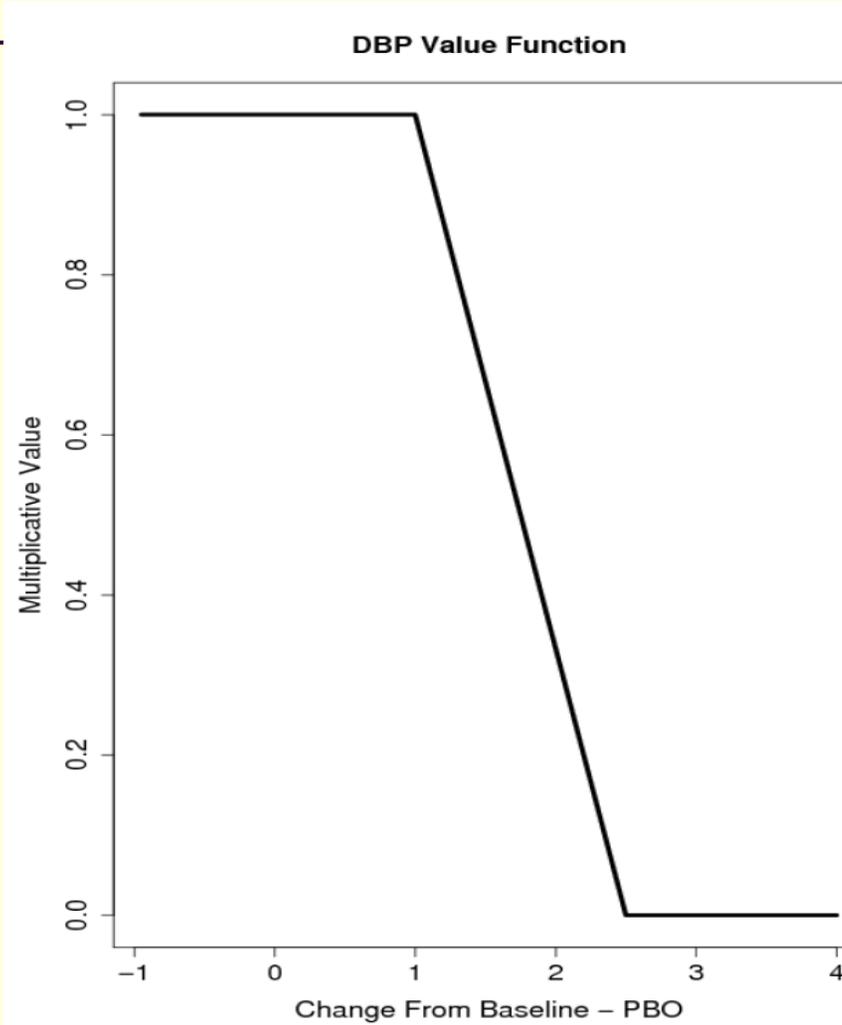
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- ◆ POC: Is there evidence of dose-response?  
Any evidence of treatment effect?
- ◆ How well dose-response curve is estimated?
- ◆ Dose-Finding: Which dose to bring to next stage or next phase of the drug development?
- ◆ ICH E-4: the purpose of dose-response information is to find the smallest dose with a discernible useful effect

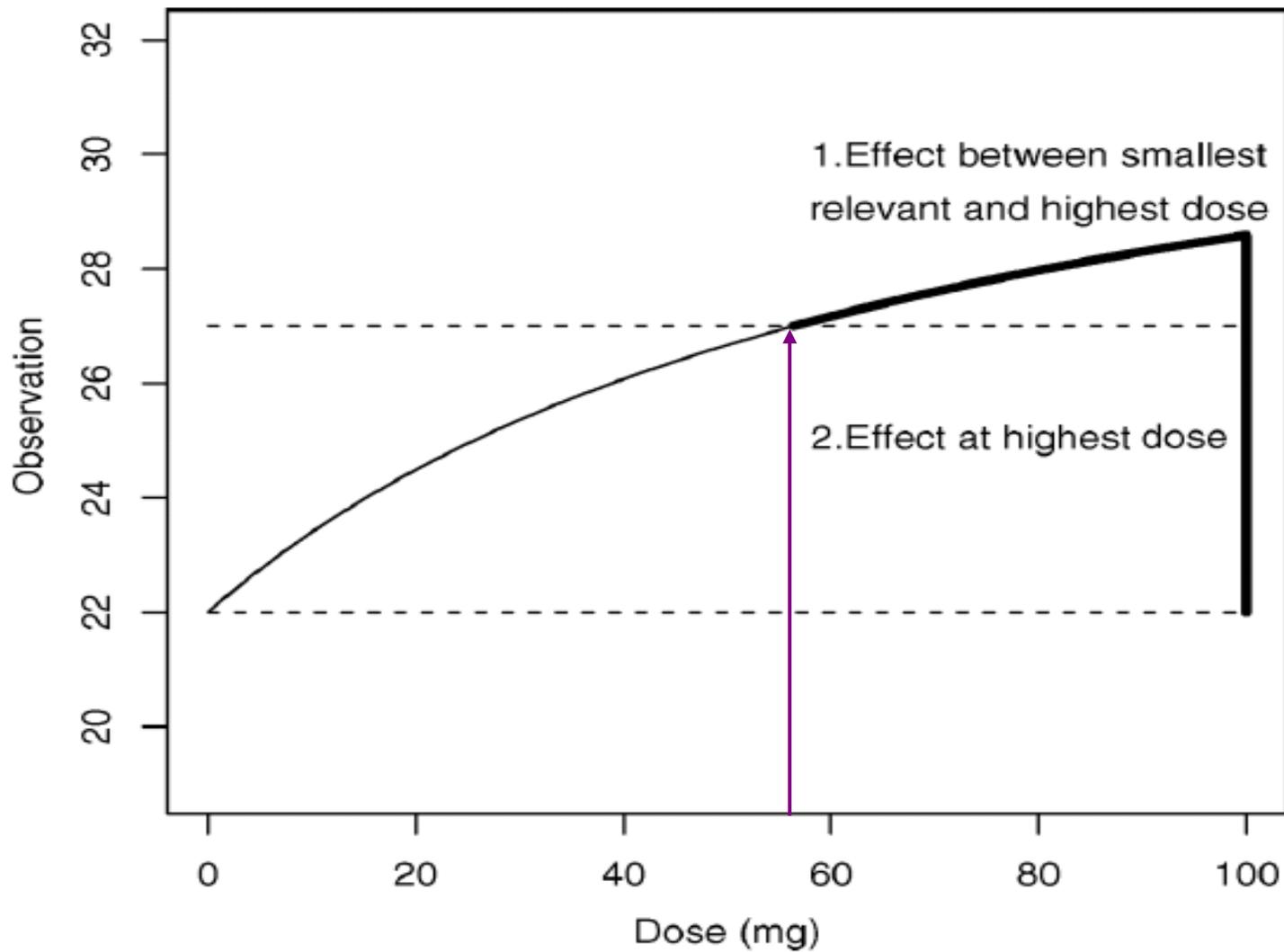
Figure 4.1. Dose-response profiles used in simulation.



# Utility Function – an example



Wang SJ, April 21, 2011



Miller et al. 2007

Figure 2 Objectives of the trial.

# When is adaptive design useful compared to optimal design under Bayesian framework ?

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- If differences between possible dose-effect scenarios are large (in relation to variability of data in interim analysis), there is gain from adaptive dosing
- If scenarios similar enough or variability large, decisions based on interim data could lead into wrong direction — especially if assumed dose-range is the relatively uninformative part, given true DR unknown

Miller et al, 2007

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The purpose of dose-response information is to find the smallest dose with a discernible useful effect

(ICH E-4)

# Early Phase or Stage of Drug Development

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- ◆ Uncertainty about drug activity, MOA
- ◆ Should be an exploratory or learning mode of investigation
- ◆ Trade-off between false negative vs. false positive vs. estimation problem
- ◆ Prerequisites before launching a confirmatory trial

# Early stage in Drug Development

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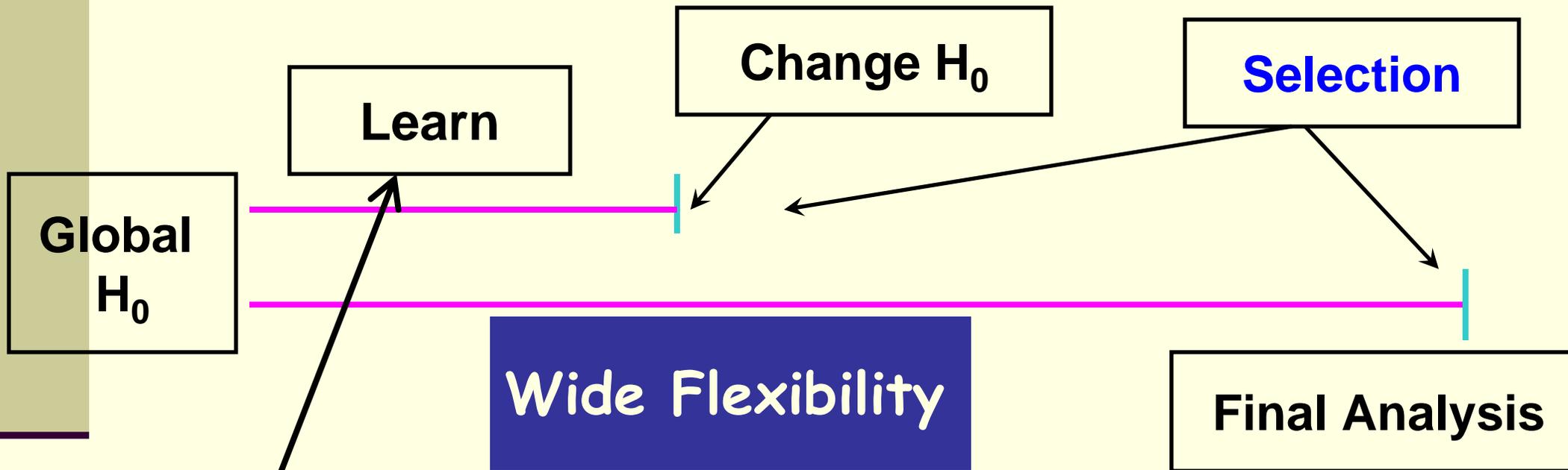
*Dose-ranging; Dose-response; Exposure-response; promising dose profile*

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

AIM: hope to maximize probability of correct selection and for future planning

# Dealing with Learning (i)

Combine Learn that Formalizes Learn in Exploratory Trials - Hypothesis generation



Patient pop'n? Corr (Early,late endpoints)? Dose range? Dose regimen(s)? Effect size? etc.

Estimation & Quantify Uncertainty

# Dealing with Learning (ii)

## (ii) Formalize learning to plan confirmatory trial

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

But, may be too optimistic with usual  $\alpha$ -level and  $1-\beta$  level

→ possibly regression toward mean

\*Wang et al. (2006, Pharmaceutical Statistics)

# "Learn Trial" versus "Confirm Trial"

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

*Caveats:*

if pursued as one-trial for inference, learning data is a part of inference data that are subject to multiplicity

if pursued as learn vs. confirm, adaptive elements can be built-in within learn trial versus within confirm trial, but, separately

# Learn and Confirm Within Trial of Most Enthusiastic Interest

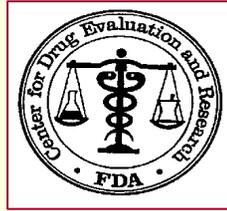
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Statistical theory has shown that learn and confirm within the same study yield **liberal type I error rate and overestimate performance characteristics if multiplicity adjustment is not formally accounted for**, e.g., commonly used internal cross-validation of model built using the same or a part of the data

e.g., in gene expression or whole genome screening or gene association studies, rigorous confirmation of the prediction accuracy should be performed in an independent dataset

**Multiplicity issue and regression to the mean issue**

# Adaptive Design



- Prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study
- Analysis of the accumulating study data are performed at prospectively planned time-points within the study
- Analyses can be performed in a fully blinded manner or in an unblinded manner, and can occur with or without formal statistical hypothesis testing

# Clinical Trial Designs and Objectives

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

# Concepts & Terminology

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

# Some Design Considerations

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- When large amount of data collection is not feasible in early phase studies
- When large amount of data collection is routinely practiced in late phase studies
- Accurate modeling relies on large amount of data
- Desired to pursue modeling in early phases because of little data

# Design with Little vs More

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## ■ Philosophy 1

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

## ■ Philosophy 2

- What is the clinical question or objective ?
- Choice of study design to address the Qs.

# Learn/preliminary confirm for Decision

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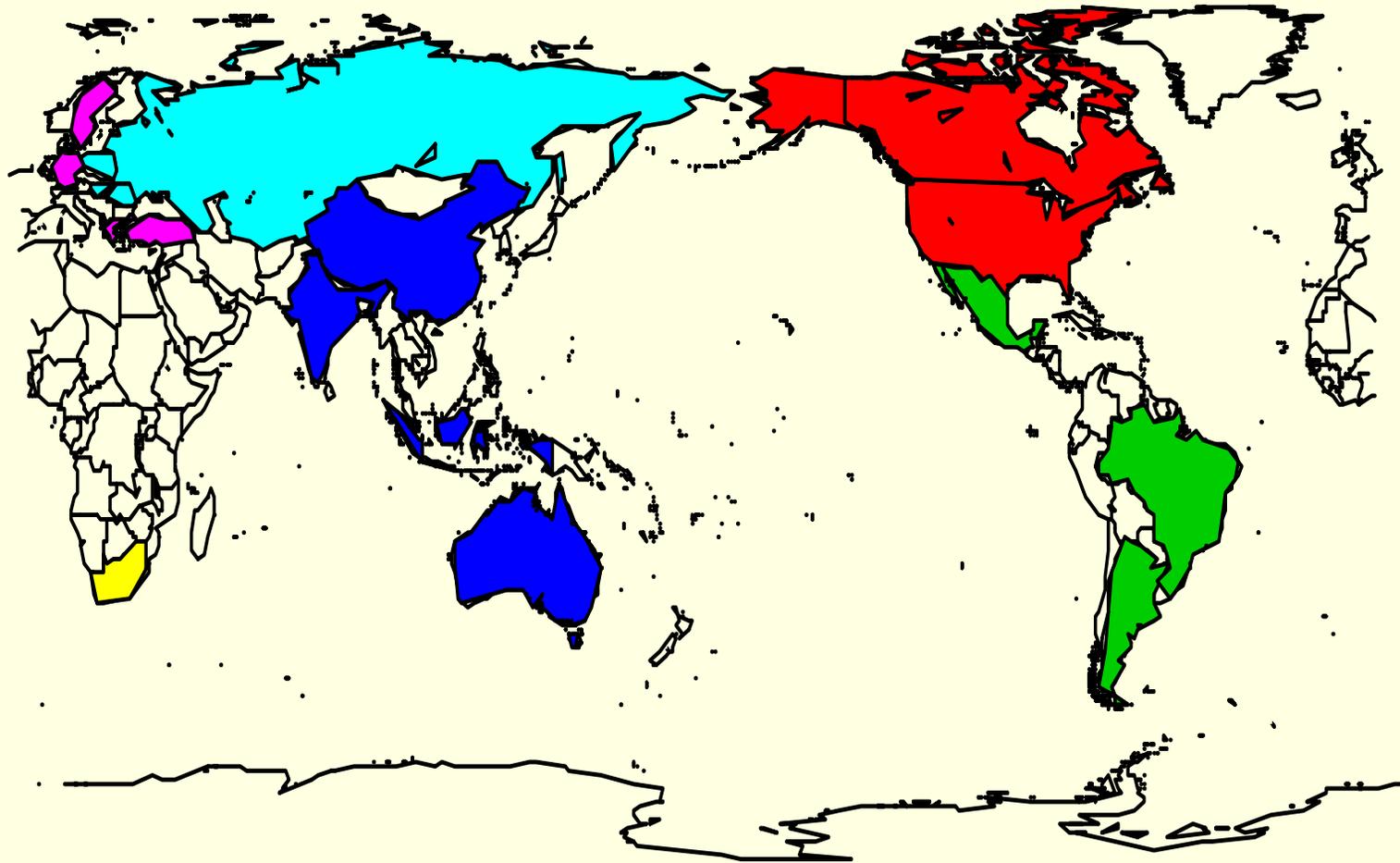
- Correct go/no-go decision is critical
- To improve the probability of correct selection based on early phase exploration relies upon
  - Being able to make no-go decision
  - Being able to also make go decision
- Patient population starts narrow
  - cannot anticipate degree of heterogeneity, effect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

# Adequate & Well-Controlled (A&WC) 21CFR314.126



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

# Regions in Schizophrenia MRCT\*



Wang SJ, April 21, 2011

12585 patients from 37 countries<sup>41</sup>

# Regional Variability in Mortality

## A Scenario of an SOC

Patient distribution	Europe (50%) 3-countries	Latin America (50%) 7-countries
RDS mortality – 14d	11.7%	7.2%
All cause mortality – 14d	20.5%	12.1%
Non-RDS related mortality	8.8%	5.7%
All cause mortality – 28d	26.2%	14.6%

**Q: Are region specific mortality intrinsic ?**

# Scientific Principles

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

# Scientific Principles

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

