

# **Optimal Adaptive Designs**

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# What is an Adaptive Design?

- PhRMA Working Group Workshop on adaptive design held November 2006:

“A clinical study design that uses accumulating data to decide how to modify the study as it continues without undermining the validity and integrity of the trial.”

*What about non-clinical adaptive designs?*

# What is an Adaptive Design?

- Experimental design where the observations are collected sequentially
- The choice of each new observation or group of observations is based on the information collected earlier
- Allows for the modification of the characteristics of ongoing study
- Can be used in variety of studies

# Example

## Reference:

Jones B, Atkinson G, Ward J, Tan E, Kerbusch (2006). Planning for an adaptive design: a case study in COPD. *Pharmaceutical Statistics*. Volume: 5, Issue: 2, Pages: 135-144.

Phase IIa dose-ranging trial

COPD - chronic obstructive pulmonary disease

Primary endpoint - change from baseline to end of treatment in FEV1 (forced expiratory volume in 1 sec).

# Example (continued)

## Important

- Two objectives (assess safety and tolerability)
- Compare top 2 doses with placebo
- Emax model for dose response
- Consider shortening the study and lowering the cost

# Example (continued)

**Agreed** to consider (*prior to start*)

- Stopping for either futility or efficacy  
(interim analysis)
- Adding or dropping a dose
- Re-estimating sample size
- Varying randomization ratios

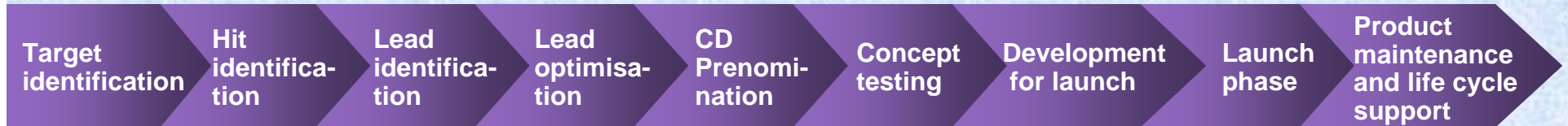
# Example (continued)

- Use of software for the design, simulation of 10000 trials and interim monitoring - EAST 3.1
- Report good teamwork between clinicians, pharmacometric modellers and statisticians
- Report savings as a result of using adaptive designs

# Example (continued)

Option	Design	\$ mil	Approximate time to complete
1	Standard trial	5	1.5 years
2	Choice of difference to detect to reflect accepted clinical practice and use of mean baseline to reduce variability	3	1 year
3	Option 2+ interim for futility and continue recruitment during interim analysis	2.2 3	6 months (if stop for futility) 1 year (if don't stop)
4	Option 2+ interim for futility and stop recruitment during interim analysis	1.4 3	6 months (if stop for futility) 1.3 years (if don't stop)

# Drug Discovery Process



- **Cascade of experiments**
- **It takes around 16 years to launch 1 drug**
- **It costs around \$450 million**

# Opportunities

- Reduce required time / cost
- Increase number of new drugs
- Ethical (e.g. better treatment of patients)

## **BY**

- Making the most of the accumulated knowledge at each stage

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# Accuracy

- Estimate parameters (e.g. efficacy and safety)
  - Potency
  - Optimal safe dose (OSD)
  - Maximum tolerated dose (MTD)
  - Minimum effective dose (MED)
- **Statistical properties of estimates depend on**
  - **Experimental design**
  - **True parameter value**

# Adaptive Design Algorithm

- Stage 1: Collect some data  
(e.g. static design or normalization)
- Stage 2: Estimate parameter(s) of interest
- Stage 3: *Select* a design for the next stage  
(single or group of observations)
- Stage 4: Re-estimate parameter(s) of interest  
(Back to Stage 3 or move on to Stage 5)
- Stage 5: *Stop*

# Mechanism for Selection

- Add one observation at a time
- Add a group of observations
- \* It might be necessary to make a new selection before all data are available

# Criteria for Selection

- Statistical considerations
  - Efficiency – use **Optimum Design Theory**
  - Power
  - Coverage
- Practical considerations
  - Ethical (e.g. use ineffective treatment as little as sensible)
  - Cost (e.g. time)

# Criteria for Selection

- Combined
  - New observation(s) bring maximum information ( $D$ -,  $D_A$ -,  $D_S$ -optimality)
  - Penalty for high cost
  - Penalty for hazard (e.g. use of potentially toxic dose)

# Criterion for Stopping

- Level of uncertainty at acceptable level  
(e.g. power, clear evidence)
  - Time elapsed
  - Resources spent
- \* Early/late stopping may bring cost benefits

# Optimal Design Theory

Model based approach of assessing statistical properties and construction of experimental designs.

Some references:

- Fedorov (1969, 1972)
- ...
- Atkinson, Donev and Tobias (2007)

# What to Adapt

- Design region
- Location of observations in design region
- Stopping (early or late), i.e. change size of design and time of study
- ...

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# Response Adaptive Designs

Typical scenario:

Phase 3 clinical trial; 2 treatments

- Bivariate response
- Looking for  $c\%$  improvement
- Initially unknown variability to power study
- Total number of observations  $n = n_1 + n_2?$
- \* Adaptive design

# Literature

- Zelen (1969)
- Wei and Durham (1978)
- Durham, Flournoy and Li (1998)

...

and many more!

# Biased-Coin Designs

Proposed by Efron (1971).

Main ideas:

- Balance and randomisation required
- Probability to use Treatment 1, when  $n_1 < n_2$ :

$$\pi_E(1 | x_{n+1}) = \frac{2}{3}$$

# Unbalanced BCD

- Proportion  $p$  ( $n_1/n$ ) allocated to Treatment 1
- The rest - to Treatment 2.
- The efficiency is

$$E_n = 4p(1-p)$$

# BCD with Covariates

- Proposed by Atkinson (1982)
- Model (2 treatments,  $q$  covariates)

$$y_i = \alpha_1 h_1 + \alpha_2 h_2 + \sum_{j=1}^{q-1} \beta_j z_{ij} + \varepsilon_i$$

where  $z_{ij}$  is known function of covariate  $x_j$

$$E(Y_n) = G_n \varpi = H_n \alpha + Z_n \beta$$

# BCD with Covariates

- Interest in

$$a^T = \{p \quad (1-p) \quad 0 \quad \dots \quad 0\}, \quad 0 \leq p \leq 1$$

and

$$\text{var}\{a^T \hat{\omega}\} = \sigma^2 a^T (G_n^T G)^{-1} a$$

with a minimum value  $\sigma^2 / n$  for  $p^*$

# BCD with Covariates

- For patient  $n+1$  with covariates  $x_{n+1}$

$$\sigma^2 \text{var}(\hat{y}_{n+1}) = d_A(j, n, x_{n+1})$$

Allocate treatment  $j$  with **probability**

$$\pi_A(j | x_{n+1}) = \frac{p_j^* d_A(j, n, x_{n+1})}{\sum_{s=1}^2 p_s^* d_A(s, n, x_{n+1})}$$

# Adaptive BCD with Covariates

- Proposed by Atkinson and Biswas (2005)
- Continuous response
- Skewed allocation towards better treatment(s)
- Loss function
- Method: update  $p^*$  and  $d_A(j, n, x_{n+1})$

# Adaptive BCD With Covariates

- Apply one of the rules:
  - Deterministic. If  $d(1, n, x_{n+1})$  is largest

$$\pi_D = (1, x_{n+1}) = 1$$

- $D_A$ -optimum ( $t$  treatments) – avoids selection bias

$$\pi_A(j | x_{n+1}) = \frac{p_j^* d_A(j, n, x_{n+1})}{\sum_{s=1}^t p_s^* d_A(s, n, x_{n+1})}$$

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# Adaptive Dose-Finding Designs

- Proposed by Dragalin and Fedorov (2004)
- Maximize the expected increment of information
- Uses Optimal Design Theory

# Adaptive Dose-Finding Designs

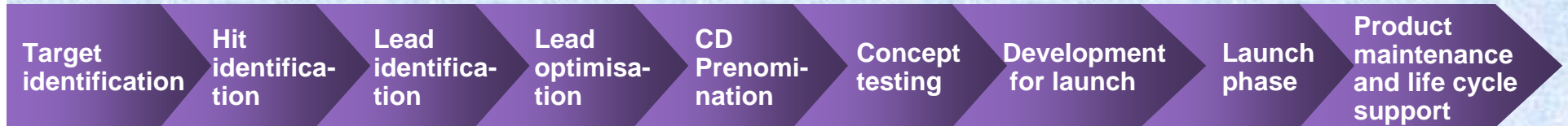
## Design optimality

- D-optimality criterion  
 $|M(\xi, \theta)|$  maximized
- Locally optimal designs  
(as  $M(\xi, \theta)$  depends on  $\theta$ )
- Performance evaluation – simulation studies

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# Drug Discovery Process

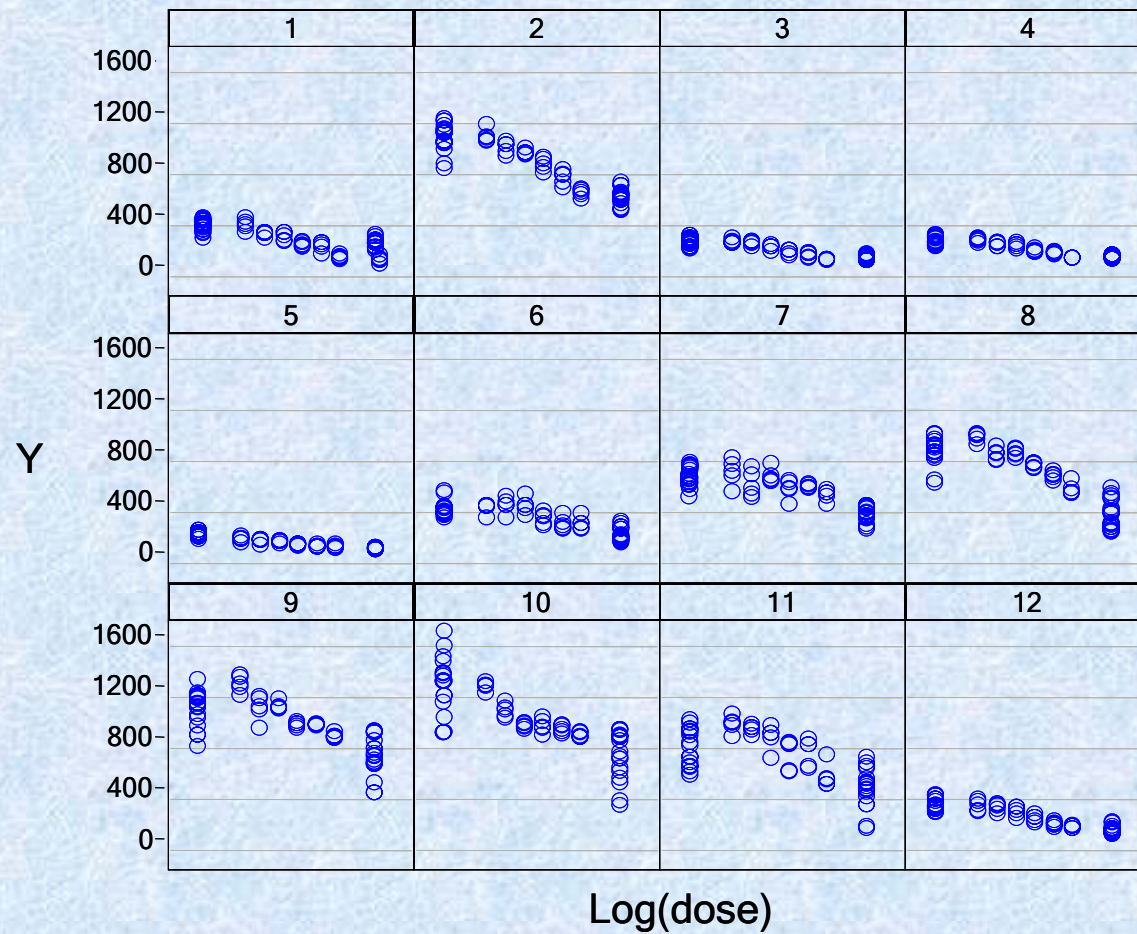


- **Cascade of experiments...**

# Studies

- Compounds to compare
- Compounds are studied on a number of occasions
  - Opportunity to use adaptive designs
  - Between-occasions variability!

# Example: data collected on 12 occasions



# Statistical Models

In general

$$y_j = f(\mathbf{x}_j, \boldsymbol{\beta}) + \varepsilon_j$$

$j$ -th observation, 1 occasion

$$f(\mathbf{x}_j, \boldsymbol{\beta}) = \gamma + \frac{\delta - \gamma}{1 + 10^{(x_j - \alpha)\lambda}}$$

$x_j - \text{Log}_{10}(\text{Dose})$

# Adaptive Bioassay

Chaudhuri and Mykland (1993, 1995) (CM method).

- Start with a ‘static’ design
- Add one observation at a time based on local D-optimality
- Often impractical
- Ignore the between-occasion variability

# Adaptive Bioassay

- Start with a static design  
(serial pipetting,  $k$  doses, dilution factor 2 or 3)
- Sequentially augment this design
  - Locally D-optimum design (Method A)
  - Repeat the static design (Method B)
  - CM method
- Update  $\beta$  as new data become available;  
Consider smaller  $n$  for next occasion

# Occasions

- Choice of models
- Consider data collected at a particular occasion as a 'block'
- Shared parameters: do not change across blocks

# Nonlinear Models With Blocks

For the remaining parameters:

1. Fixed blocks: different parameters for each block
2. Random blocks: random parameters

Models:

1. Nonlinear mixed effect models
2. Population nonlinear regression models

# Example: B Blocks

- Fixed blocks (shared LogIC50):

$$y_{ij} = \gamma_i + \frac{(\delta_i - \gamma_i)}{1 + 10^{(x_{ij} - \alpha)\lambda_i}} + \varepsilon$$

$y_{ij}$  -  $j$ th observation in the  $i$ th block

$x_{ij}$  - the logarithm of the dose

# Example: B Blocks

- Random blocks: random shared effects (shared LogIC50)

$$y_{ij} = \gamma + \frac{(\delta - \gamma)}{1 + 10^{(x_{ij} - \alpha)\lambda}} + \varepsilon$$

$\lambda$ ,  $\gamma$  and  $\delta$  - random parameters

(e.g.  $\gamma \sim N(\Gamma, \sigma_\gamma^2)$  not independent from  $\delta$ )

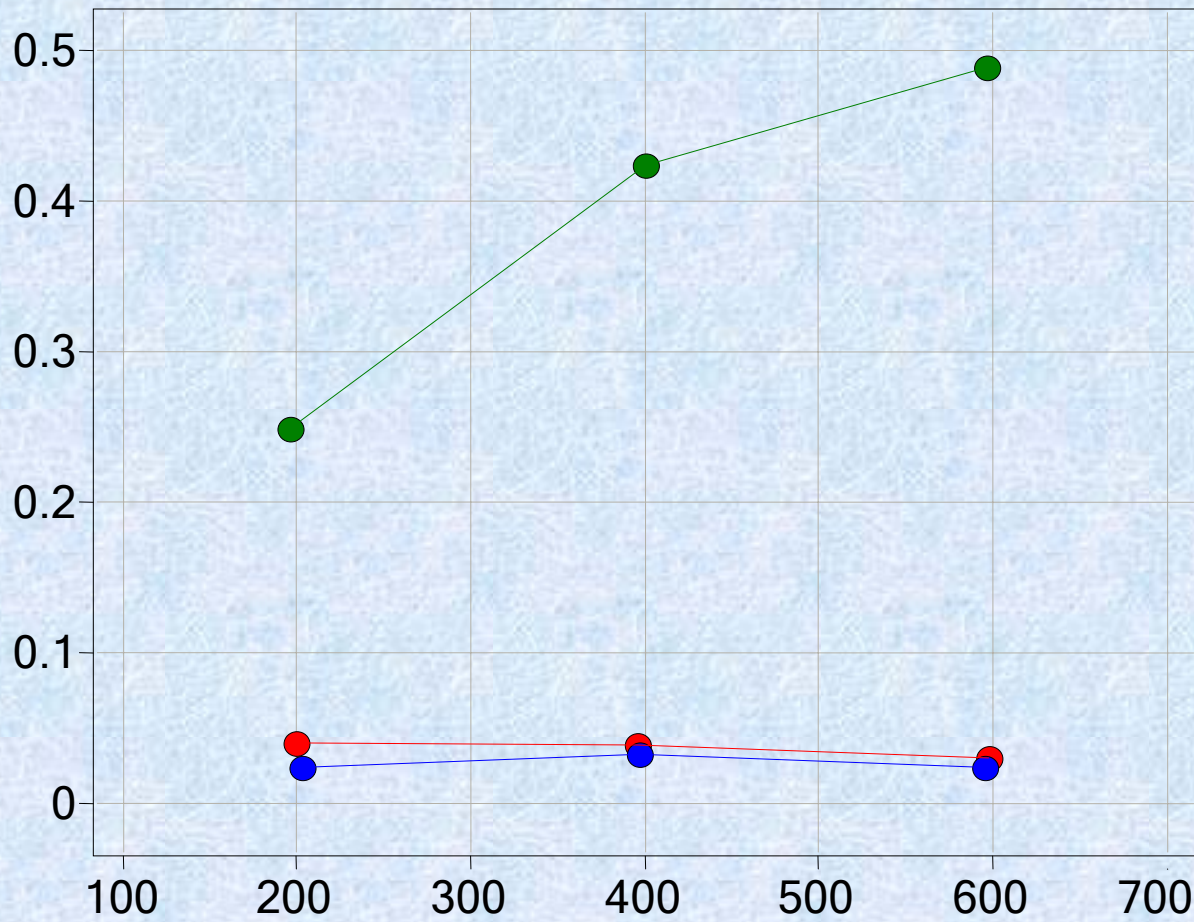
# Comparison of Designs

- Standard criteria
- At each occasion we need to estimate:
  - Assay window
  - LogIC50

# Simulations

- Parameters as in the real dataset
- Between occasions variability affecting assay window (range) and  $\lambda$
- Between occasion variability - different assay windows
- 2 occasions for Method A and Method B

# MSE for LogIC50



Color by Method:



A



B



CM

Window Range

# Results

- CM method – not suitable! (Not surprising!)
- Locally D-optimum designs – useful!
- Serial pipetting designs are excellent! (**Which one?**)
- Adaptive designs allow:
  - update the plate design and  $n$
  - review doses
  - reduce cost ...

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# Summary

## Optimal Adaptive Designs

- Optimisation problem of design augmentation with constraints
- Have been used in practice
- Approval by regulatory authorities

# Further work

Develop new ideas

- Respond to business needs
- Review criteria of optimality
- Design robustness, power and stopping rule
- Simplicity of implementation
  
- **It is team work!**