

PhRMA Adaptive Designs Workshop

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Overview of Adaptive Dose Finding Methods

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The Lilly logo is a stylized, cursive script of the word "Lilly" in white.

Answers That Matter.

Broad Topic

Focus:

- Population (group) average dose response studies in patients

Other important considerations:

- Exposure-response models
 - Increase understanding of population dose response
 - Adjust individual dosing in practice
 - Useful to develop adaptive dose-response designs
- Final conclusions on dose-response from entire database
 - Not restricted to studies designed to inform about dose response

Outline

Challenges

Objectives of dose-response studies

Analysis Methods

- Multiple Comparisons
- Model Based

Adaptive methods

- Early exploration
- Later stage development

Recommendations

Some Challenges

High failure rate in Phase III

- 45% (Kola and Landis, 2004)
- Wrong dose(s) into Phase III

More information about dose response earlier

- Large sample sizes are often needed
- Low Pr (TS)
 - 62% of candidates fail in Phase II

Development costs escalating

- Risen by 55% in the last 5 years (FDA Critical Path, 2004)

Objectives of Dose Response Studies

First: Is there any evidence of an effect?

Currently:

- Tendency to explore too high doses
 - Maximize probability of technical success by taking highest tolerated dose into PoC
 - Take highest tolerated dose into efficacy studies

Many Potential Questions

What is the nature of the dose response?

Minimally effective dose (MED) ?

Maximum useful dose ?

- Maximum effective dose (MaxED)

- e.g. ED95: dose producing 95% of Emax

Maximum tolerated dose (MTD) ?

ICH e4 “...practical study designs do not exist to allow for precise determination of these doses.”

Analysis Approaches

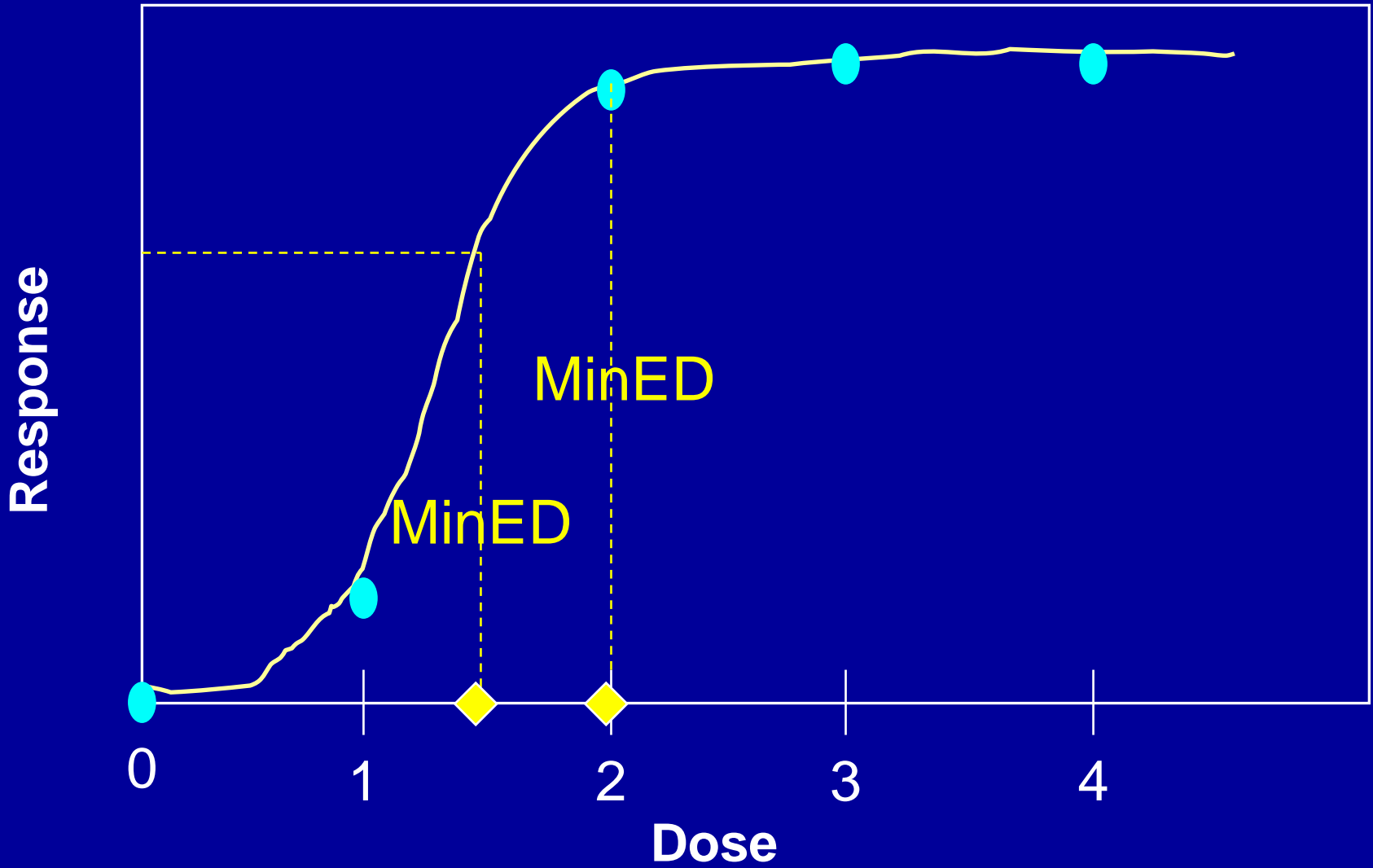
Multiple Comparison Procedures

- Very few (or no) assumptions about dose response shape
 - E.g. monotonic $u_1 \leq u_2 \leq u_3 \leq u_4$
- ONLY gives information about the doses observed
- NO information about what is happening between doses

Some inefficiencies:

- Typically requires high sample sizes per dose group
 - Feasibility limits number of doses explored
- May identify if dose response exists **BUT**
- Provides limited information on dose-response

Fixed Dose Design



Analysis Approaches (continued)

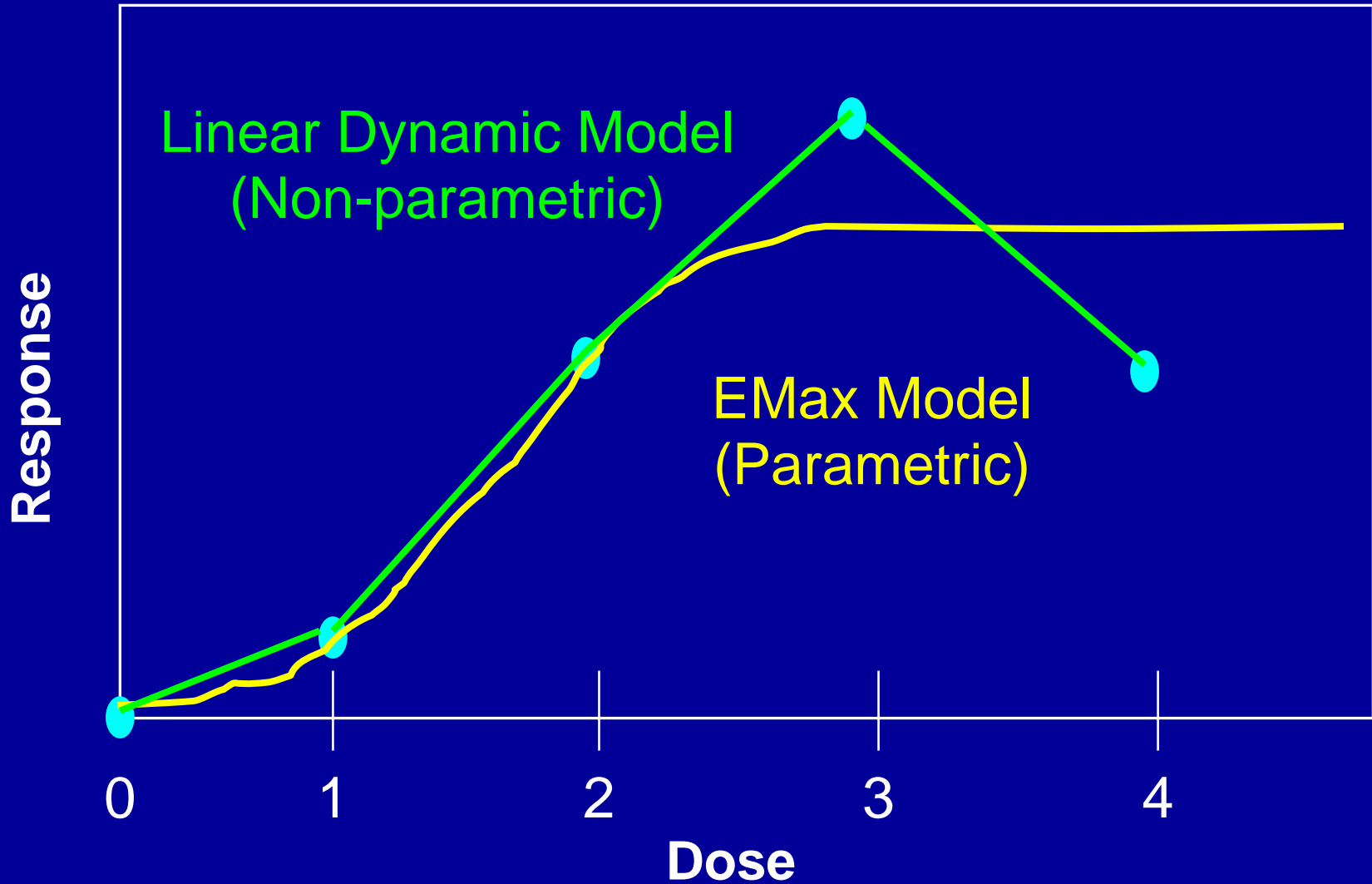
Model Based Approaches

- ASSUMES a functional relationship between the dose and response
 - Parametric & Non-parametric model-based approaches
- Estimates, such as ED95, inferred from the model

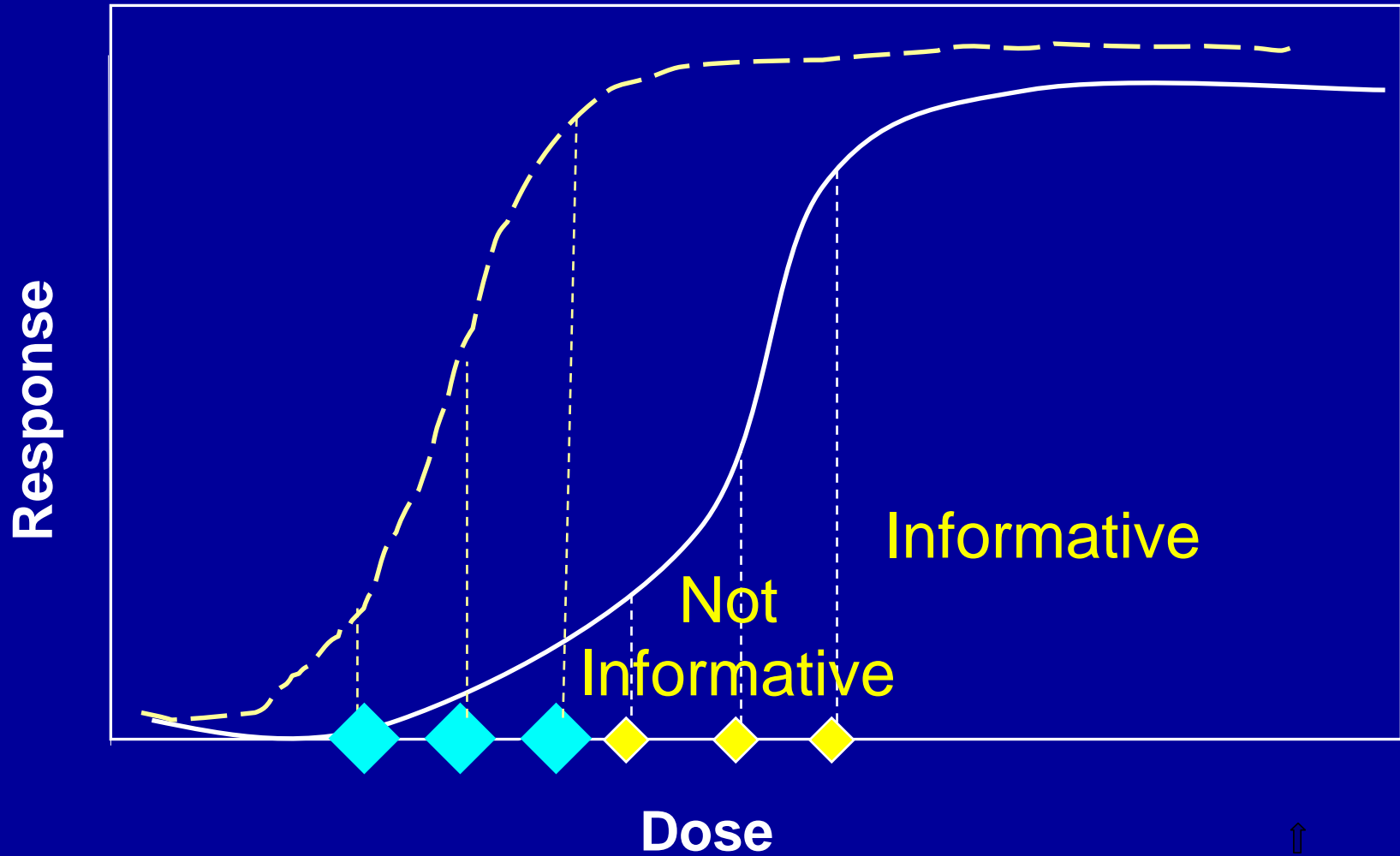
Potential inefficiencies with fixed dose design:

- Provides limited information on dose-response
 - Same number of patients assigned to each dose
 - Often high likelihood doses selected a-priori are not optimal
 - Unlikely to identify at predetermined levels of precision, e.g., MED, ED95

Parametric / Non-parametric



Fixed Dose Design



Objectives Adaptive Dose-Response

Getting information as fast as ethically possible about key aspects of the dose-response curve

Increased information with improved efficiency:

- Explore more doses with same sample size as fixed design
- More observations at doses that better inform the dose-response curve
- More observations on the doses that are most promising

Feasible to combine PoC and Phase II dose finding with early stopping for futility

- Shorten development timelines
- More informative Go / No Go decisions
- Improve Pr (TS) in Phase III

Adaptive Dose-Response Methods for Early Exploratory Studies

Originally designed to focus on **estimating MTD** and learning about the **response profile**

- Generalize to any response measure
- Majority of experience in cancer

Two general approaches:

- **Traditional:** No estimation in statistical sense
 - MTD is highest dose studied where say less than 1/3 toxicity was observed
- **Model-based approaches**
 - MTD is a quantile of the dose-toxicity response profile to be estimated

Some Model Based Methods

(Gaydos et.al. 2007)

Random Walk Rule

- Non-parametric model based approach to estimate MTD

Penalized D-optimal designs

- Flexible (address efficacy & safety dose-response simultaneously)

Bayesian Designs

- **Continual Reassessment Method (CRM)**
 - Dose assignments converge to MTD
- **modified CRM**
 - Limits dose escalation

Bayesian Designs (continued)

Escalation with overdose control

- Controls for subsequent treatment assignment exceeding MTD

Bayesian D-optimal designs

- Targets the overall dose response curve

Bayesian decision-theoretic approaches

- Very flexible
- Simultaneously optimize over a set of objectives customized for the given study

Adaptive Treatment Selection based on Combination Tests

Typically more applicable to later stage development

Controls family-wise type I error rate

Adaptations:

- Dropping and/or adding treatment arms
- Stopping early
- Sample size re-estimation
- Changing primary endpoint

Bauer and Keiser (1999), Hommel (2001)

Combination Tests (continued)

Approach:

- Trial analyzed in a series of independent stages
- Very flexible
 - Do NOT have to define what you will adapt in advance
 - CAUTION: interpretation
 - Do have to define a-priori how you will combine the test statistics from the stages to make inference

Adjustments are needed for inference (Posch et.al. 2005)

- Multiplicity adjusted p-values for dose-control comparisons
- Point estimates and CI adjusted for
 - Early stopping
 - Treatment selection

Adaptive Designs are NOT always “Better”

You can “adapt” too quickly

- *Appear* to be learning faster than you are and adapt incorrectly
- Simulations are needed to understand trial behavior

Increased complexity

- Scientifically more complex
- Computationally intensive
- More time needed for planning

Risks, Costs & Benefits Need to be Assessed

- Adaptive VS Fixed Designs
- Across adaptive design methods

General Recommendations

Consider adaptive dose-response designs in exploratory development

- Assess potential gains against those of standard fixed designs
- Balance complexity with potential gains

Consider Seamless PoC/Phase 2 dose-response study

Recommend model based approaches

- More informative of dose response profile than multiple comparisons
- Critical to assess model assumptions
- Non-parametric models less restrictive

Adaptive BY Design:

- Define the dose assignment mechanism prospectively

Recommendations (continued)

Leverage information from disease state and exposure-response models

- Selecting dose-response model
- Defining prior distributions for model parameters
- Development of adaptive algorithm (decision criteria)
- Trial simulations to assess design performance

Committee must monitor the study on an ongoing bases

- Ensure protocol is followed (no programming errors)
- Unanticipated safety signals not accounted for in the adaptive algorithm

Engage the committee early in scenario simulations

- Prior to protocol approval

Select References

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