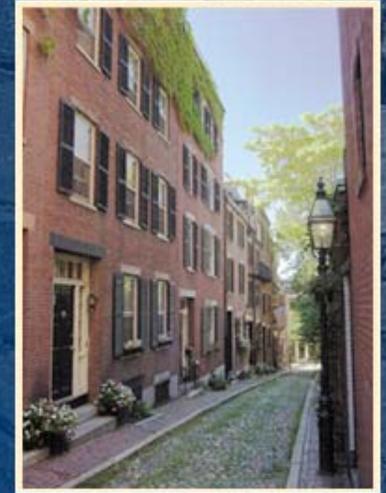




44TH
Annual Meeting



Boston 2008

Experience with Adaptive Dose-Ranging Studies in Early Clinical Development

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Thanks to members of the PhRMA Adaptive Design Working Group

Cytel
STATISTICAL SOFTWARE & SERVICES

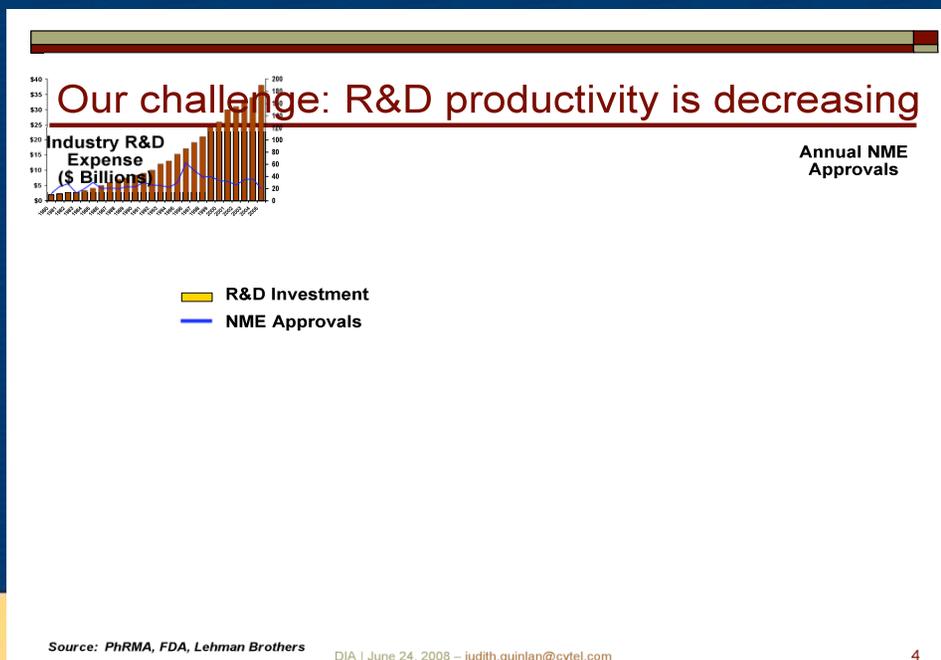
Our objective

- To bring safe and efficacious medicines to patients as quickly as possible
- This is a common goal of patients, regulatory agencies and industry



Where are we coming from?

- R&D productivity is decreasing
 - Insufficient understanding of the dose-response
 - Key factor for unnecessary rework in potentially efficacious drug
 - Failure in phase III due to wrong dose selection



Where do we want to be?

- We want to increase R&D productivity
 - Sufficient understanding of the dose-response to
 - Avoid unnecessary rework in efficacious drugs
 - Minimize phase III failure due to wrong dose selection



How do we get there? FDA Critical Path Initiative

- Not enough applied scientific work has been done to create new tools to get fundamentally better answers about how the safety and effectiveness of new products can be demonstrated, in faster time frames, with more certainty, and at lower costs.
- A new **product development toolkit** -- containing powerful new scientific and technical methods such as
 - animal or computer-based predictive models,
 - biomarkers for safety and effectiveness, and
 - ***new clinical evaluation techniques***is urgently needed to improve predictability and efficiency along the critical path from laboratory concept to commercial product.



Definition: Adaptive Design



- **Adaptive by design**
 - not an *ad hoc* change of the trial conduct and analysis
 - not a remedy for poor planning
- Use accumulating data
 - to decide on how to modify aspects of the study
 - without undermining the *validity* and *integrity* of the trial



The Principle

- The Best Design
 - Highest **information value** per resource unit invested
- Learning and decision making in real time
 - Make the Correct Decision
 - At the earliest time point
 - In the most efficient way



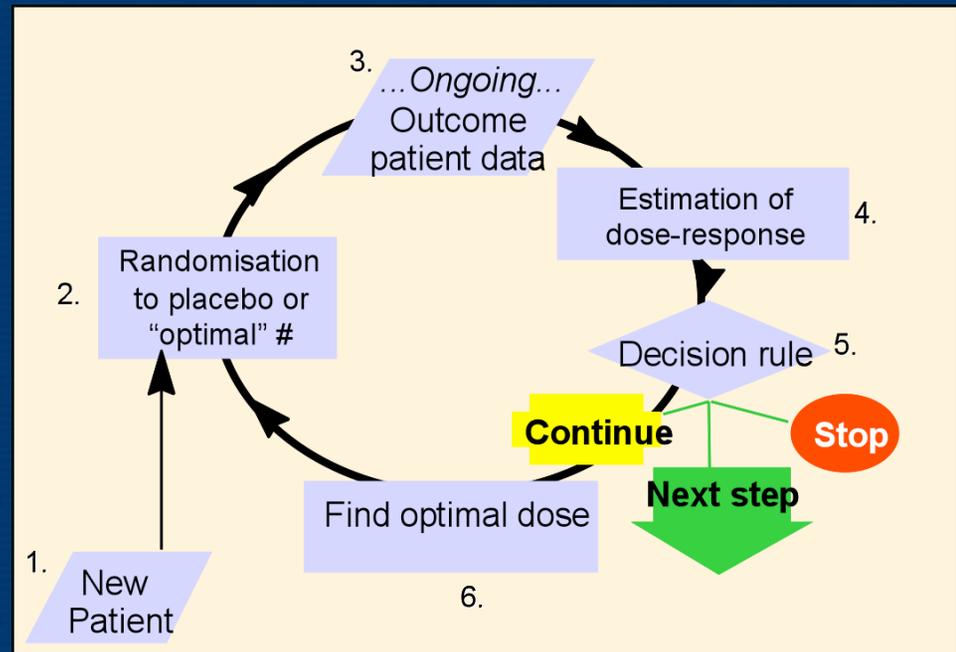
Myth-busting

- Adaptive designs
 - will NOT make drugs work, which don't work
 - are NOT a panacea for everything
 - might early on redirect our attention to promising assets
 - might increase the “information value” per \$\$ investment (in a resource constrained environment)
 - are an “enabler” for
 - a) team-building (discovery, clinical, biostatistics, IT, regulatory, project management, clinical operations, marketing) and
 - b) earlier and better planning, decision-making
 - c) simulation guided clinical drug development
- Focus on learning about the dose-response
 - “What is the correct dose to take forward into phase III?”

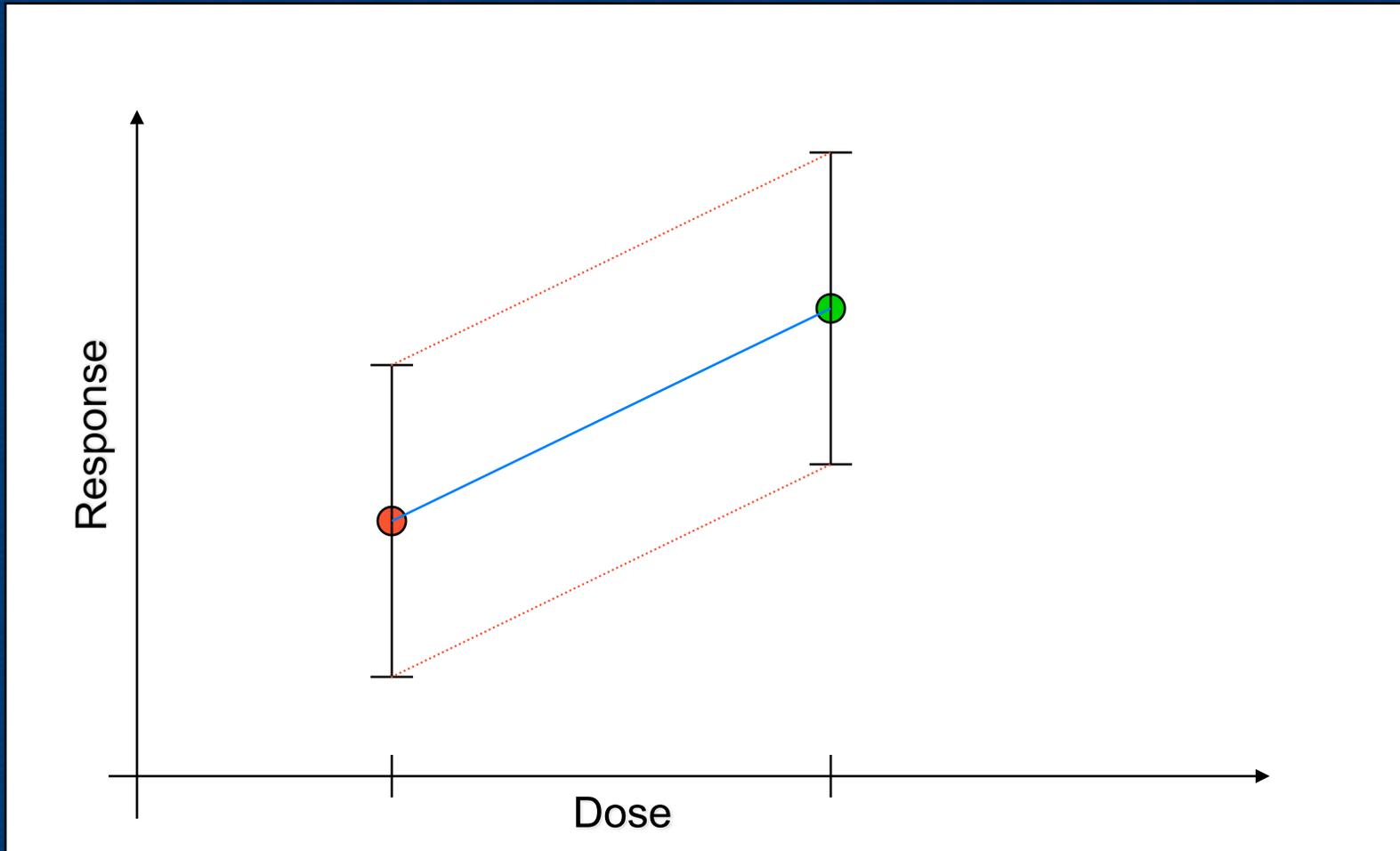


Biggest challenge: Getting the dose right

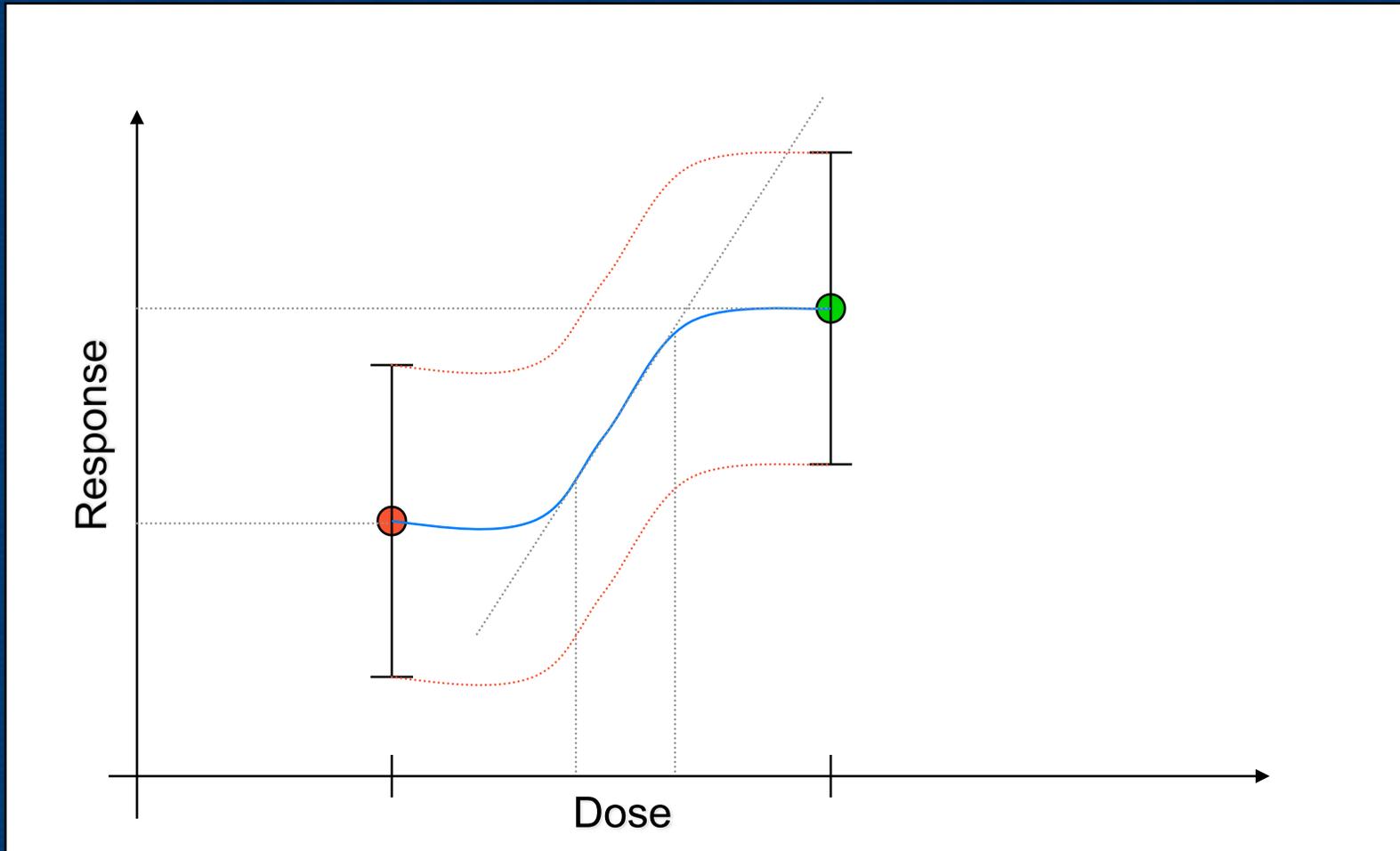
- Identifying the correct dose to take into phase III
 - The first time round
 - Better, faster, cheaper
- Early drug development: Adaptive dose-response finding
 - “Succeeding efficiently”



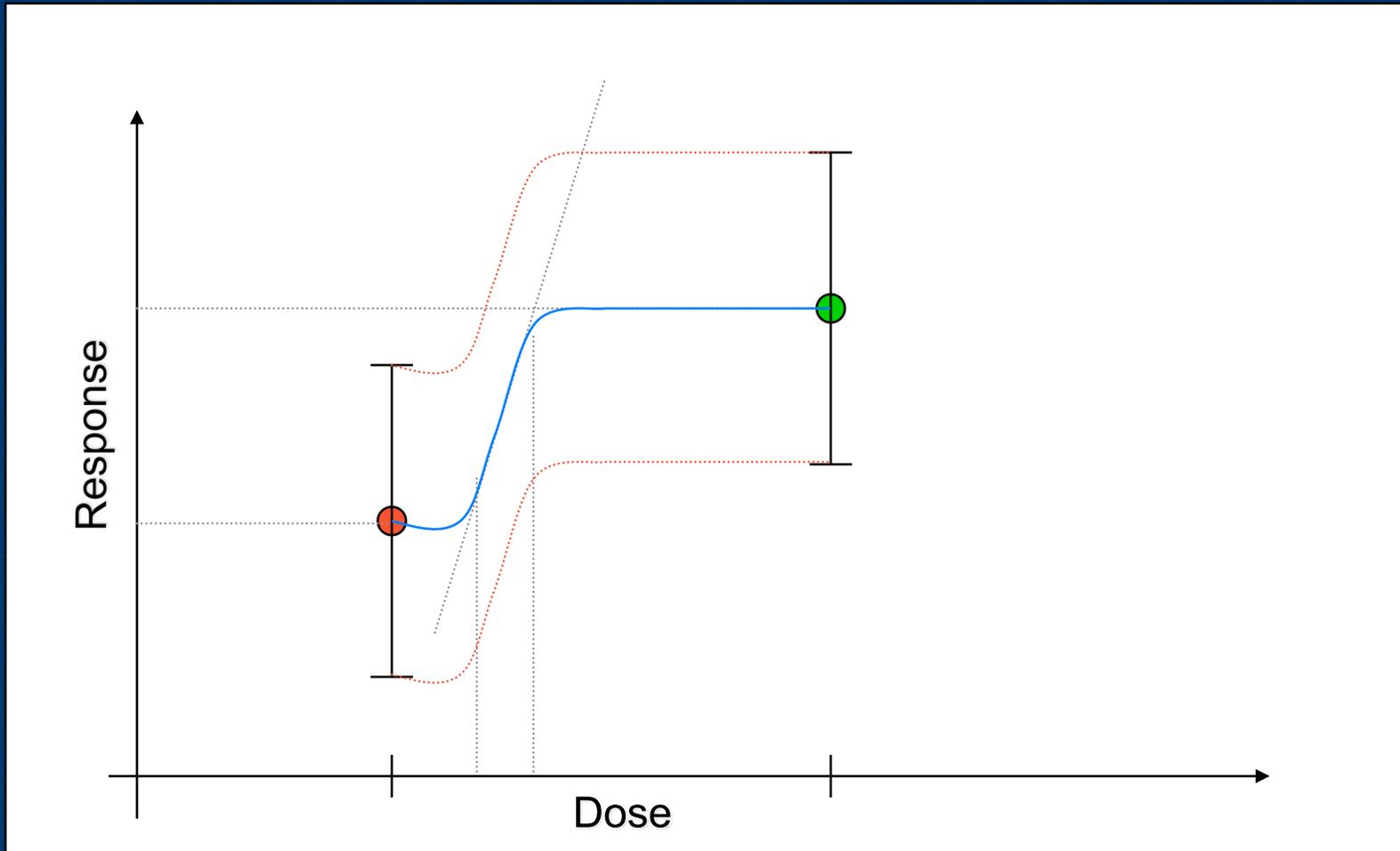
Adaptive dose-response finding



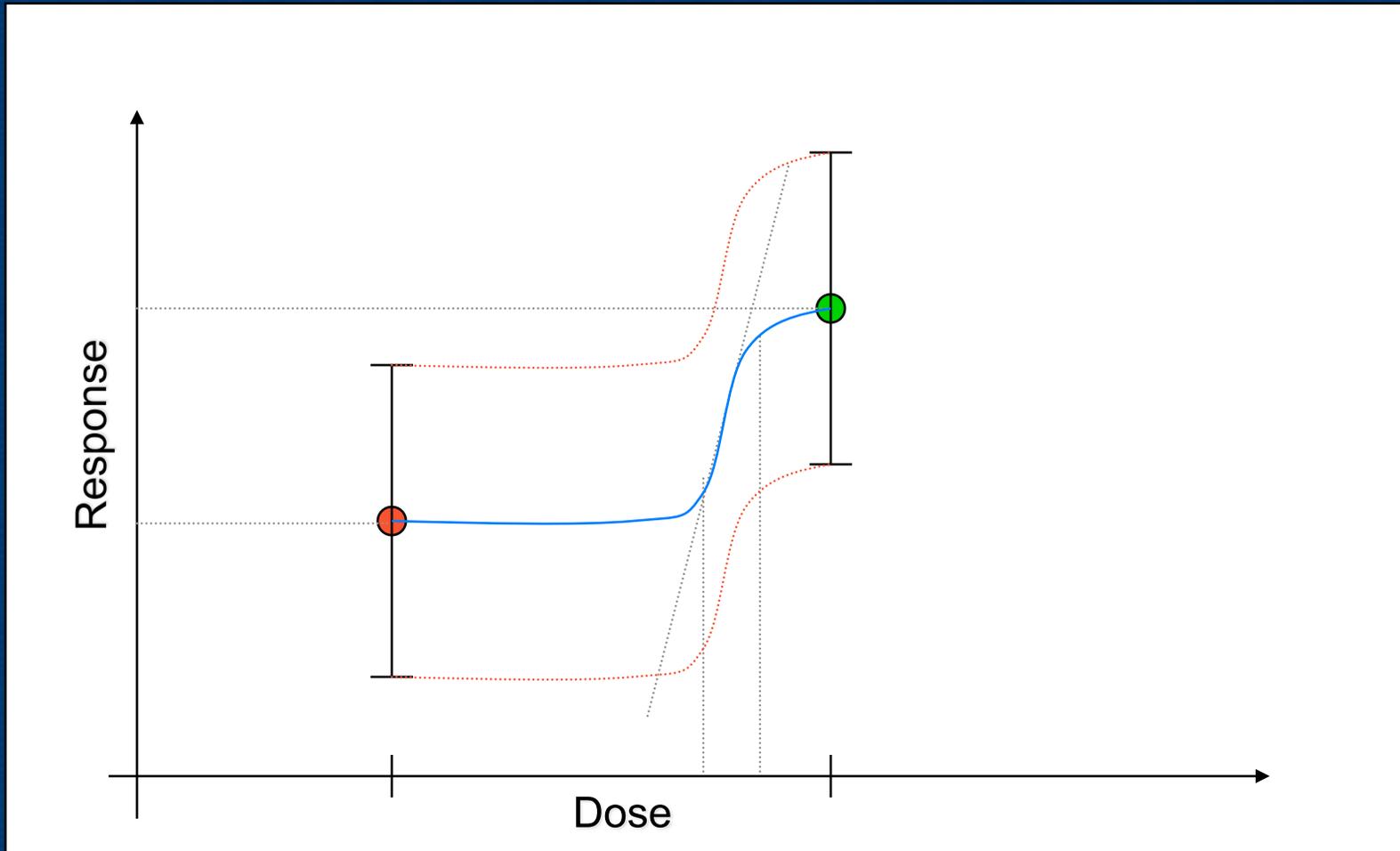
Adaptive dose-response finding



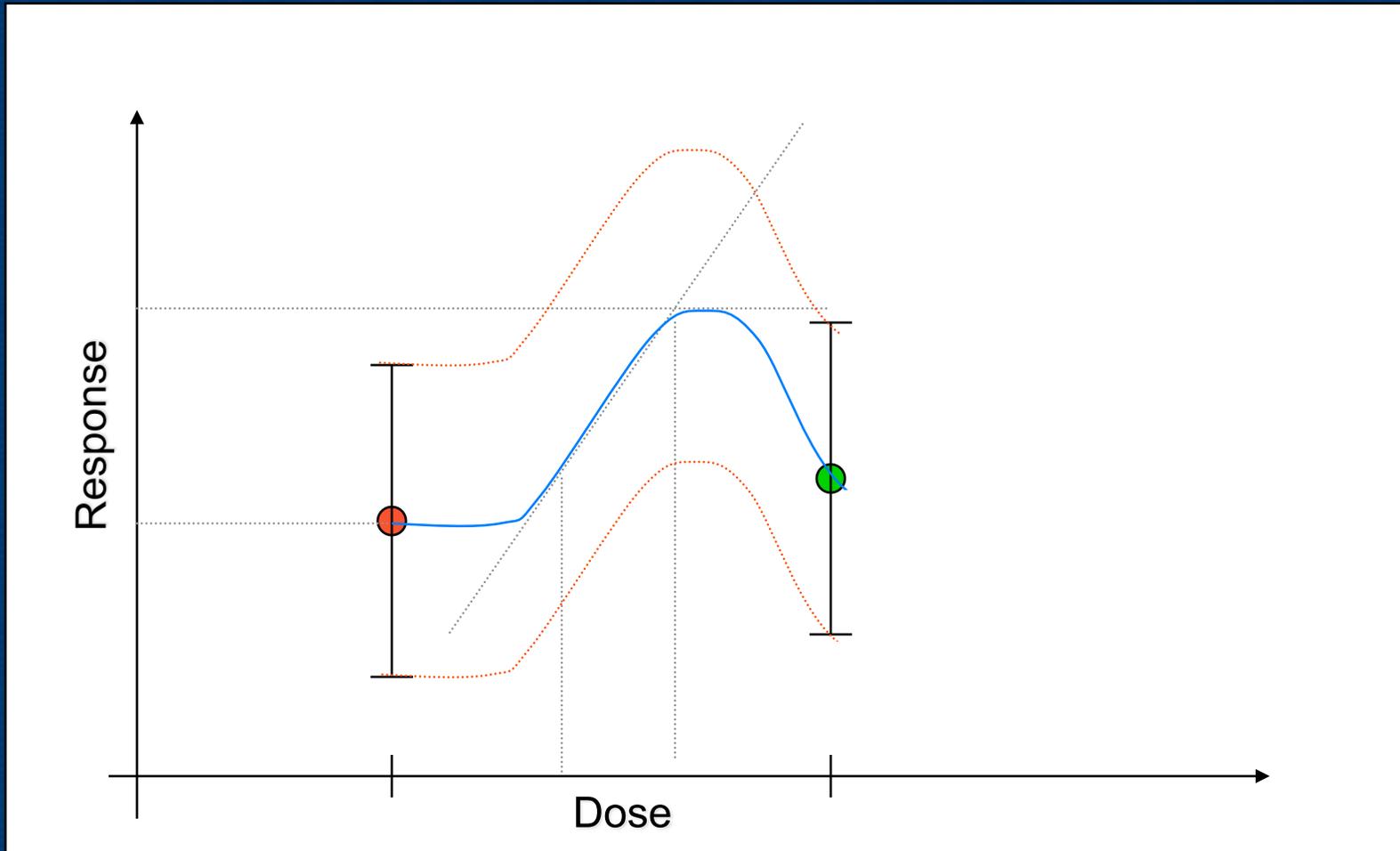
Adaptive dose-response finding



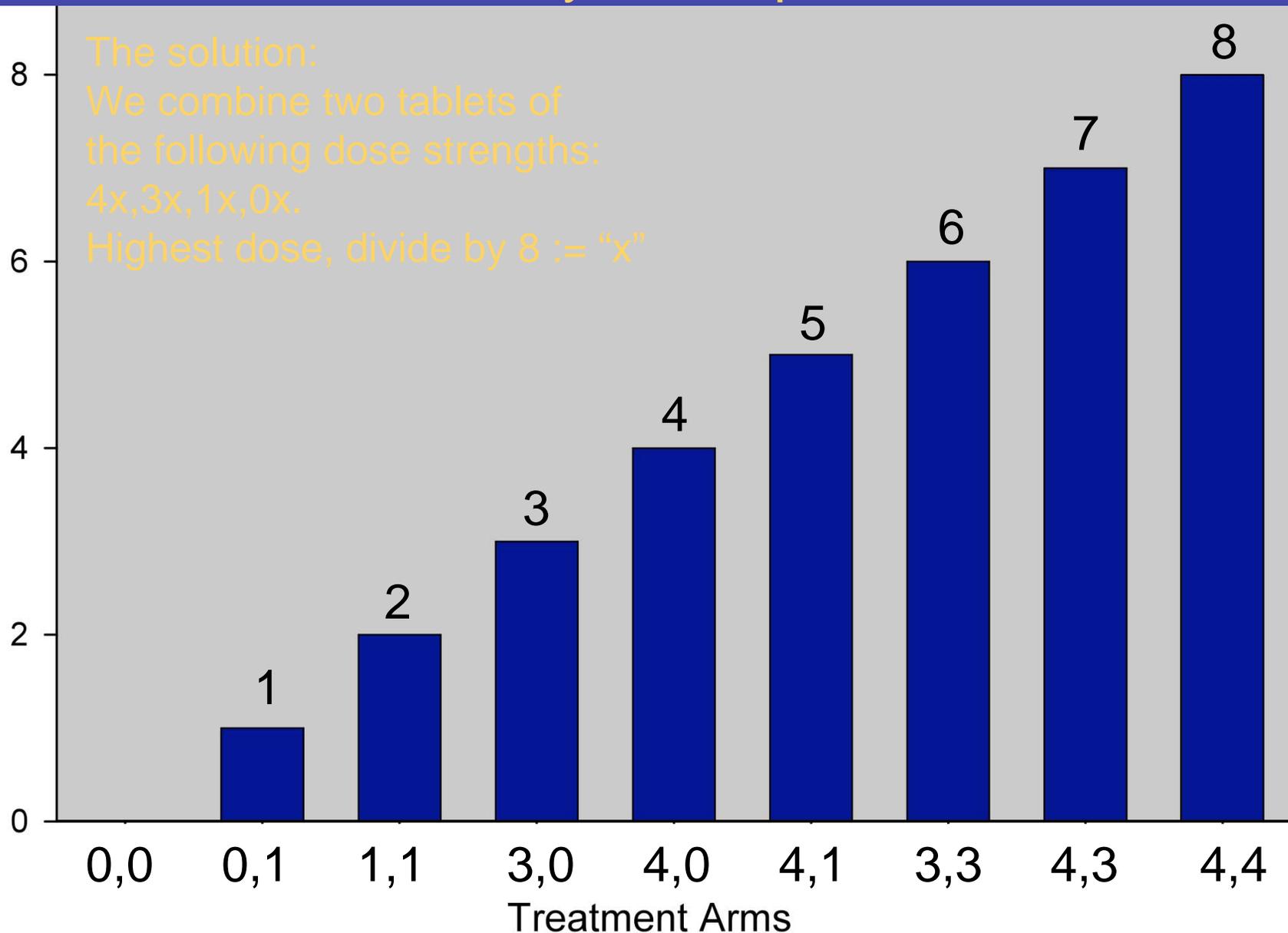
Adaptive dose-response finding



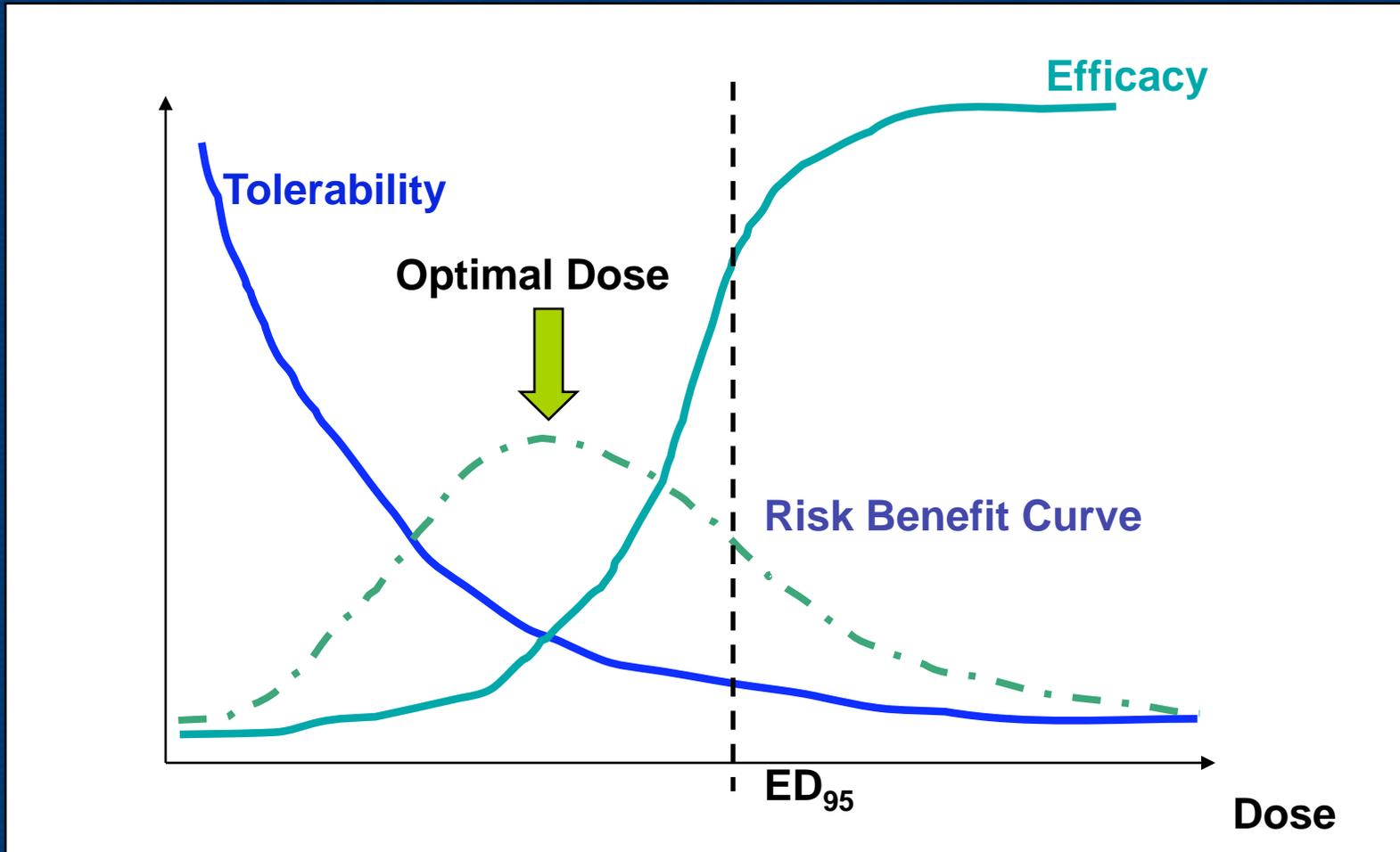
Adaptive dose-response finding



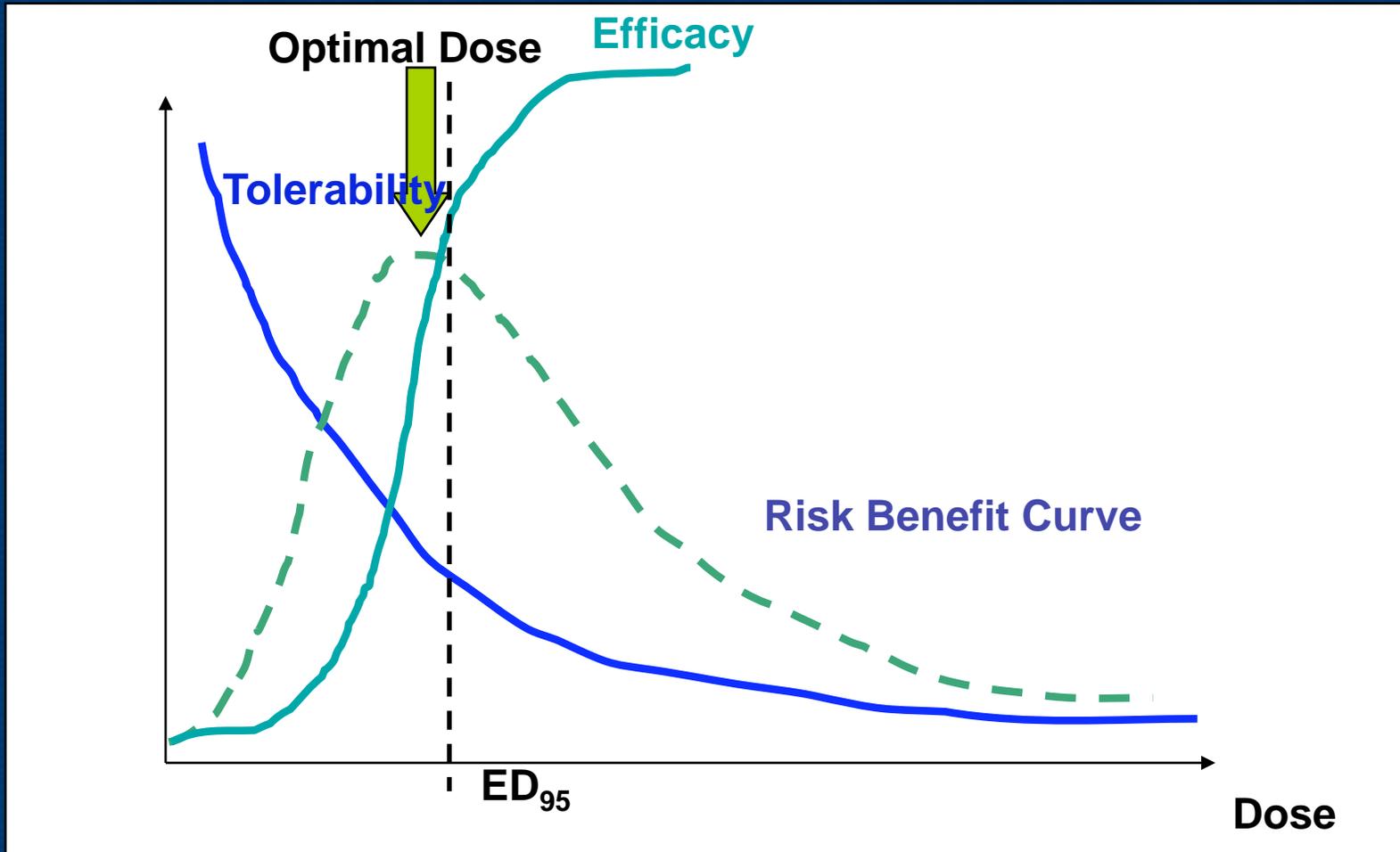
Large number of doses can be conveniently supplied in early development



Phase II: risk/benefit

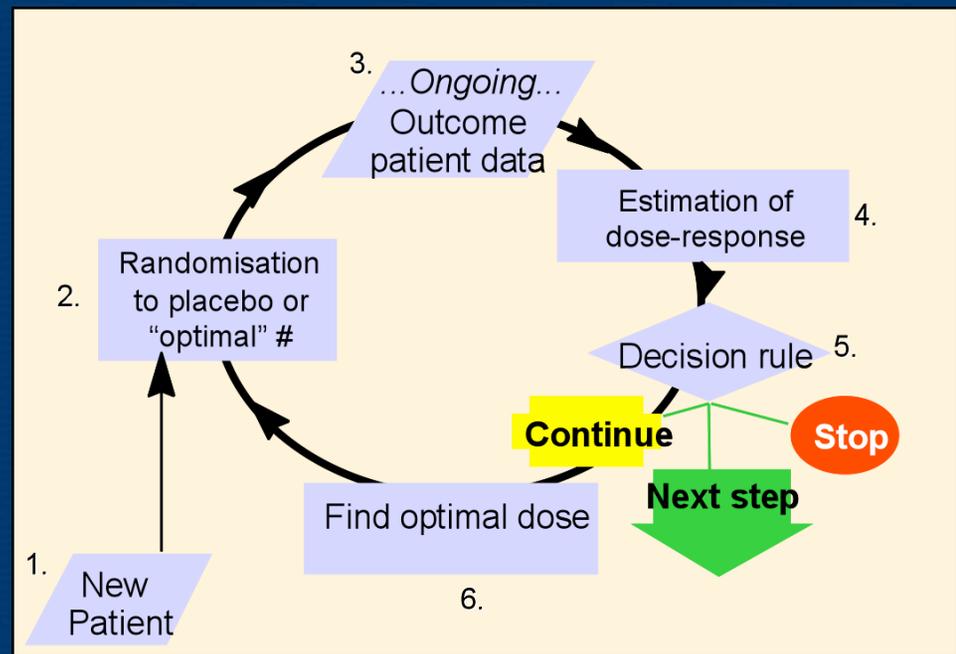


Phase II: risk/benefit

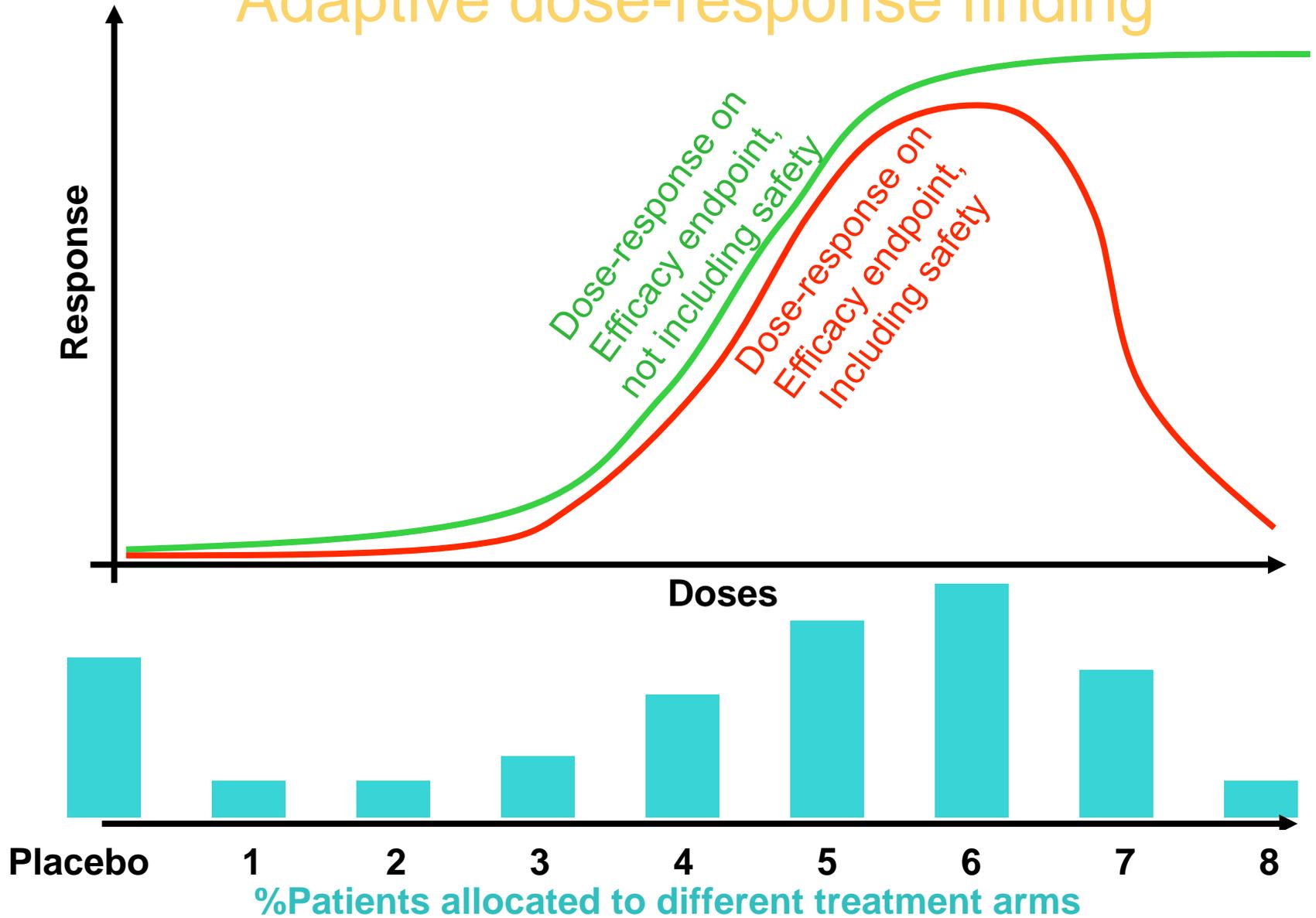


Biggest challenge: Getting the dose right

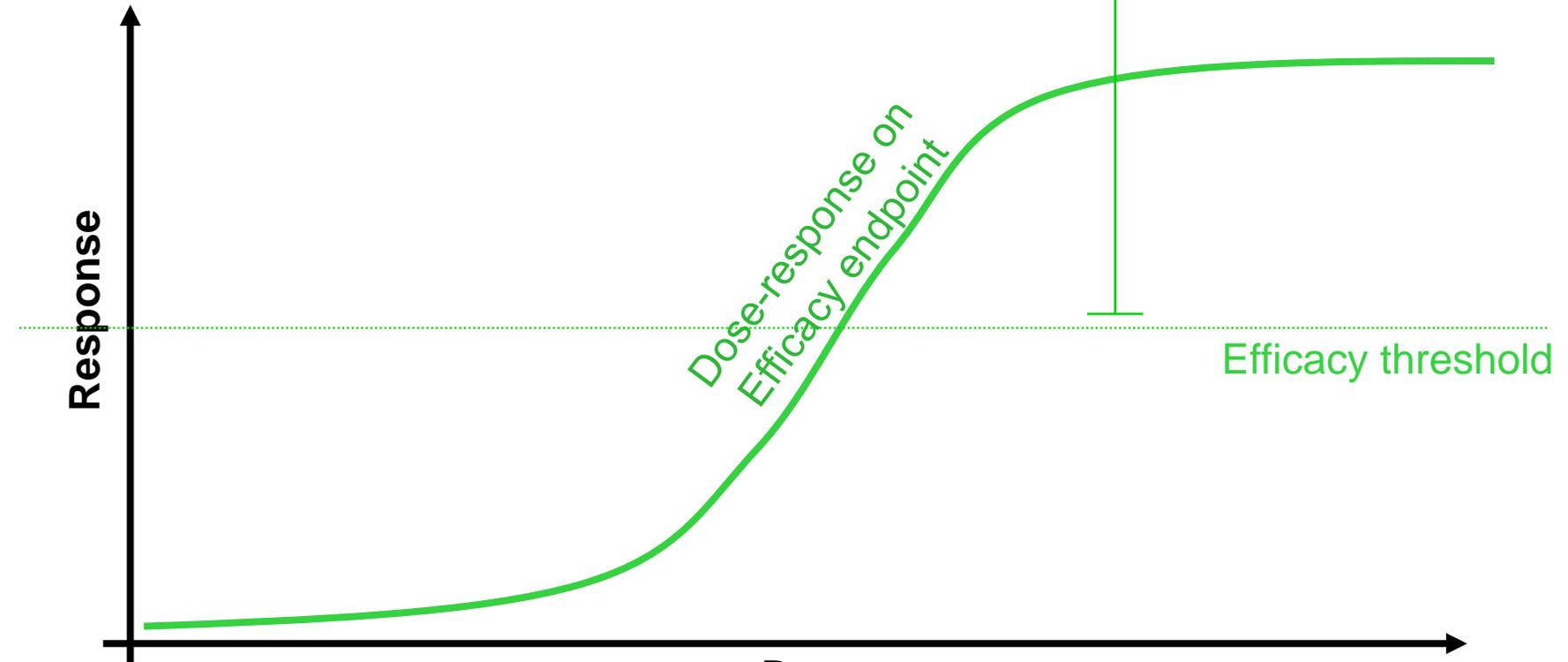
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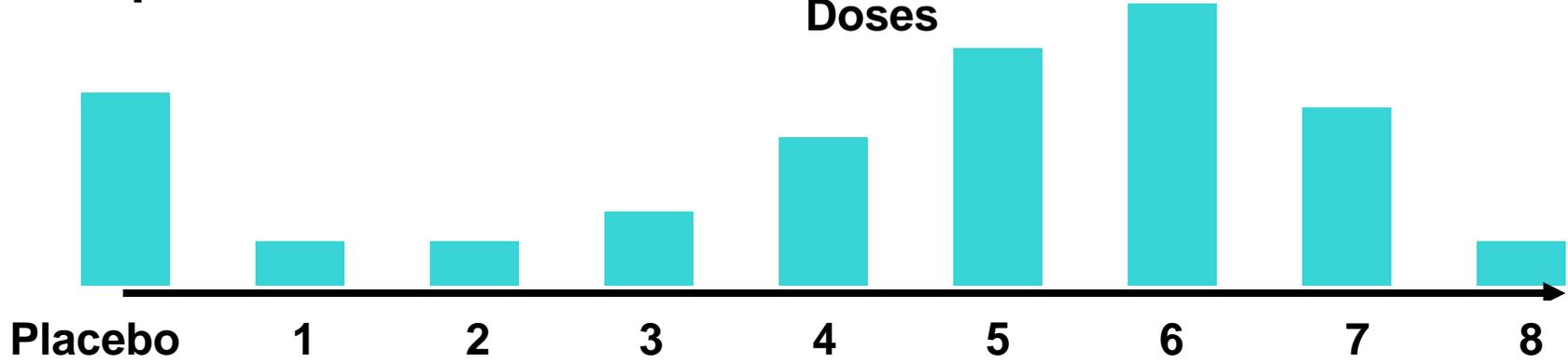
Adaptive dose-response finding



Dynamic termination

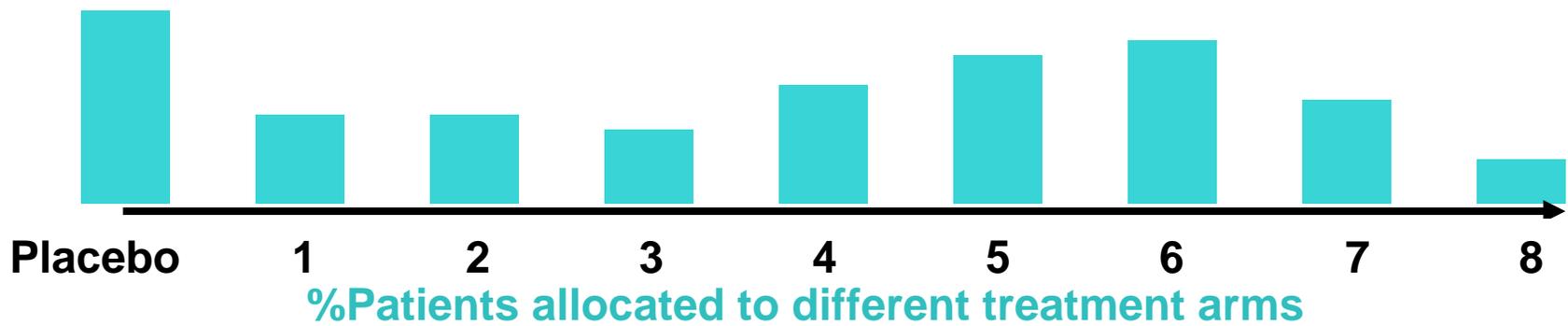
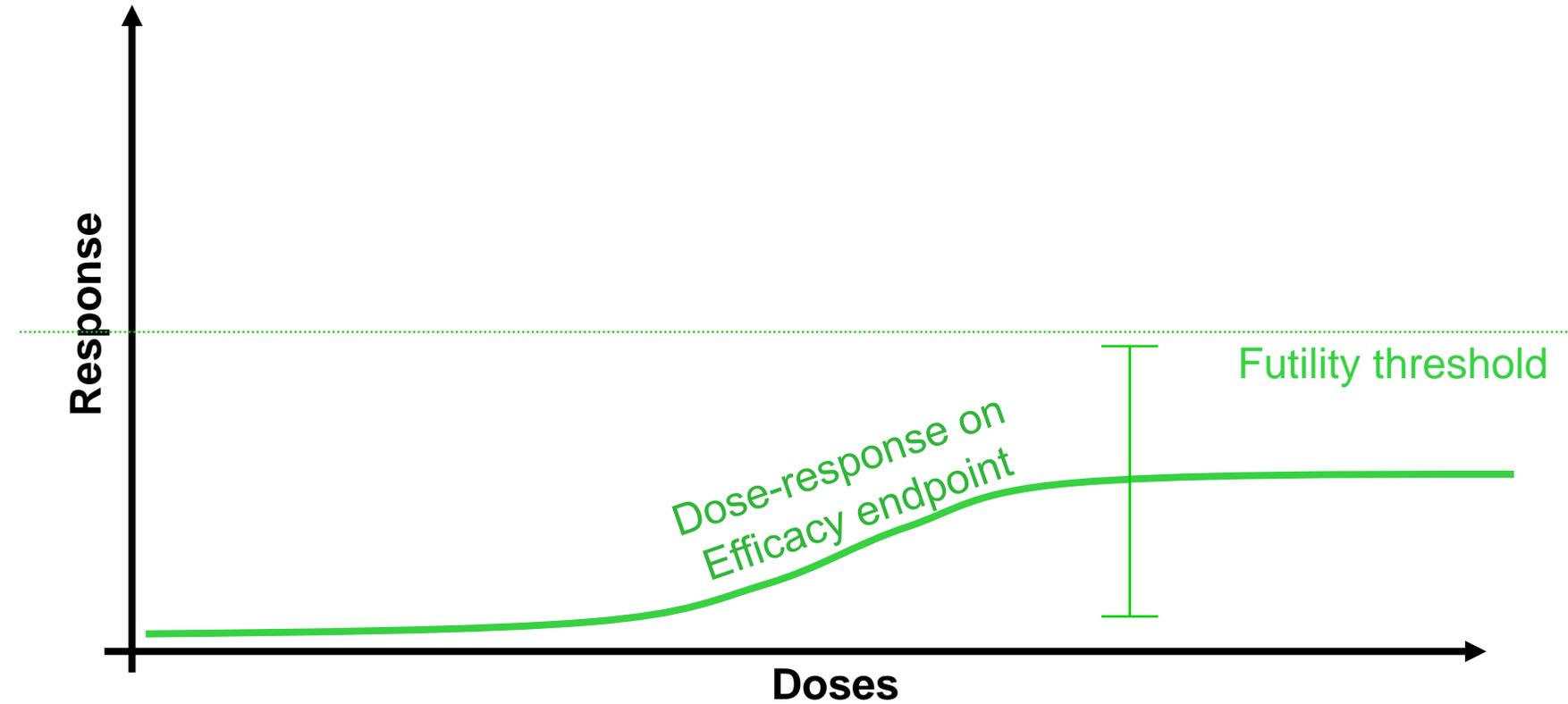


Doses



%Patients allocated to different treatment arms

Dynamic termination



Adaptive dose-ranging

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INNOVATIVE APPROACHES FOR DESIGNING AND ANALYZING ADAPTIVE DOSE-RANGING TRIALS

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Bornkamp et al.,
Innovative Approaches for
Designing and Analyzing
Adaptive Dose-Ranging Trials.
White paper from the PhRMA
working group on adaptive
dose-ranging, with discussion.
J Biopharmaceutical Statistics
2007;17:965-995 or
<http://biopharmnet.com/doc/doc12005.html>



Challenges (1)

- Not enough time to think
 - EARLY interaction: Opportunities for adaptation?
 - Ideally pre-IND
 - 3-6 months to conduct scenario analyses and simulations
- Decision-problems/research questions not clearly defined
 - Align utilities across functions, e.g. between Commercial, Regulatory, Clinical...
- Value of model-based design poorly understood
 - There is a world out there beyond pairwise comparisons
 - In particular for studies in “Learn”
- Brainwashed into “Fast Recruitment”
 - Identify OPTIMAL recruitment speed given all utilities
 - Simulate execution of the trial and do sensitivity analysis on different recruitment speeds:
Which one provides the highest information value per research unit invested?



Challenges (2)

- Implement change *AND* win people's hearts and minds
 - Early planning
 - Interaction between statisticians, clinicians, PK modelers
 - Integrating biomarkers into model-based Learn studies
 - Reward
- Build enabling infrastructure
 - Cross-functional effort with remit across the portfolio
 - Strong support from senior management
 - Software tools for simulation purposes
 - Resource
- Create modern review process for appropriate interactions between regulatory agencies and sponsors



Where do we want to be? The future

- Increased R&D productivity
 - Sufficient understanding of the dose-response by applying adaptive principles built on
 - sound assumptions
 - fully integrated knowledge management (e.g. biomarkers, endpoints)
 - High quality implementation (selection of patients, training of sites)

