

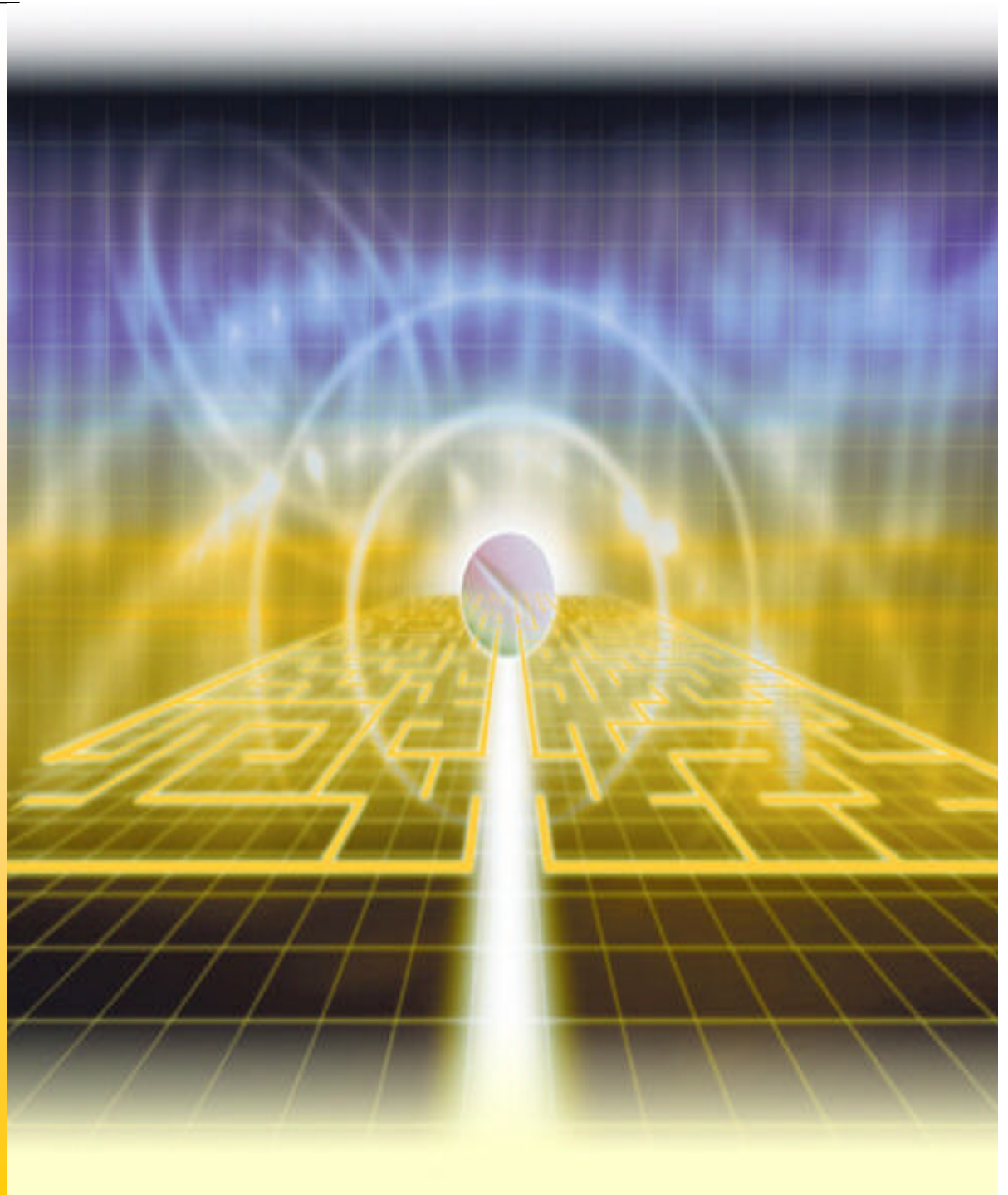
High Value Applications of Modeling and Simulation (M&S) in Early Clinical Drug Development

*William R Gillespie, PhD
Drug Development Consulting
Services*

*Pharsight Corporation
bgillespie@pharsight.com*

Pharsight

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Presentation objectives:

- To present my current views on the role and value of modeling and simulation in early clinical drug development.
- To illustrate high value applications of modeling and simulation with 2 contrasting examples.

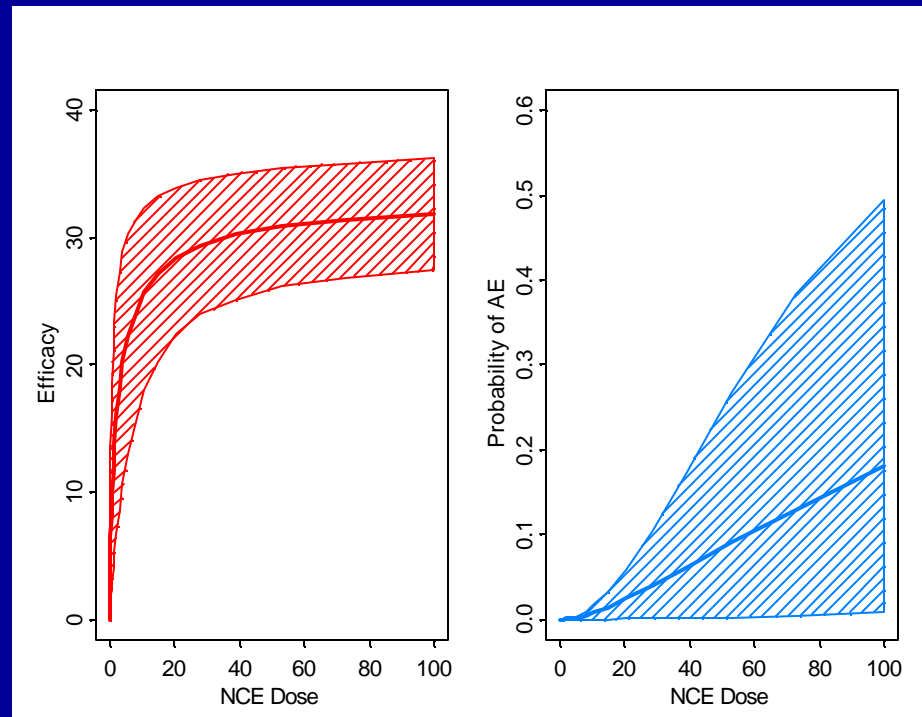
Role of M&S in Decision-Making During Early Clinical Development

- Key challenges in early clinical drug development:
 - Identify what dose or dose range, if any, provides a marketable risk/benefit profile in a certain patient population.
 - Efficiently & accurately reach a high value proof-of-concept (PoC) decision.
- Typically such decisions are based on review of summary statistics and hypothesis tests applied to one or more trials NCE-specific trials. M&S typically plays little or no role.
- But there are major opportunities for improvement in analysis and planning using M&S:
 - Integrate knowledge derived from various information sources, e.g., information for other drugs and from in vitro and animal studies.
 - M&S provides a low-risk means for quantitative exploration of untested treatment regimens and novel trial designs.
 - Quantitatively evaluate competing strategies from medical, business and ethical perspectives.
- Apply M&S to effectively answer the strategic questions:
 - What is an effective phase II (and earlier) strategy that will provide a clear, quantitative rationale:
 - For picking the dose or dose range for evaluation in Phase III?
 - To efficiently reach an high value go/no-go decision?

High value M&S involves the integration of several different models

1. Drug & Disease Models

Quantify probability distribution of safety and efficacy measures as a function of drug, patient and disease features given current knowledge and assumptions



PK-PD Modeling has contributed mostly by improving dose selection and competitive position by better understanding the treatment strategy for the patient population

High value M&S involves the integration of several different models

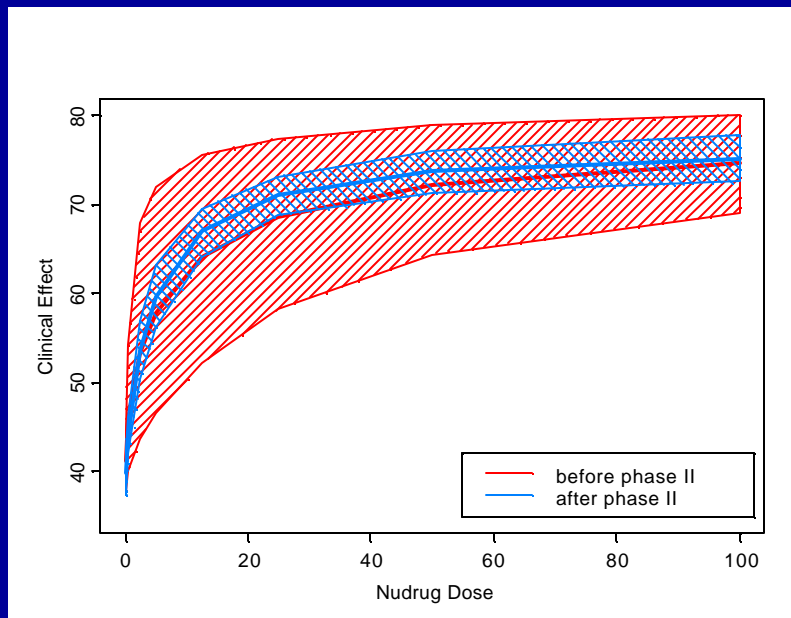
1. Drug & Disease Models

Quantify probability distribution of safety and efficacy measures as a function of drug, patient and disease features given current knowledge and assumptions

Quantify how a certain trial or trial sequence can reduce uncertainty around safety, efficacy

2. Trial Models

Trial simulation (CATD) has contributed mostly by improving trial design by better understanding the relationship between information yield of the trial and trial design features, trial cost/duration, and assumptions and uncertainties



High value M&S involves the integration of several different models

Drug & Disease Models

Quantify probability distribution of safety and efficacy measures as a function of drug, patient and disease features given current knowledge and assumptions

Predictive Market Models

Quantify the probability distribution of the market value of a certain safety/efficacy profile

Trial Models

Quantify how a certain trial or trial sequence can reduce uncertainty around safety, efficacy

Dynamic Financial Models

Quantify the probability distribution of the net value of a development strategy

Integrates all available information on NCE, analogues and markets to predict outcomes, quantify uncertainty, and understand trade-offs

The M&S and development strategies should depend on the amount/type of prior information

| Amount of Information | Example | Number of Assump-tions | Uncertainty in Predictions | Goals of M&S | Trial Designs | Role of preclinical & biomarker data |
|-----------------------|---|------------------------|----------------------------|---|---|--|
| High | Preclinical models Known MOA N th in indication N th in class | Few | Low | Shorten & focus development | Fixed-dose dose-finding Skip PoC & dose-finding? | Quantitative prediction Rescales existing clinical models |
| Low | No preclinical models Unknown MOA 1 st in indication 1 st in class | Many | High | Enhance learning efficiency & manage risk | Adaptive stopping Adaptive dose-assignment | Limited Qualitative |

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| Intermediate | Mixture | Intermediate | Intermediate | Robust strategy | Fixed-dose PoC & dose-finding Adaptive stopping? | Semi-quantitative Mechanistic rationale |
| Low | No preclinical models Unknown MOA 1 st in indication 1st in class | Many | High | Enhance learning efficiency & manage risk | Adaptive stopping Adaptive dose-assignment | Limited Qualitative |

Let's illustrate this approach with two real (but blinded) examples near the extremes

- Case example 1: High prior information
 - Objective: Proof-of-concept & dose-finding
 - Marketed competitor with same biological target
 - Phase I results available

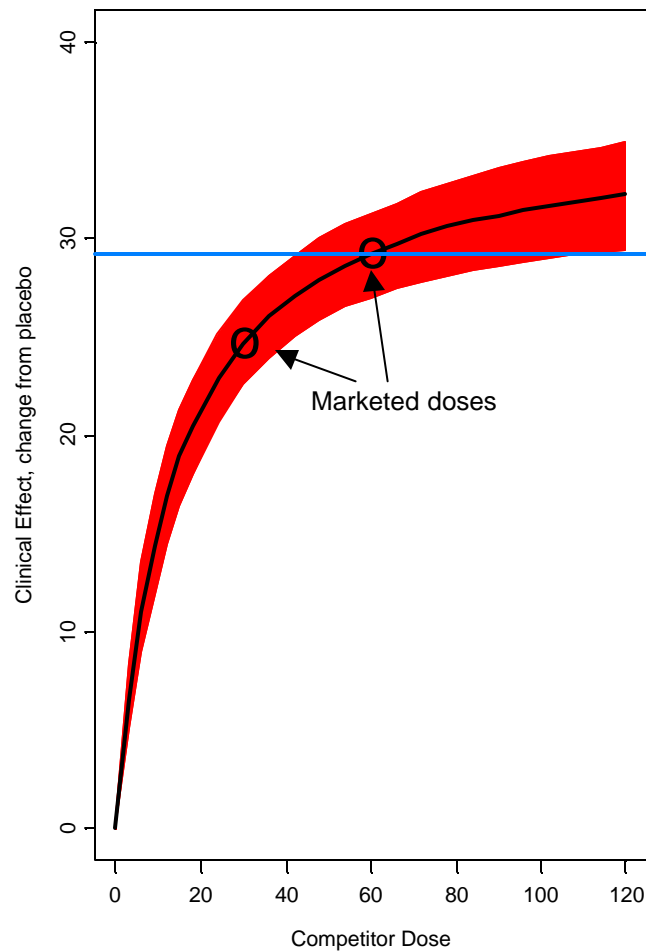
- Case Example 2: Low prior information
 - Objective: Proof-of-concept & dose-finding
 - Novel mechanism of action & biological target
 - Potential CNS indications with no good mechanistic models relating biological target to clinical outcomes

Case Study 1

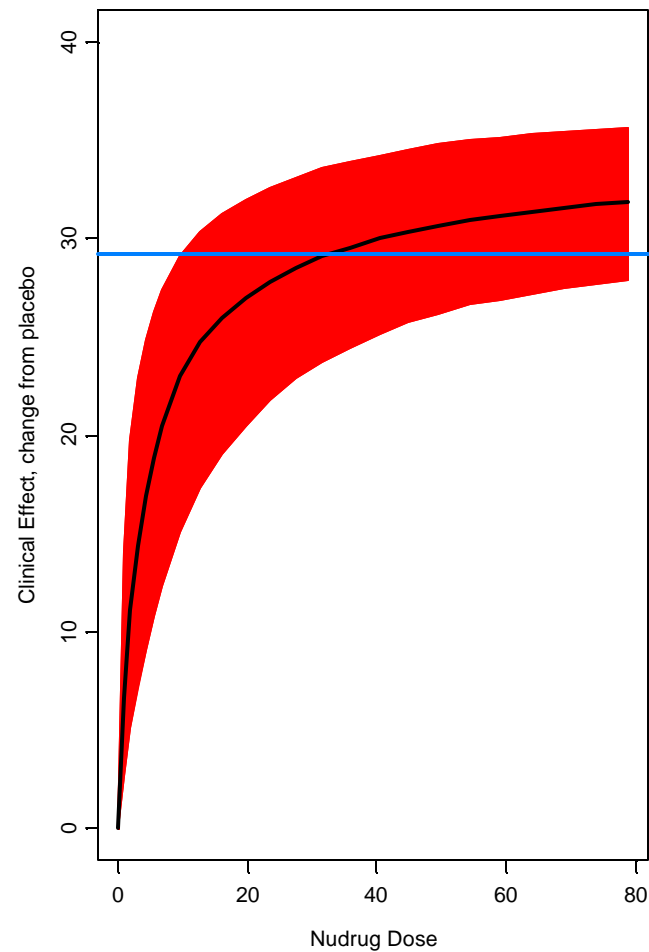
- How would one apply trial simulation to design a phase II dose finding strategy for a n^{th} in class compound?

Infer the likely clinical dose-response relation for Nudrug by scaling the dose-response of a competitor with some estimate of relative potency/efficacy

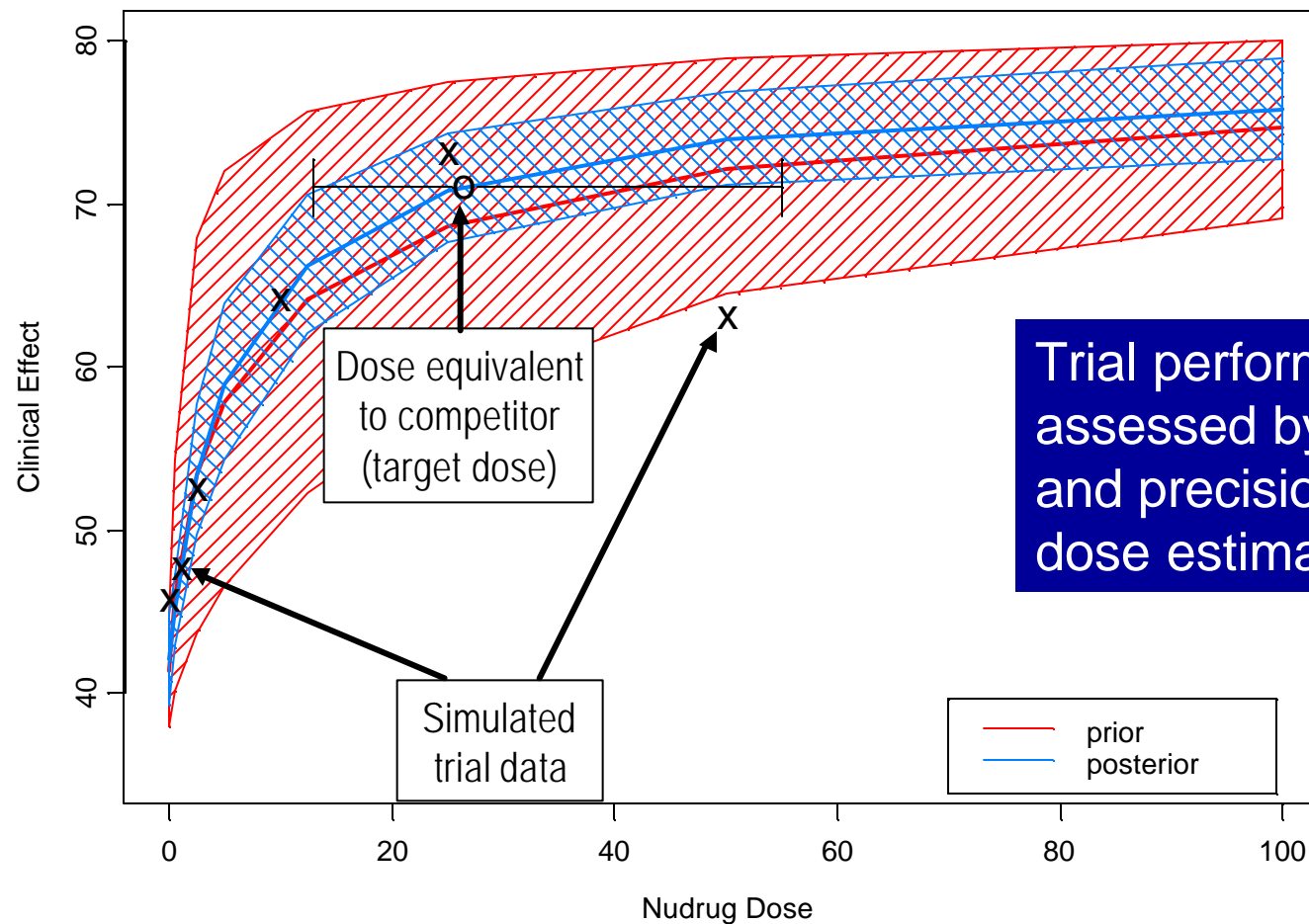
From several Phase II/ III trials



On basis of preclinical relative potency



We can then evaluate the performance of a certain trial strategy to improve the understanding of the dose response relationship



Trial performance is assessed by the accuracy and precision of the target dose estimate

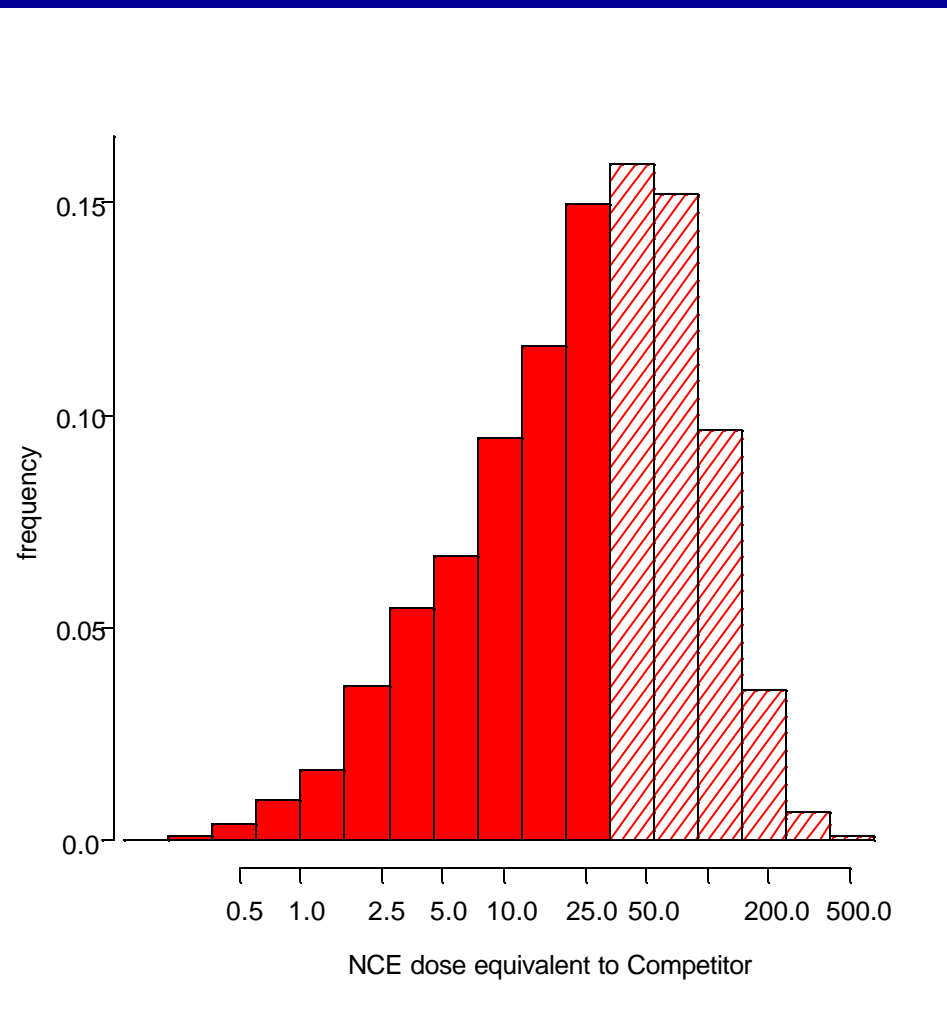
Which can be used to compare the performance of different trial strategies

- Performance criteria is precision and accuracy of the target dose (dose equivalent to competitor)

| Duration | Dose groups | Include historic data in analysis | #patients/arm | Total | Precision (SE) | Accuracy (est/true) | Eq. Sample size |
|----------|--------------------------|-----------------------------------|---------------|-------|----------------|---------------------|-----------------|
| 12 week | 0, 1, 2.5, 10, 25, 50 | Yes | 33 | 198 | 2.07 | 1.00 | - |
| 12 week | 0, 1, 2.5, 10, 25, 50 | No | 33 | 198 | 2.67 | 0.99 | 350 (58) |
| 4 week | 0, 1, 2.5, 10, 25, 50 | Yes | 33 | 198 | 4.49 | 0.99 | 850 (141) |
| 4 week | 0, 1, 2.5, 10, 25, 50, C | Yes | 28 | 196 | 2.79 | 0.97 | 400 (57) |
| 12 week | 0, 1, 2.5, 10, 25 | Yes | 40 | 200 | 2.10 | 0.94 | 206 (41) |

- A joint analysis of the phase II trial with informative priors based on historic competitor data provides a 33% reduction in sample size.
- The option of a trial of shorter duration could result in a significant loss of power due to the potential impact of treatment duration on treatment effect
- Inclusion of an active control (C=competitor at marketed dose) can provide cheap insurance (reduction of 50% in sample size) against changes in the patient population impacting efficacy.
- The 50 mg arm can be removed without loss of performance

PoC issue: Safety studies show that doses > 25 mg are not viable for the market



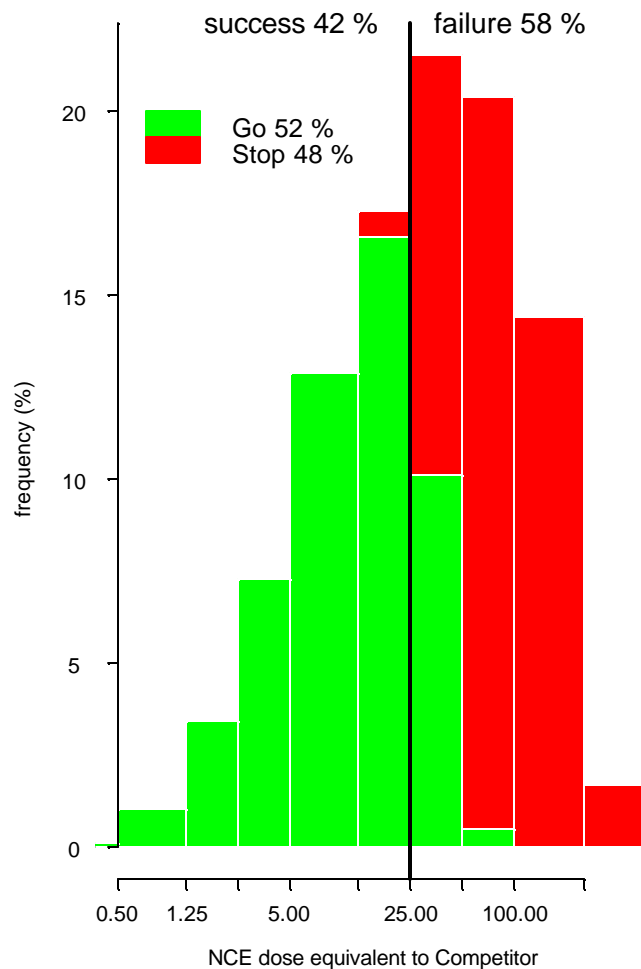
There is ~58% chance that the target dose range for Nudrug is greater than 25 mg.

The drug is not marketable if the target dose is > 25 mg.

How well can the trial support a decision to stop if the drug is a failure (target dose > 25 mg) and to go if the drug may be a success (target dose \leq 25 mg)?

Trial performance for the PoC objective: Compare trial designs based on probabilities of getting the correct or incorrect answer

Example: Trial with 0, 1, 2.5, 10, 25, 50 mg at 35 patients/arm.



You want to minimize:

- $\Pr(\text{fail}|\text{Go})$ ~ probability of a Phase III or market failure
- $\Pr(\text{Stop}|\text{succeed})$ ~ probability of a lost opportunity

For this example:

- $\Pr(\text{fail}|\text{Go})=20.4\%$
- $\Pr(\text{Stop}|\text{success}) = 1.7\%$

fail = target dose > 25 mg

success = target dose \leq 25mg

But the question remains: what sample size or decision rule should we use?

| sample size | P(Stop success) | P(fail Go) |
|-------------|-----------------|------------|
| 10 | 3.6 | 29.2 |
| 20 | 2.4 | 23.8 |
| 35 | 1.7 | 20.4 |
| 50 | 1.4 | 18.9 |

- That depends on the value of the information derived from the trial vs. the costs of obtaining that information.
- Which depends on the cost of Phase II vs. sample size, cost of a failed Phase III, revenue of a successful compound, loss of revenue by stopping a success, etc.

To be able to make these trade-offs there is a need to look at the business and medical aspects

Why is this necessary for decisions on **Treatment Strategy**?

- Because we have to make tradeoffs among the drug effects comprising the product profile (Safety, Efficacy, etc.), balancing the benefits and risks.
- A Clinical Utility Index (CUI) quantifies these tradeoffs by providing a single metric for the multiple dimensions of benefit and risk.

Why is this necessary for decisions on **Trial Strategy**?

- Because we have to make tradeoffs between the value of the information derived from the trial vs. the costs (time and direct cost) of obtaining that information.
- NPV quantifies these tradeoffs by providing a single metric for net value of each potential decision path.

This leads us to Bayesian decision analysis using CUI and NPV as utility functions

Possible early development strategy with low prior information

- Enhance efficiency by learning as you go, e.g., proof-of-concept and dose-finding via adaptive trials
 - Adaptive trial = trial design that change in response to interim results:
 - Adaptive stopping
 - Adaptive treatment assignment/allocation
- Manage risk
 - Use simulation to explore the performance of proposed development strategies over a range of potential realities
 - Integrate PK/PD and financial models
 - Understand both the potential medical and economic consequences:
 - Of competing development strategies.
 - Of specific decisions, e.g., go/no go or dose selection

Case Example 2:

Phase II Strategy for NCE with novel mechanism of action

Compound: ■ **CNS, novel mechanism of action**

Status: ■ **Phase I completed**

Competitor: ■ **On market for 5 years**

Target Product Profile: ■ **Similar or better efficacy than Competitor with reduced side-effects**

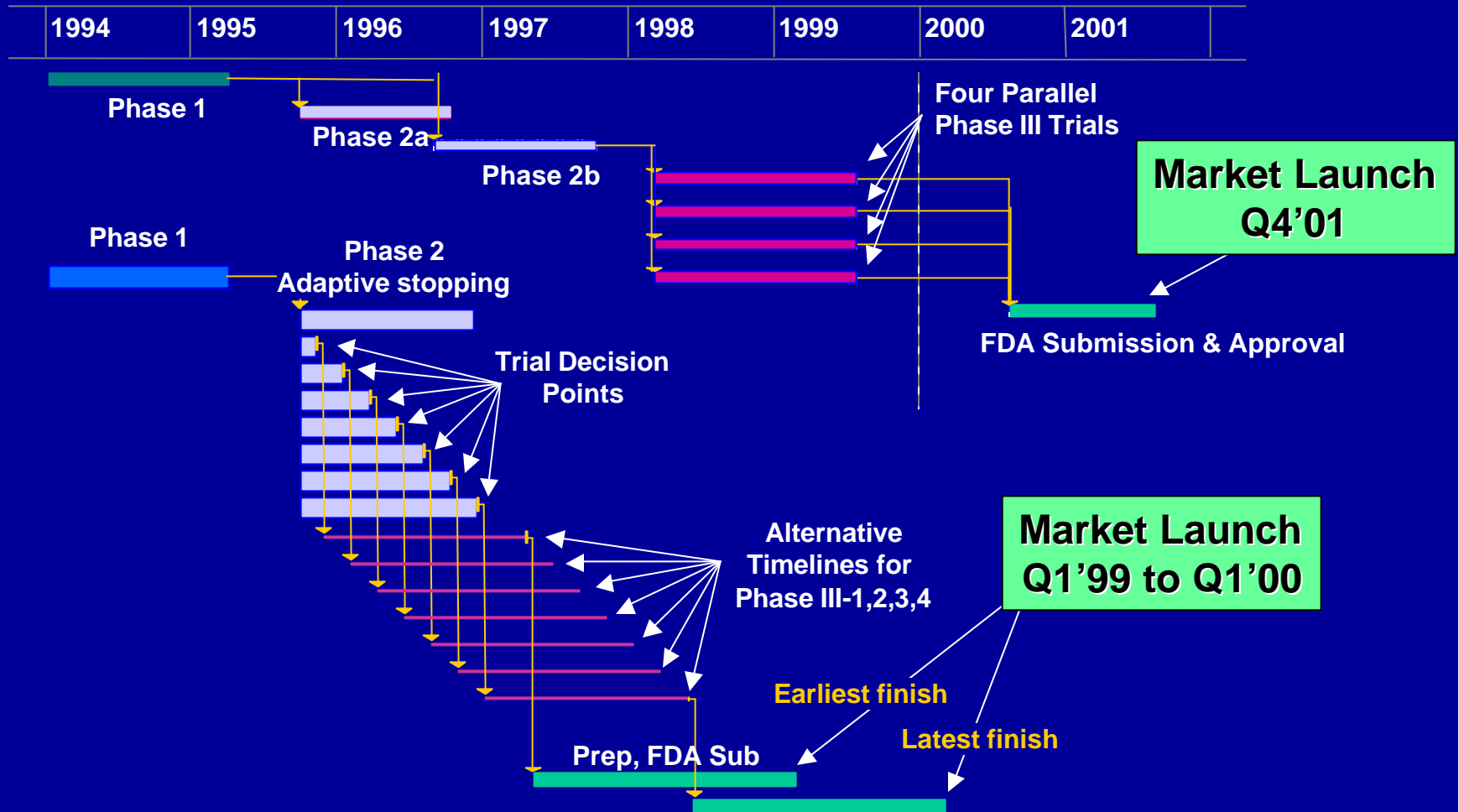
Issues: ■ **What is the best (highest NPV) Program Strategy for determining:**

- **If Drug X is a “dud” and should be killed?**
- **If “Effective”, how and when to move to Phase III?**

Our mission was to find a way to improve decision making and phase II/III trial execution.

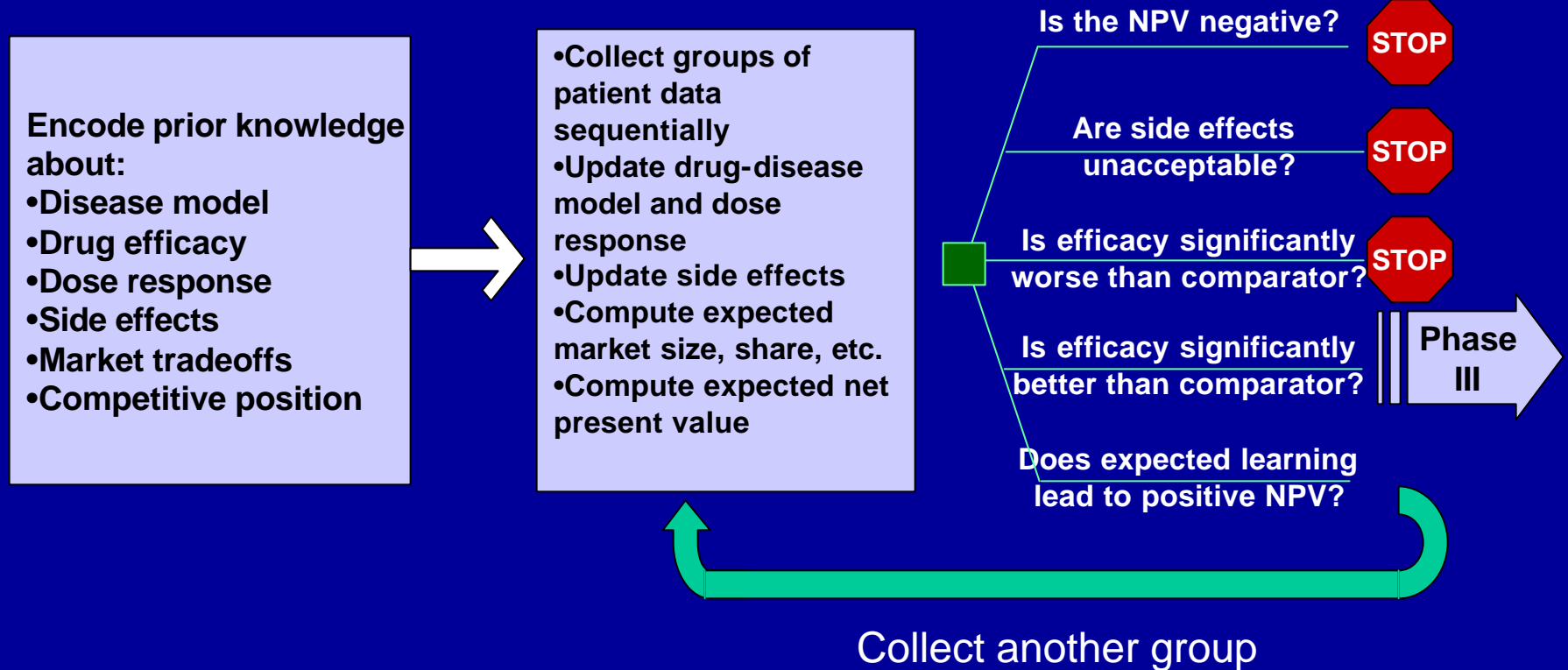
- This was actually a post-mortem of a development program that failed in Phase III.
- We were initially blinded from the results of the Phase II/III trials.
- We proposed a phase II design which we believed would be more effective than the client design.
- The Phase II data was then provided and used for model construction.
- The proposed design was simulated.
- The phase II results, time and cost were compared for competing designs

Models allowed design of a development program that was up to two years faster

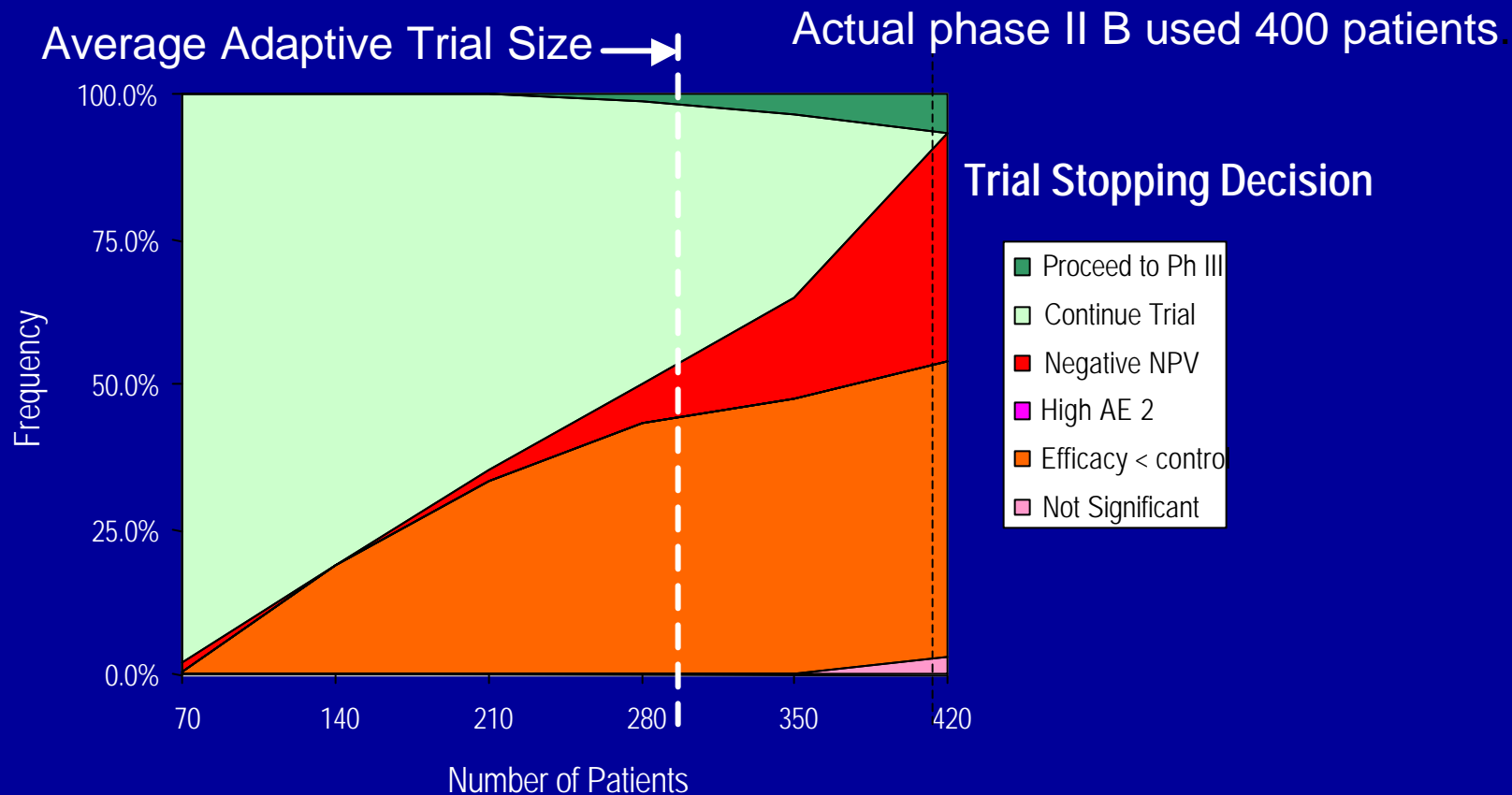


For phase II, adaptive designs can provide multiple learning and decision opportunities.

The Proposed Phase II Design



Repeated simulations showed that the drug would have failed early in the adaptive trial design.

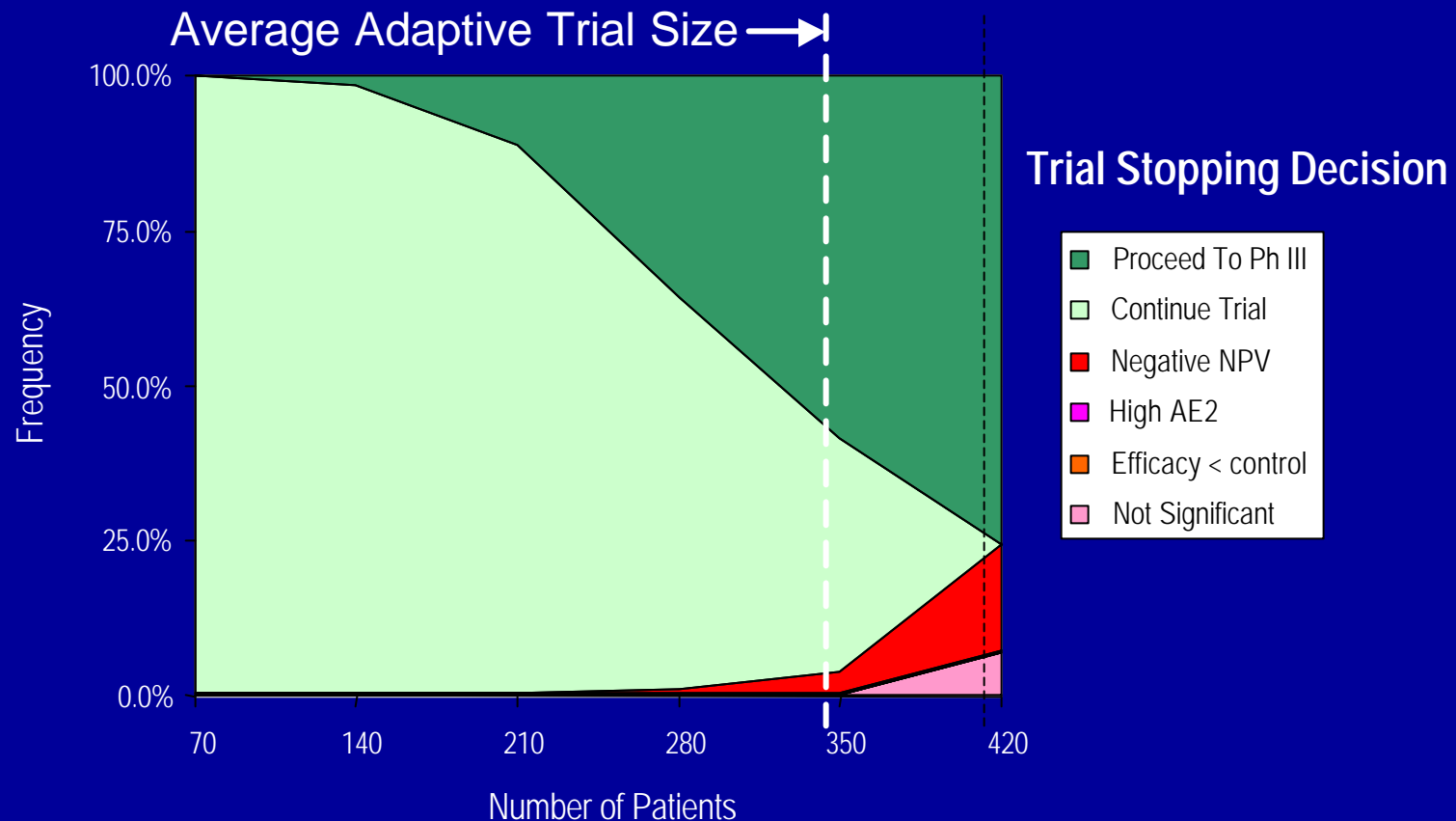


- **Average trial accrued 295 patients in ~10 mo. An erroneous “GO” decision given 6.5% of the time.**
- **The client had equivocal results and proceeded to phase III.**

What if the client had a more efficacious drug?

In 76% of the simulations, the adaptive trial design recommended starting phase III given a drug efficacy profile similar to the positive control.

Actual phase II B used 400 patients.



➤ **Average trial accrued 341 patients in ~12 mo.**

With blockbuster efficacy the proposed trial recommended starting phase III much earlier.

Actual phase II B used 400 patients.



- **Average trial showed significant efficacy with 235 patients in ~9 mo.**
- **Compared to the original design, the expected value of the compound would increase by 26% due to a quicker time to market.**

Current directions in high value M&S applications

- Increasing use of fully Bayesian modeling from model development through simulation and trial analysis.
- Increasing use of Bayesian decision analytic methods:
 - Dose or treatment regimen optimization using a utility function that considers multiple aspects of efficacy and safety.
 - Trials using adaptive stopping based on $E(NPV)$ (or other comprehensive measures of benefit and risk) and more rigorous treatment of the sequential decision problem.
 - Trials using adaptive treatment assignment.
 - Optimal selection of trial designs or development strategies based on measures of overall value, e.g., $E(NPV)$.

Summary of the key points

- Decision-making in clinical drug development can be enhanced by use of M&S.
- M&S have high value roles in all stages of clinical drug development even when there is limited prior information.
- Role and methodology of M&S vary as a function of the amount of prior information.
- M&S provide a low risk means for exploring novel clinical development strategies.

Key contributors to the examples presented here

- Jaap Mandema
- Bob Korsan
- Kevin Dykstra

