



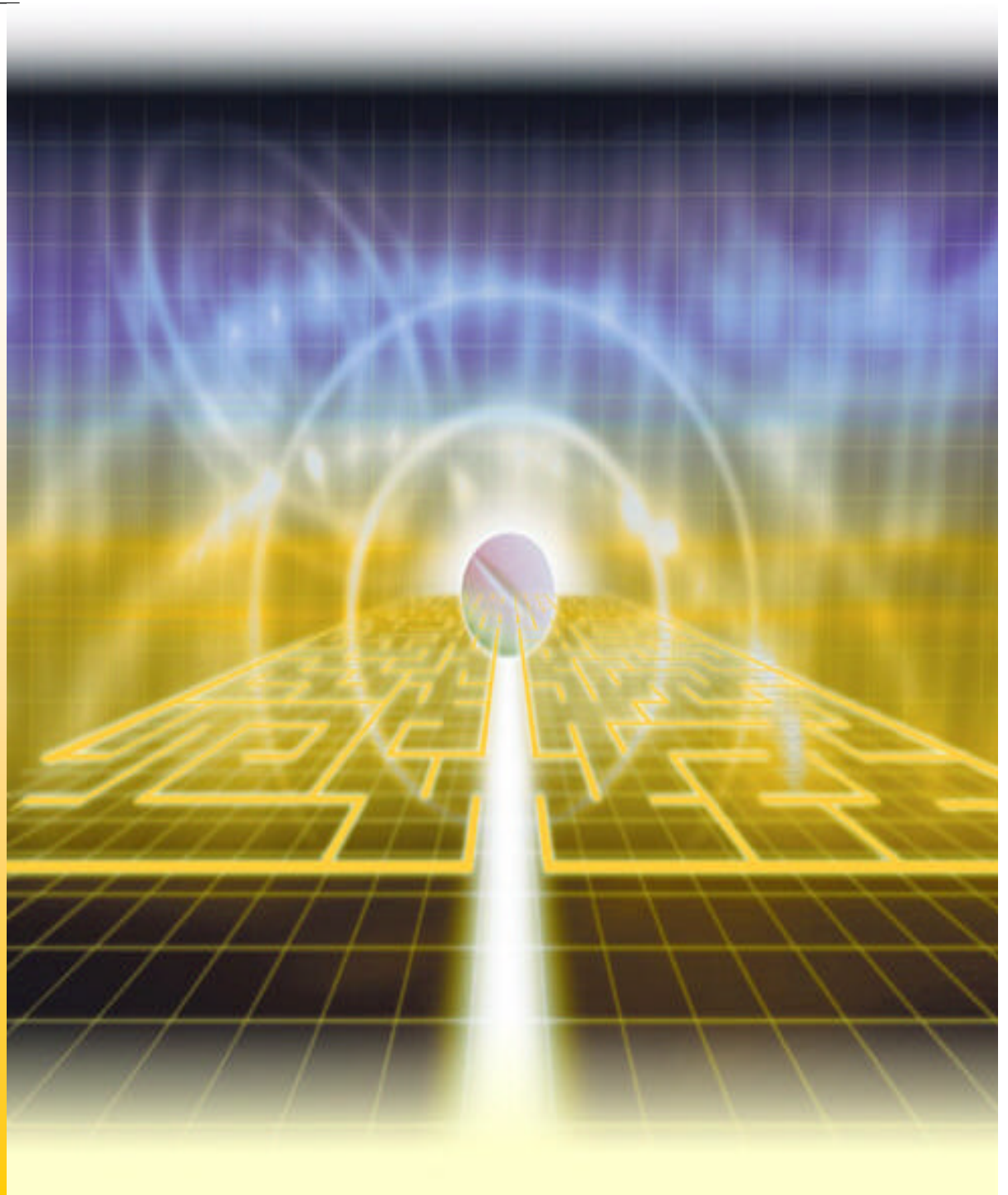
**Kevin H. Dykstra, PhD**

**How to Leverage Prior  
Knowledge on Competitors  
and Analogues to Achieve  
R&D Productivity Gains**

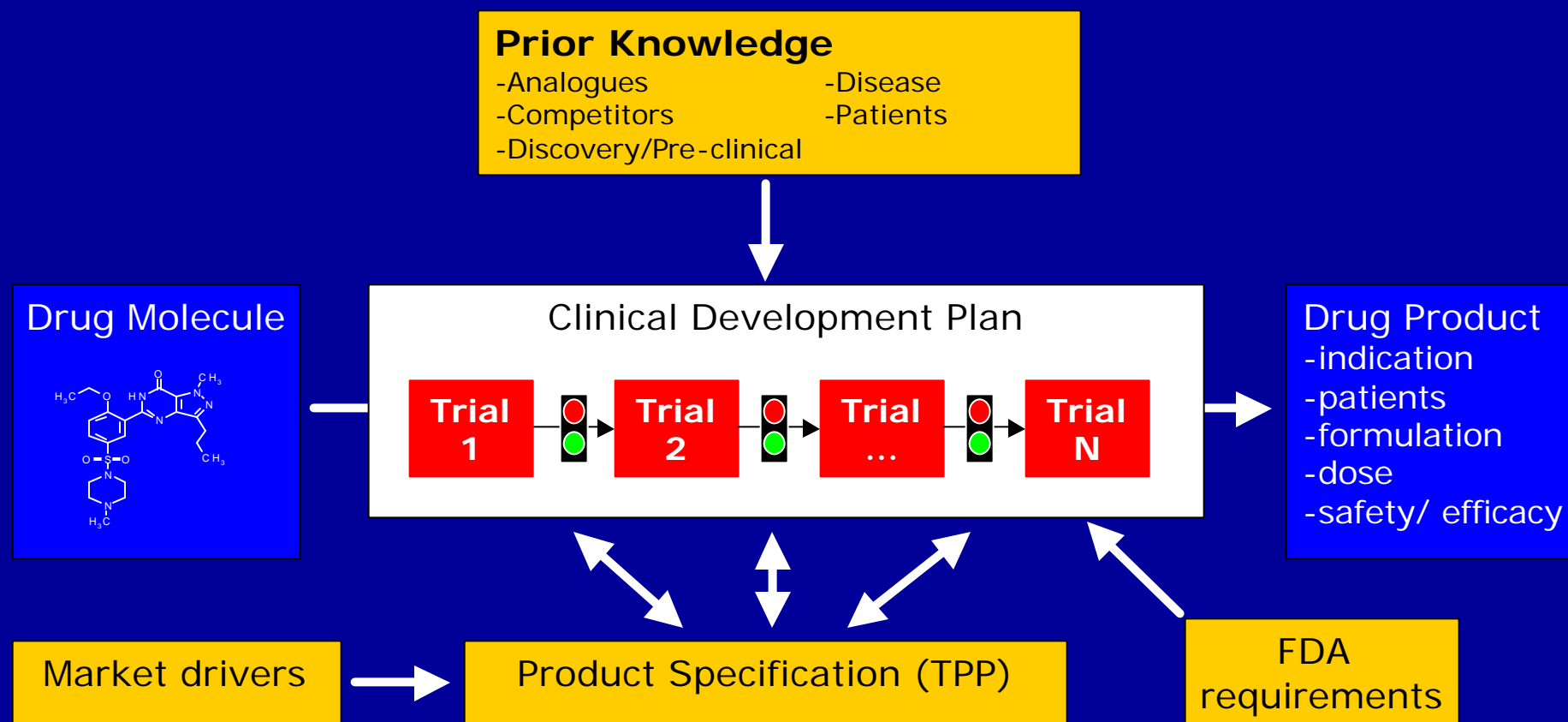
**R&D Leaders Forum**

**Scottsdale, AZ**

*7 April 2003*



# Drug development is complicated, requiring use of knowledge from many different sources



➤ **Goal of process is to get the highest value product approved and marketed**

***“Quantitative Decision-Making” leads to enhanced productivity and reduces risk***

**A systematic, quantitative, model-based decision-making method**

- **Increase drug development productivity**
  - **Decrease late stage attrition**
  - **Decrease time to market**
  - **Increase # of drugs reaching market/ \$ invested**
- **Improve clinical quality and commercial performance of final product**

*Everyone makes models ... we just write them down for later use*

## Drug & Disease Models

Quantify probability distribution of safety/ efficacy profile 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

Quantify how a certain trial or trial sequence can reduce uncertainty around safety, efficacy (information yield vs. time/ costs)

## Trial Models

## Dynamic Financial Models

Quantify the value of a certain asset or development strategy at various points in time (levels of uncertainty)

# *Integrated modeling and simulation can be used to address the critical questions impacting project value*

*“What’s the best dose and schedule?”*

*“Is it worth developing a new dosage form?”*

*“Should we continue this development program?”*

*“What is the optimal patient population for this drug?”*

*“Is this treatment likely to be as good as the competitors?”*

*“What’s the probability of success in Phase III?”*

*“Is there a clinical trial design that will show PoC and find the best dose?”*

*“Should we in-license this compound?”*

*“Which indication should we go into first?”*

*“What are the most important attributes of a 2<sup>nd</sup> generation compound?”*

# The typical development strategy depends on the amount/ type of prior information

Amount of Information	Example	Number of Assumptions	Uncertainty of Predictions	Goals of Modeling & Simulation	Role of Preclinical and biomarker data
High	<ul style="list-style-type: none"> <li>• Pre-clinical models</li> <li>• Known MOA</li> <li>• N<sup>th</sup> in indication</li> <li>• N<sup>th</sup> in class</li> </ul>	Few	Low	<ul style="list-style-type: none"> <li>• Shorten and Focus Program</li> </ul>	<ul style="list-style-type: none"> <li>• Quantitative prediction</li> <li>• Rescale existing clinical models</li> </ul>
Intermediate	Mixture	Intermediate	Intermediate	<ul style="list-style-type: none"> <li>• Robust Strategy</li> <li>• Optimize knowledge gain</li> </ul>	<ul style="list-style-type: none"> <li>• Semi-quantitative</li> <li>• Mechanistic rationale</li> </ul>
Low	<ul style="list-style-type: none"> <li>• No pre-clinical models</li> <li>• Unknown MOA</li> <li>• 1<sup>st</sup> in indication</li> <li>• 1<sup>st</sup> in class</li> </ul>	Many	High	<ul style="list-style-type: none"> <li>• Optimize knowledge gain</li> <li>• Manage risk</li> </ul>	<ul style="list-style-type: none"> <li>• Limited and qualitative</li> </ul>

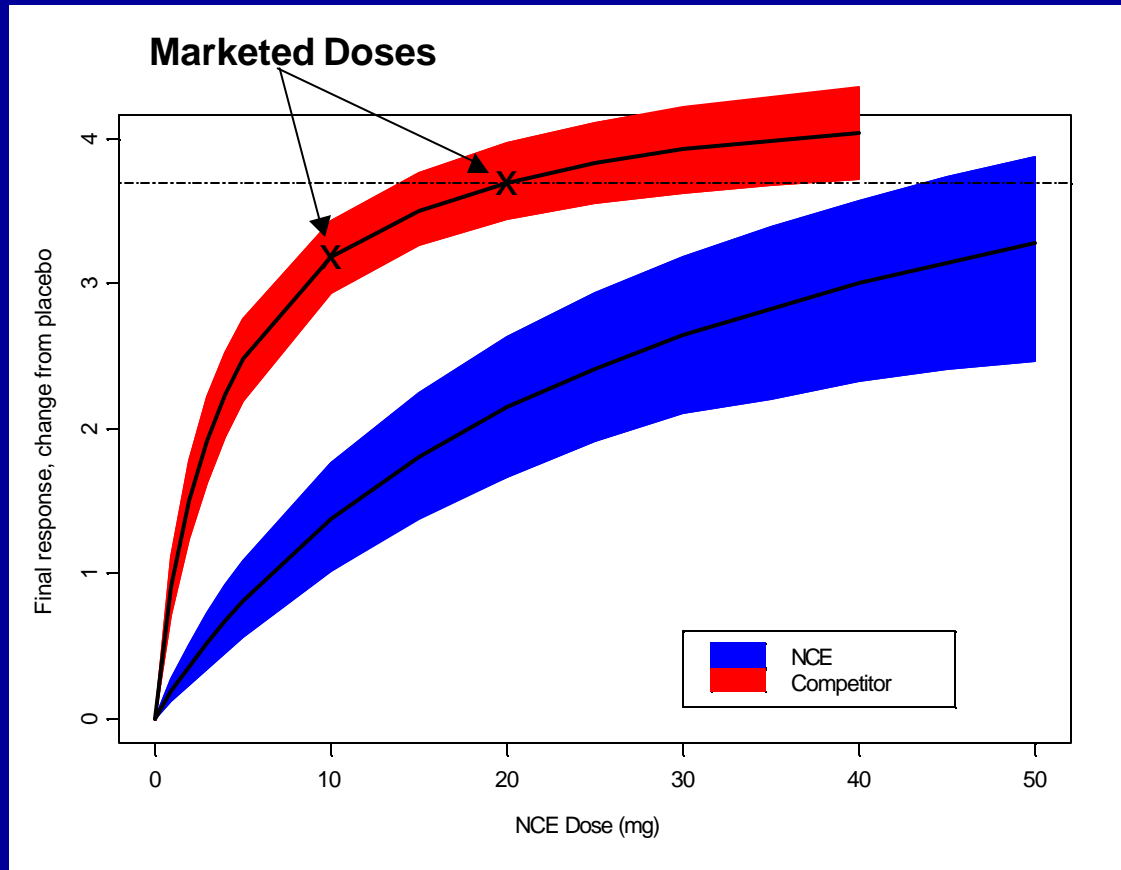
## *Example 1: Use of prior information on competitor to optimize Phase III strategy*

*Nudrug is indicated for Disease with 1 (blockbuster) competitor in the market place*

Critical Business Issue: Successful positioning this drug against the competitor

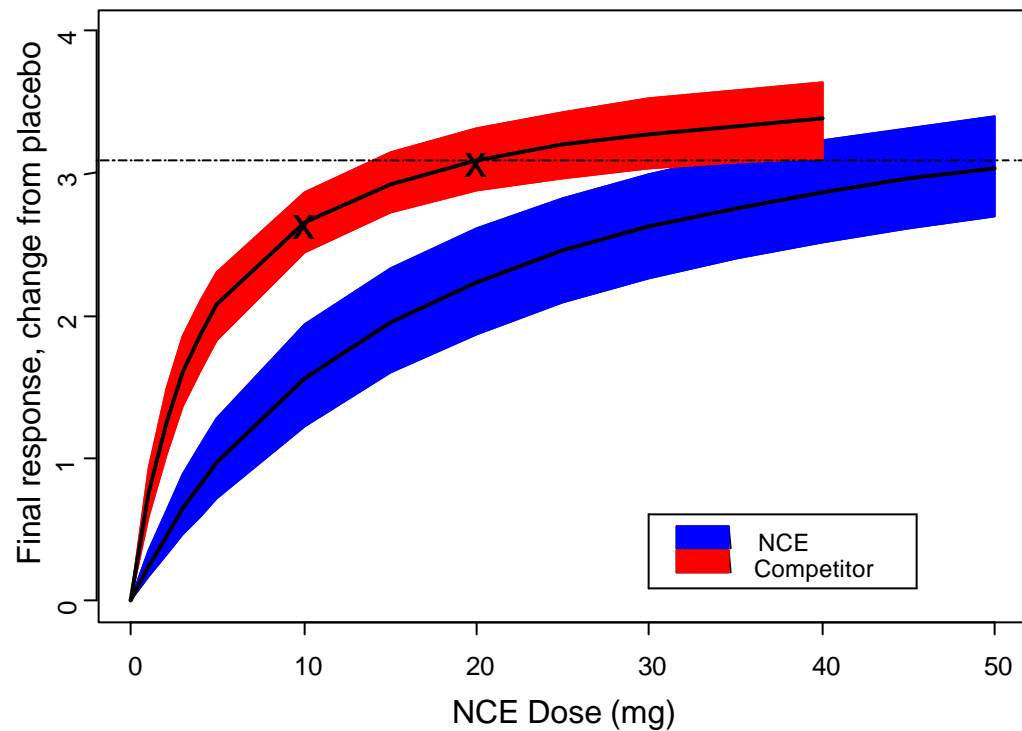
*“Do we have a drug, and if so what dose should we carry in to Phase III?”*

# Development of Nudrug was at the end of Phase II



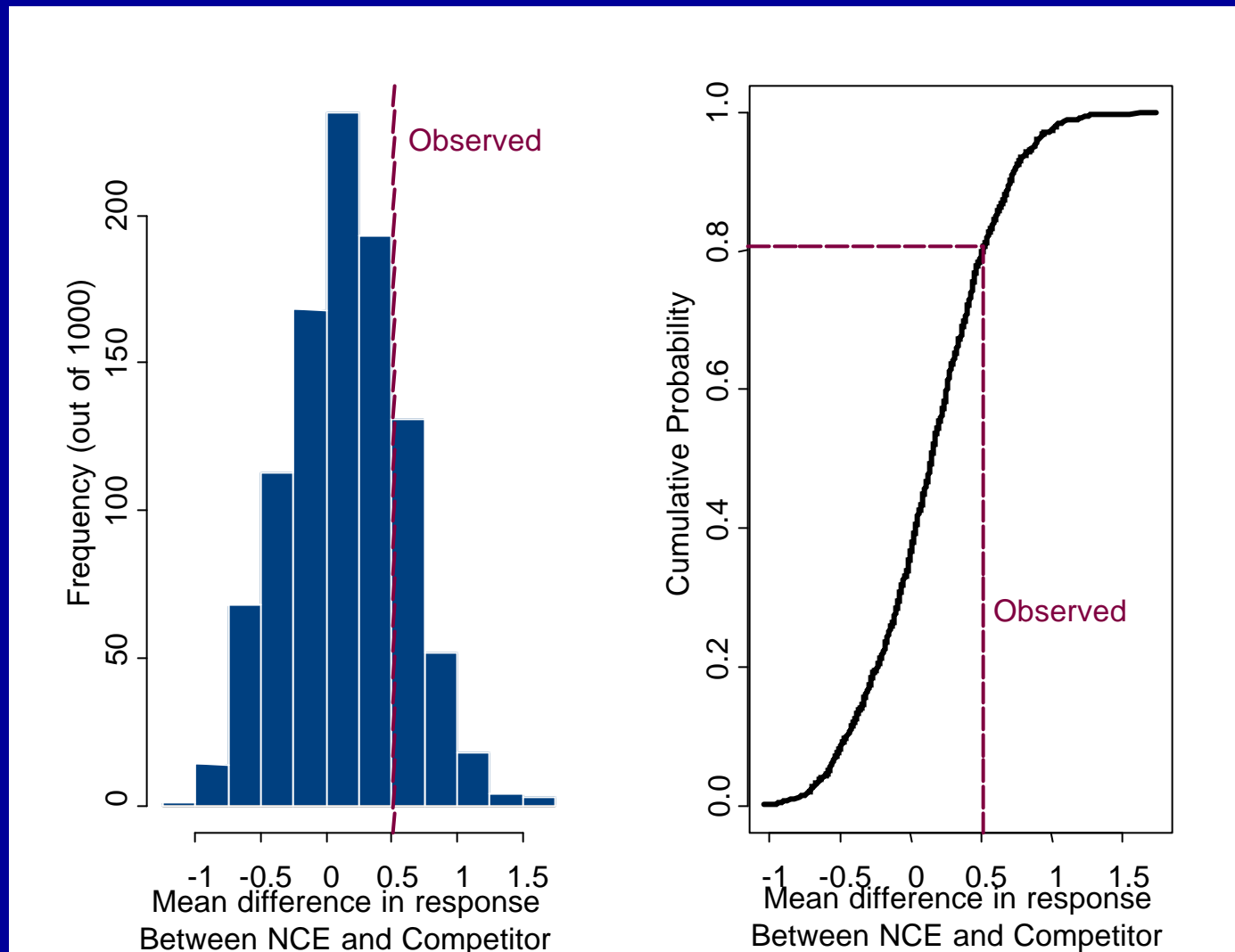
- Three phase II trials had been completed
  - Several endpoints; some continuous and some binary
- Dose response had not been quantified
- Based on initial modeling of Phase II data, the competitor looked superior to Nudrug
  - But no direct comparison available with Competitor

## *A joint dose response model for the NCE and competitor was developed that accounted for differences in patient population*



- This provided an estimate of relative potency between NCE and Competitor after correction for patient population differences
- It increased the certainty in the dose response relationship of NCE
- It provided a basis for a phase III strategy that got the dosing right and minimized risk

# The actual phase III clinical outcome fell within the simulated ranges



## *This model added substantial value to the development of Nudrug*

- It provided an estimate of relative potency between Nudrug and Competitor after correction for patient population differences. Based on this Nudrug could be positioned against Competitor to achieve similar efficacy.
- It increased the certainty in the dose response relationship of Nudrug so that the risk of failure in phase III is reduced significantly.
- It provided a basis to design a phase III strategy to optimally position Nudrug relative to Competitor at minimum risk.

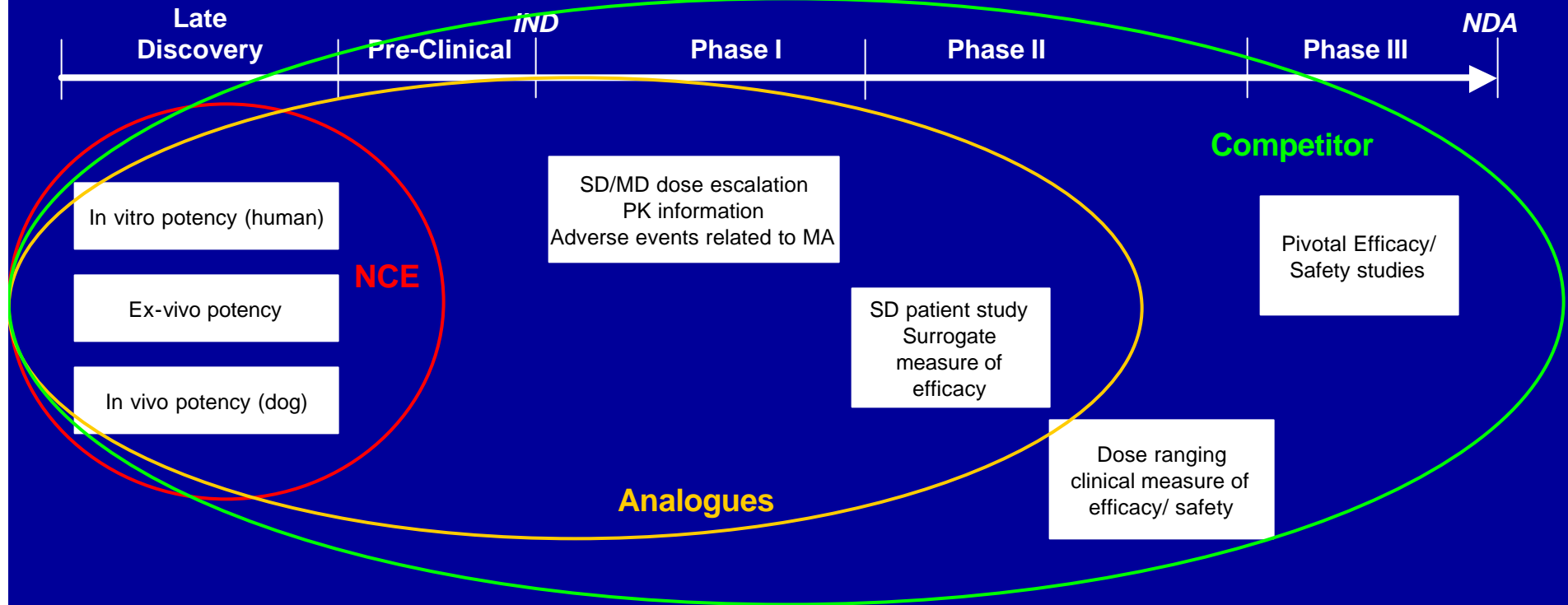
## *Example 2: Optimizing early clinical development strategy for a compound with lots of prior information*

***Nudrug is 2<sup>nd</sup> in class and has a similar mechanism of action as competitor but its selectivity offers the potential for reducing side-effects. It is currently in late discovery.***

Critical Business Issue: Develop a phase I-II strategy that will provide rationale for picking the dose or dose range (including go/ no-go) for evaluation in Phase III.

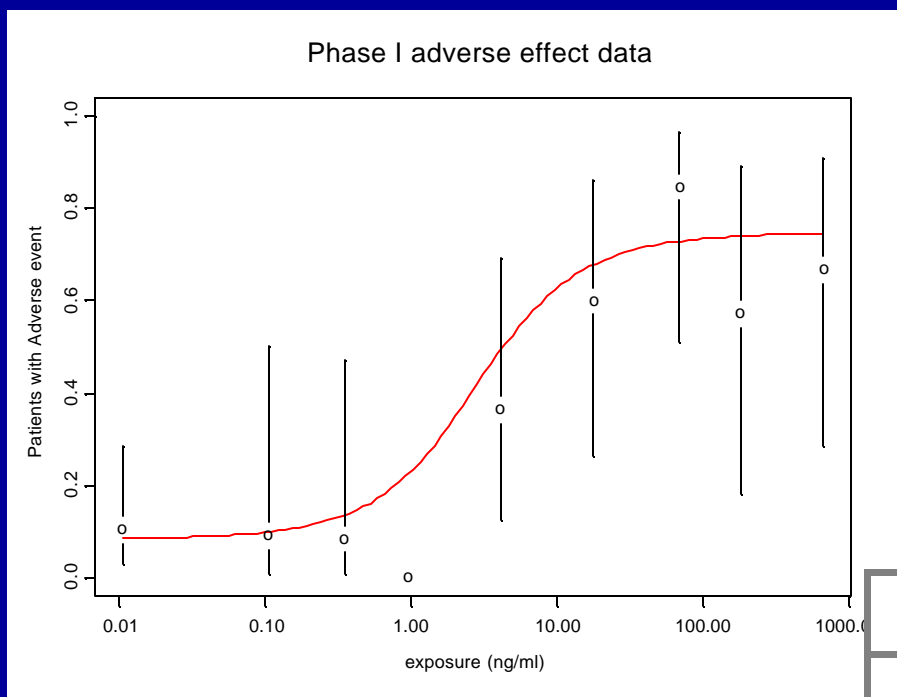
***“Can we leverage our wealth of prior information to optimize the development strategy?”***

# There is a relatively rich knowledge-base informing the potency/ efficacy profile of NCE



- Initial step is to analyze all information and build an integrated model of the relationship between the available information and the efficacy/ safety profile of the NCE
- And to determine the value of each of the trials with respect to the ability to select a dose/ dose range for further development.

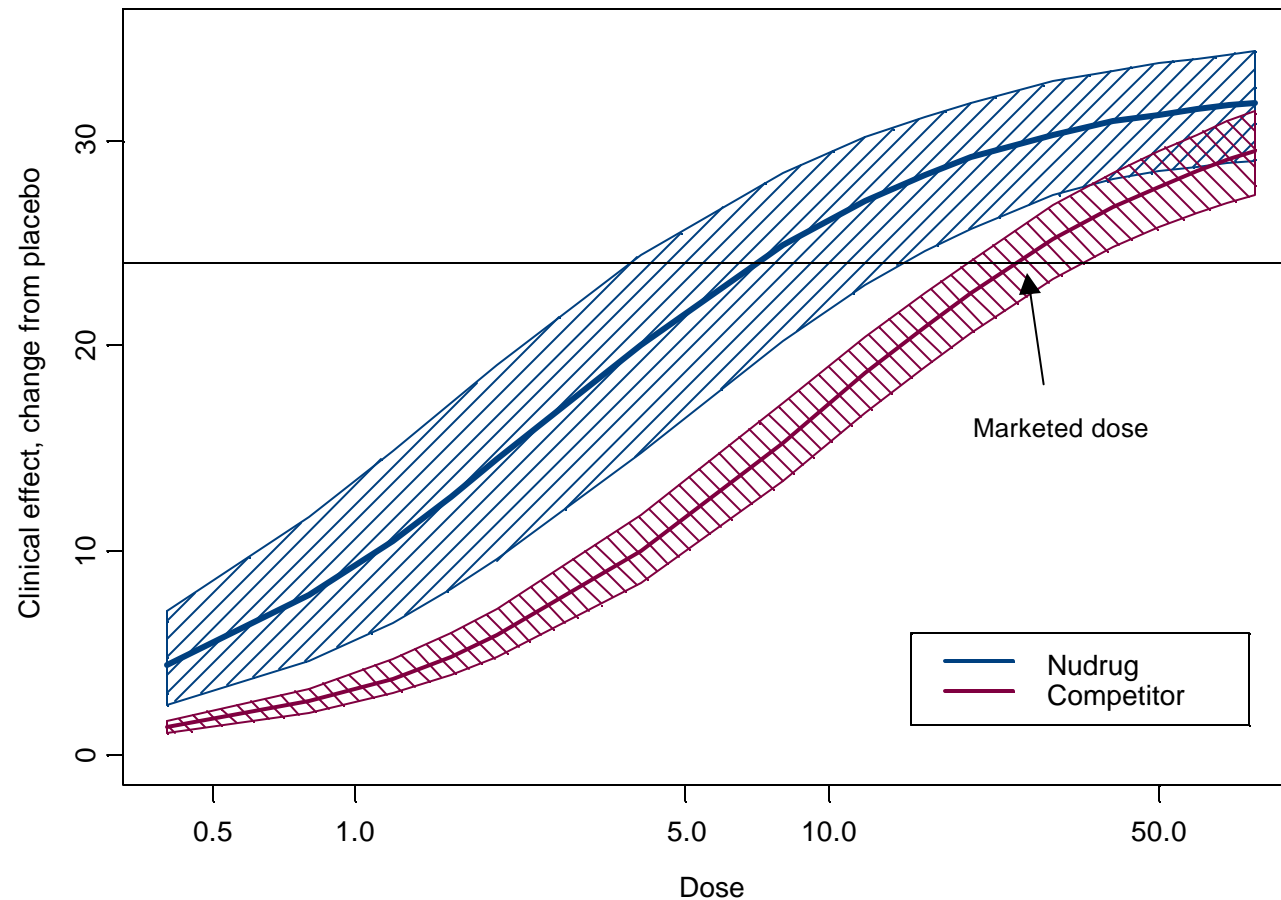
# For the analogue and competitor, drug exposure is predictive of the frequency of phase I adverse events



Similar results were found for the biomarker studies in patients

drug	Preclinical Relative potency	Phase I Relative potency	Confidence Bounds	
			5%	95%
Competitor	1	1		
Analogue 1	0.24	0.28	0.09	0.89
Analogue 2	0.15	0.13	0.04	0.46
Analogue 3	0.49	0.61	0.13	2.8

*If that correlation holds, the clinical dose response relationship of Nudrug is well known and an extensive dose ranging trial is not necessary*

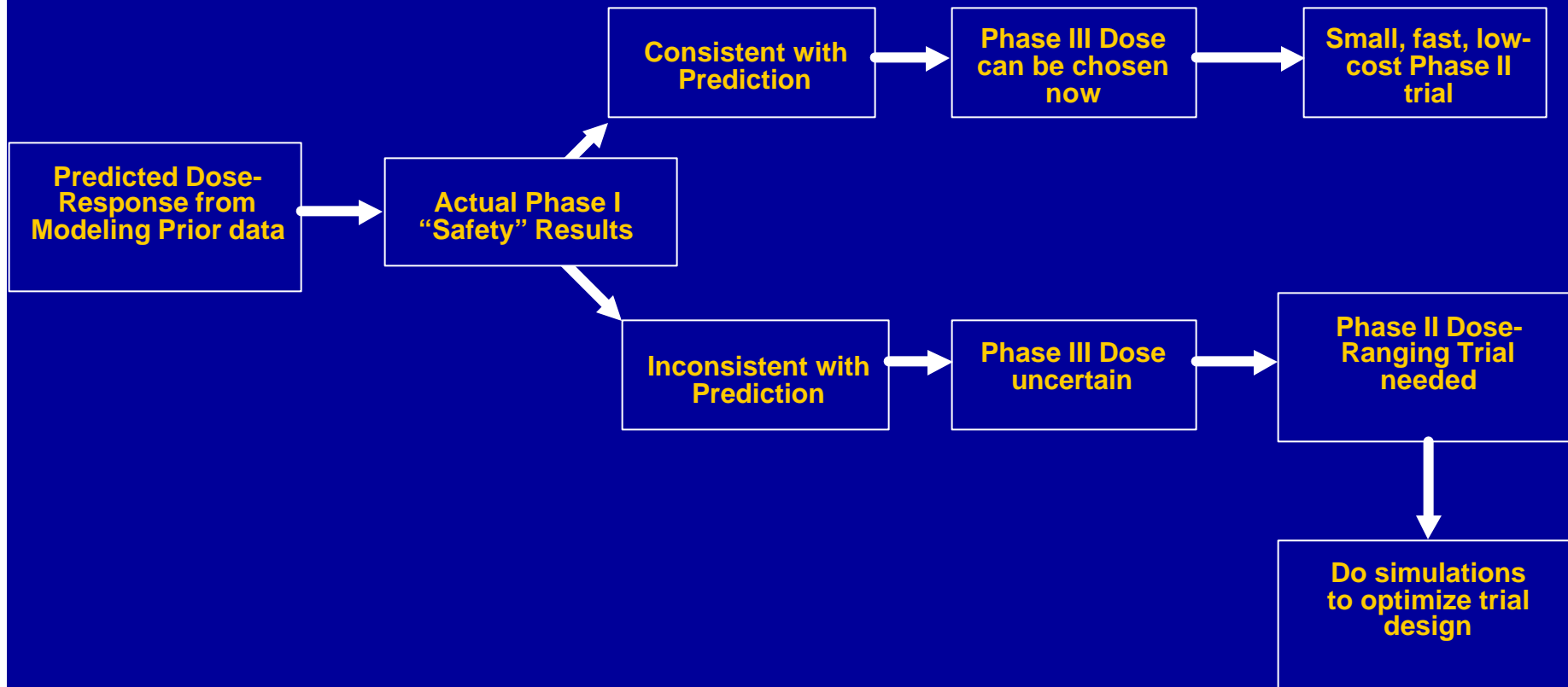


## Simulation of a surrogate trial suggests that it would not reduce dosing uncertainty enough to justify cost and lost time

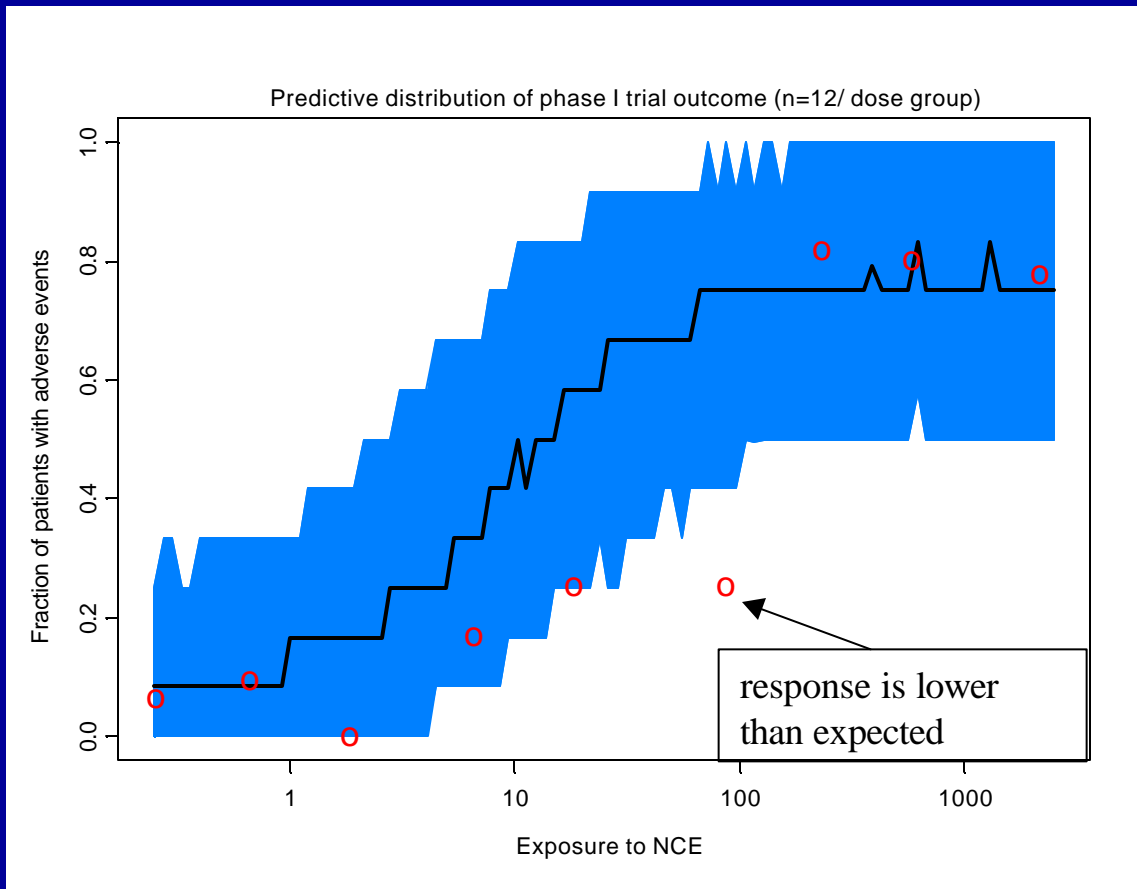
	SE log(rp)	rp <sub>obs</sub> /rp <sub>true</sub>	
		10%	90%
Preclinical (have)	0.64	0.44	2.3
Ph I Safety (need)	0.80	0.36	2.8
Surrogate (optional)	1.26	0.20	5.0
<b>Preclin + Ph1 Safety</b>	<b>0.50</b>	<b>0.53</b>	<b>1.9</b>
<b>All Three</b>	<b>0.46</b>	<b>0.55</b>	<b>1.8</b>
Clinical Data Only	0.67	0.42	2.4

- The table shows the typical standard error of the relative potency (rp) estimates derived from the three type of experiments as well as combinations of the experiments. The table also shows the 10<sup>th</sup> and 90<sup>th</sup> percentile of the distribution of the estimated relative potency as a fraction of the true relative potency.
- The table shows the value of having consistent relative potency estimates across the experiments so that the results can be combined.
- Precise estimate of Nudrug's relative potency to competitor can be obtained on basis of pre-clinical and phase I safety data. The surrogate studies will not add much to that.

***By modeling prior results, we were able to map out two possible strategies, the choice of which depended on a narrowly focused Phase I safety trial.***



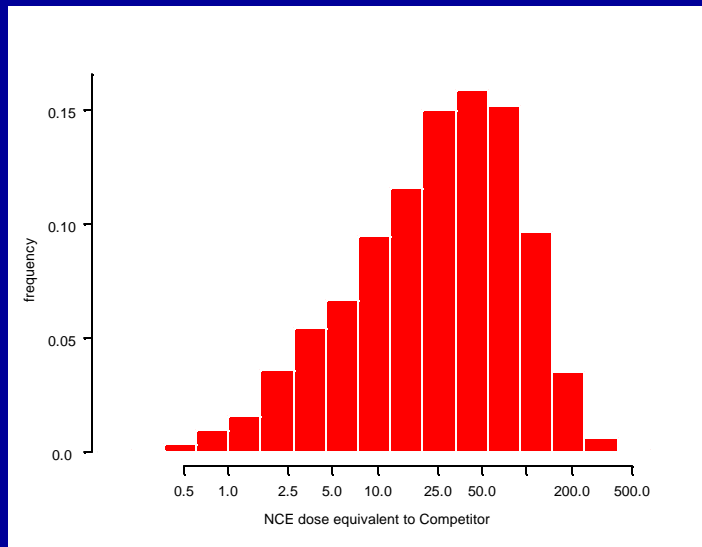
# Unfortunately, the actual Phase I results were inconsistent with expectations based on pre-clinical potency estimates



So we...

1. Update the models to incorporate the new information, and
2. Move to Plan B and work on optimizing the dose-finding strategy

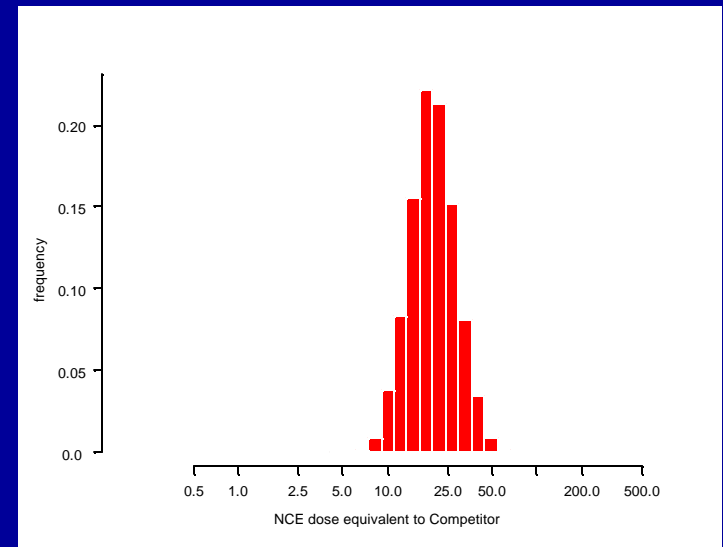
# A Phase II dose ranging trial has to provide the critical information for dose selection for phase III



Phase II trial



Dose groups  
Number of arms  
Duration  
Sample size



Current estimate of 80% range of dose that is equivalent to Competitor is 4.2-150 mg:  
Uncertainty 6

Phase II trial reduces the uncertainty in the Estimate of dose range equivalent to competitor to 10-40 mg:  
Uncertainty 2

## Clinical Trial Simulation is used to compare the performance of alternative Phase II designs

- Performance criteria is uncertainty and bias of dose equivalent to competitor

Duration	Dose groups	Include historic data in analysis	#patients/arm	Total	uncertainty	bias	Eq. Ph III 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)

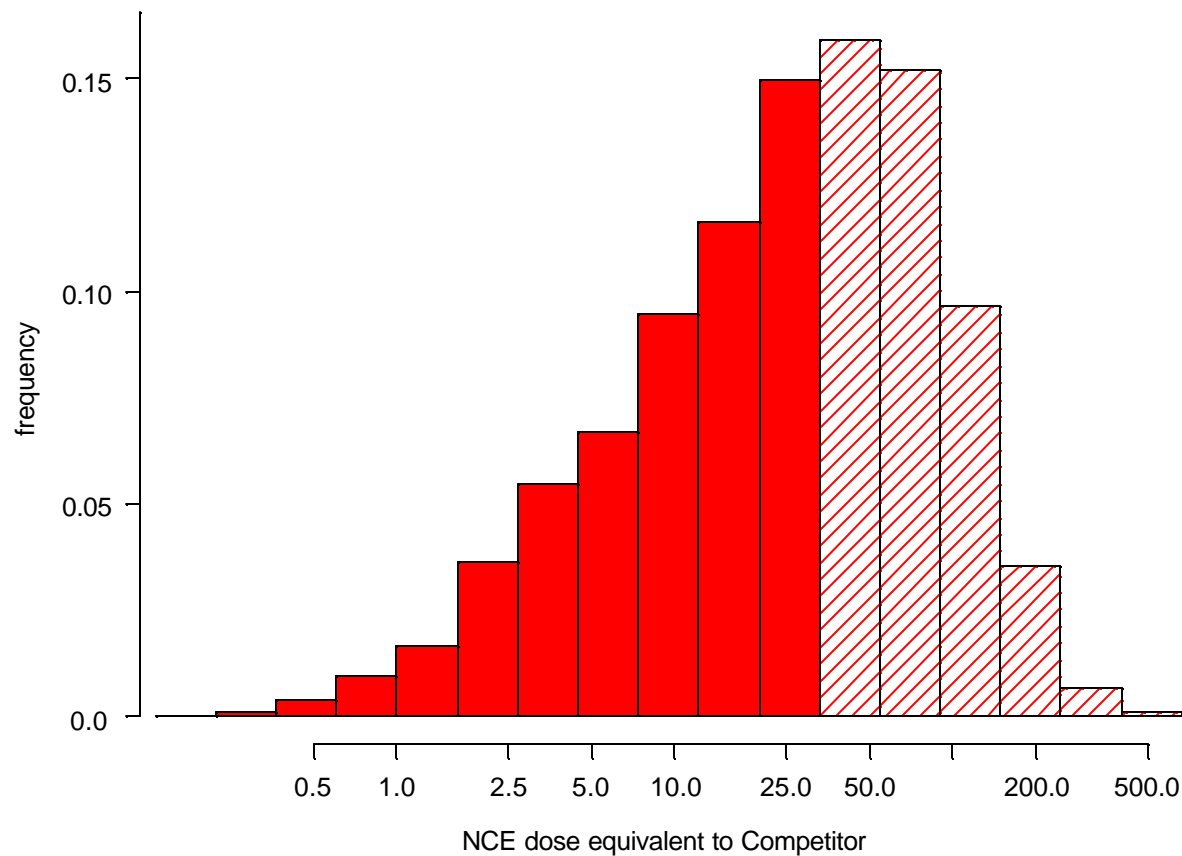
- A joint analysis of the phase II trial with historic competitor data provides a 33% reduction in sample size.
- The option of a trial of shorter duration could result in a significant loss of power due to the potential impact of treatment duration on treatment effect
- Inclusion of an active control (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

# *Safety studies have shown that doses > 25 mg have tolerability issues, and are not viable in the market place*

Therefore, we would like to understand chance that the targeted dose range for Nudrug is greater than 25 mg

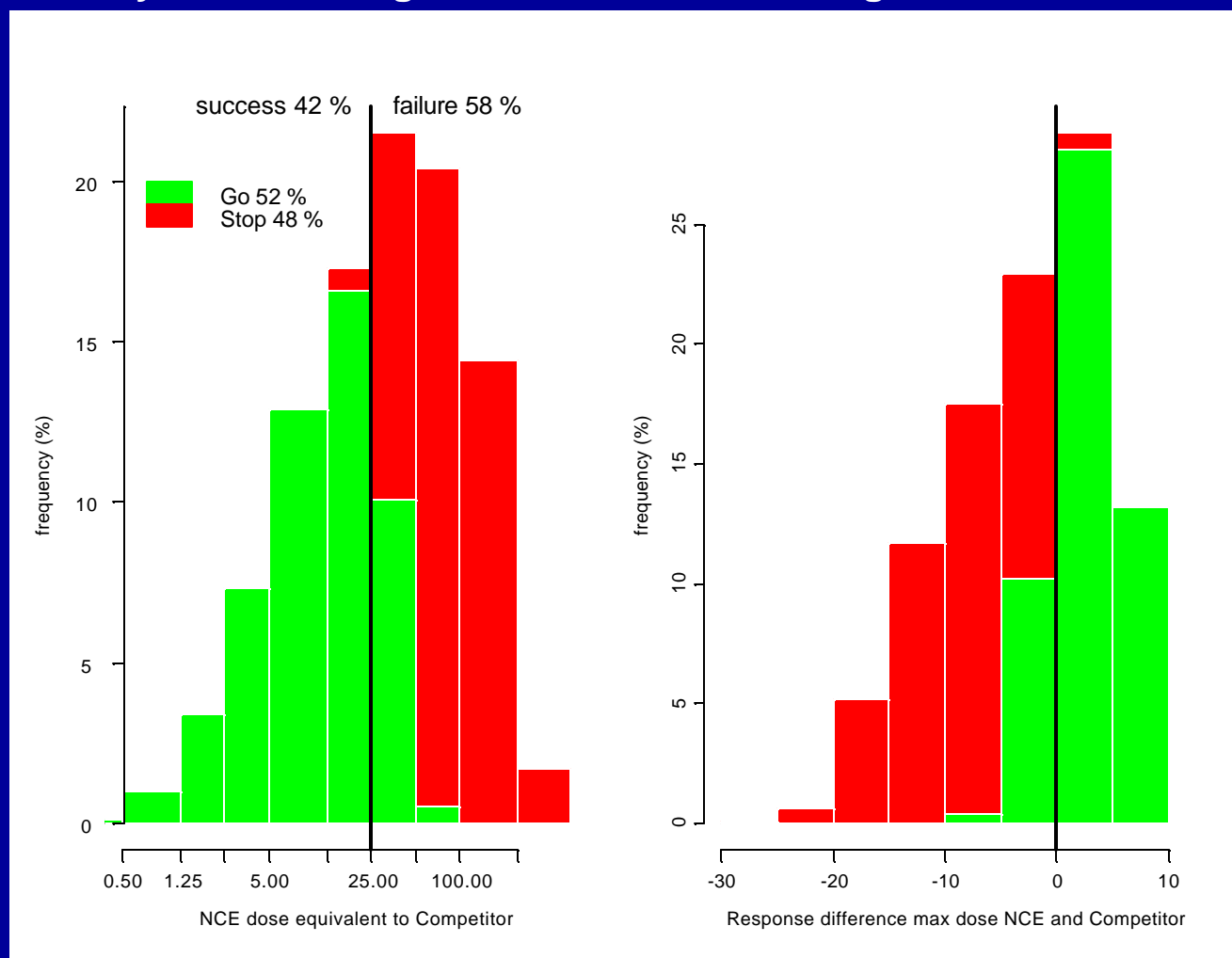
Which would lead to a decision to stop development.

it would be useful to understand how well the trial can support a decision to stop if the drug is a failure and to go if the drug is a phase III success.



# Clinical Trial Simulation is now used to evaluate the risk of making a bad decision based on Phase II results.

The decision is to STOP development if the dose of the NCE equivalent to the competitor is likely to be >25 mg, because doses > 25 mg are associated with unwanted side effects.



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

$P(\text{Stop}|\text{success})=1.7\%$

$P(\text{fail}|\text{Go})=20.4\%$

*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 of the added costs now (time and \$) vs the value of being able to make a better decision later
- 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.

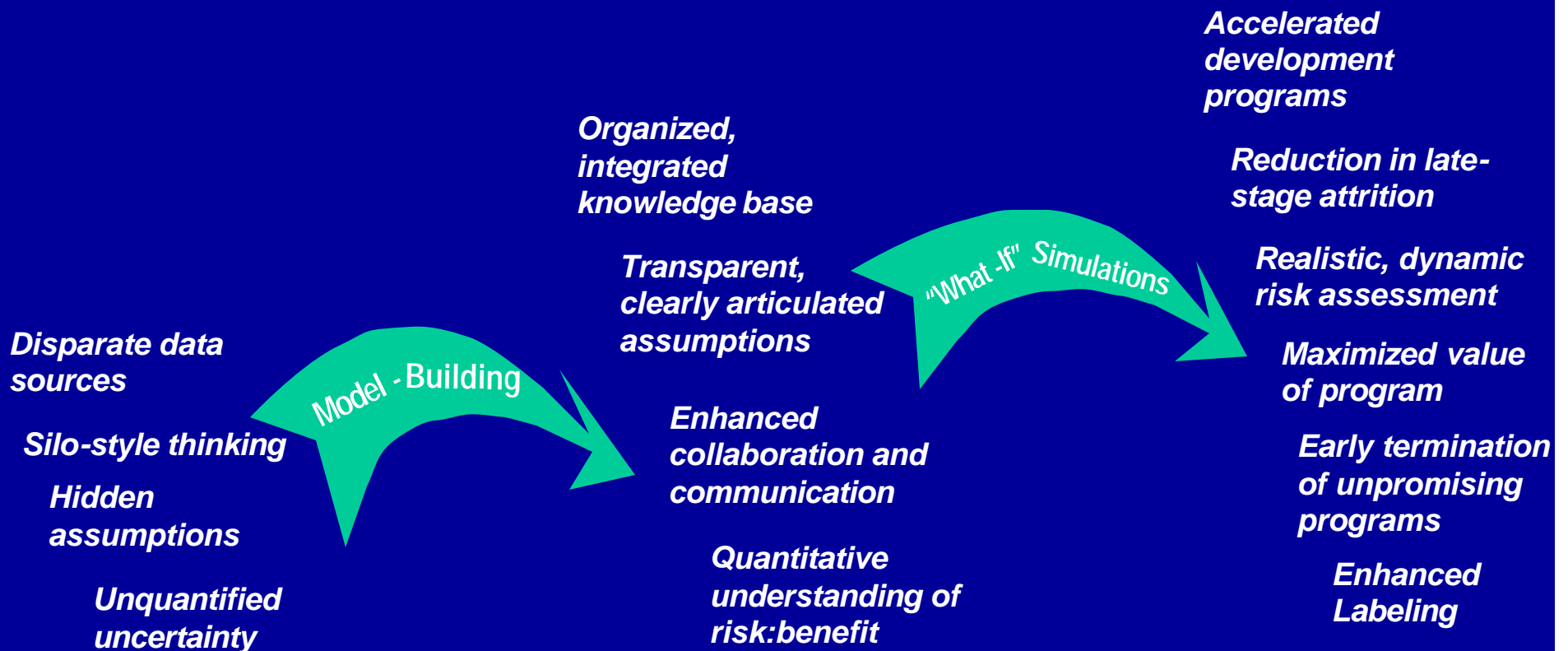
# *So, overall, did we help?*

- Cost of Phase I surrogate trial: \$1M and 6 mo  
(Note: These are thoroughly made-up numbers)
- Cost per treatment arm in Phase III: \$2-5 M, 2-4 yr
- Cost of failed phase III program: \$20-40 M, 2-4 yr
- Value of understanding risks to development program:  
***Priceless!!***

## *The Path Forward: Key Investments*

- Information Technology
  - Integrated data infrastructure
  - Knowledge management
  - Collaborative tools
  - Decision platform
  - Automation of standard tasks
- Models as Intellectual Capital
  - Build standing drug, disease, trial, and market models as TA specific IP

# *In summary, integrated use of prior knowledge can provide on-going benefit to the development process*



# *There are many factors contributing to successful use of Modeling and Simulation*

"Baseball is 90% mental. The other half is physical" – Yogi Berra

*With apologies to Yogi, the following are critical to M&S project success...*

	<b>Contribution to Success</b>
<b>Communication</b>	90%
<b>Politics</b>	90%
Analytic Insight	25%

**➤ *If the organization isn't ready, M&S won't work!***

## *Notable quotes and anecdotes from on-going implementation efforts...*

- “We don’t want any of the financial stuff—we make decisions based on the science!”—Clinical Pharmacologist
- “These examples are too focused on development questions—if they don’t show the return on investment, we can’t use it.”—Director, Biostatistics, Medical Affairs
- “If M&S gets buried deep in Clinical PK, it will go nowhere”—VP Global Marketing