

# Strategic Uses of Modeling and Simulation in Drug Development

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# What is a model?

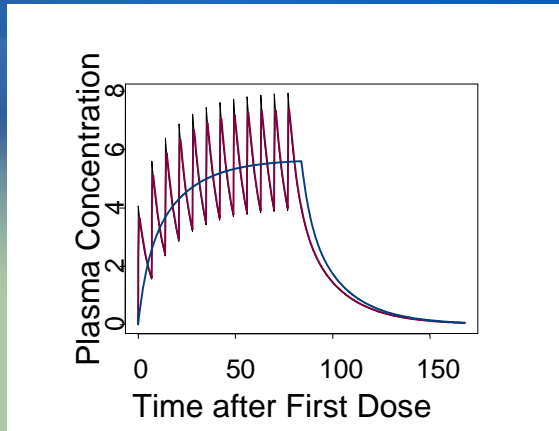
A model: A mathematical description of an outcome.

- Equations for the expected response
- Stochastic description the estimated variabilities associated with the outcome
- Uncertainty.
  - We'd like to know the true expected response, and also the variation about that expectation. We are hampered by the lack of power of our observations to tell us about those things

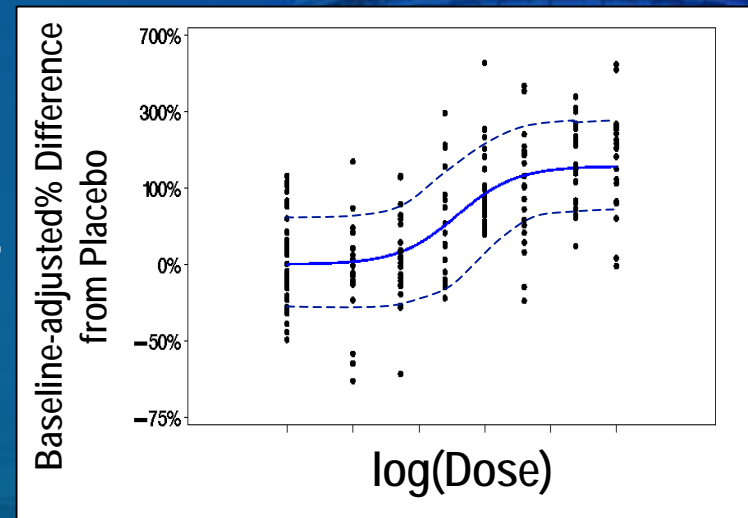
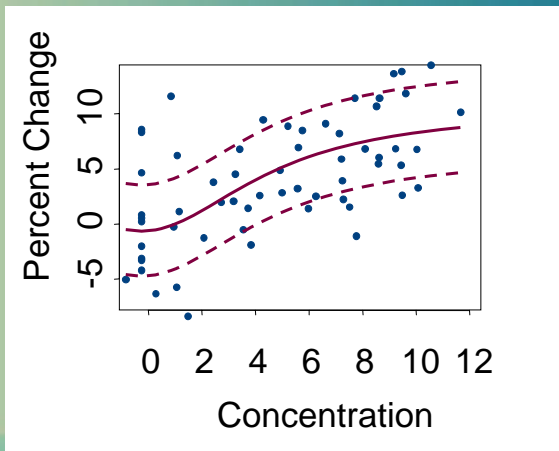
## Why Simulate?

- Simulations tell us about the consequences of our models and the depth of our uncertainty

# When you say “Modeling”, people frequently think of PK/PD Modeling



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# “Simulation” is frequently thought of as Clinical Trial Simulation (CTS)

Does our drug differ from the comparator?

By how much?

How sure are we?

How do we design a trial to show this?

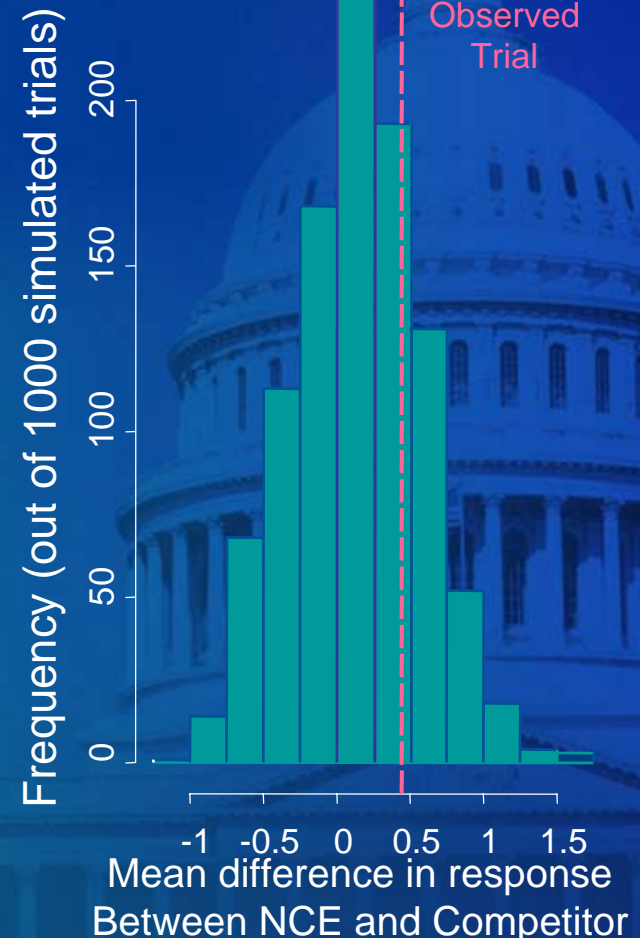
CTS allows us to investigate

Trial Design

Sample Size

Choice of Comparator

➤ *Will this trial succeed?*



## *There are some important benefits accruing from utilization of this approach*

- Reduced cost associated with trials
- Increased certainty in trial designs
- Lower rate of late-stage attrition
- Studies in an appropriate population

➤ *Smaller number of failed trials*

***However, the real world is somewhat more complicated...***

*"Drug Development decisions start off easy, but get harder and more expensive"*

*"The most important decisions are influenced by multi-faceted criteria"*

*"The reasons people should make a particular decision need to be communicated as clearly as possible"*

# The Ridiculous to the Sublime: Decisions relevant to Drug Development vary in their Sublimnity

Sublimnity Scale	Types of Knowledge Impacting Decision	Value of Decision	Example
Not very Sublime	Few	"My ¢¢"	<p><b>"Is this model cool or what?"*</b></p> <p>Individual Trial Design</p> <p>Advance to Ph III?</p> <p>File NDA?</p> <p><b>Regulatory Approval?</b></p> <p><b>Inclusion in Formulary?</b></p>
Sublime	Many	\$MM	<b>Prescribe Drug?</b>

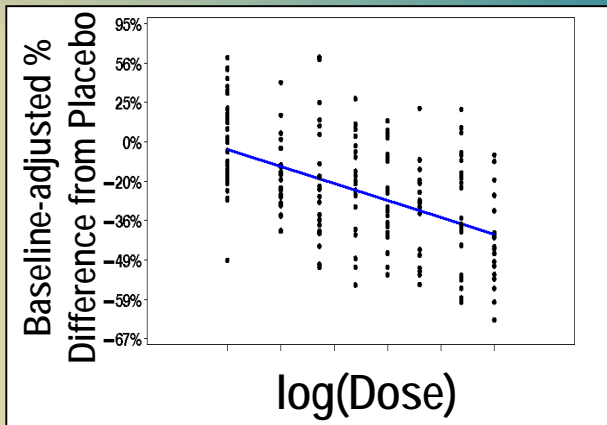
\*Decision Owners:  
**Some Pharsight Consultant**  
 Drug Company  
 External Stakeholders



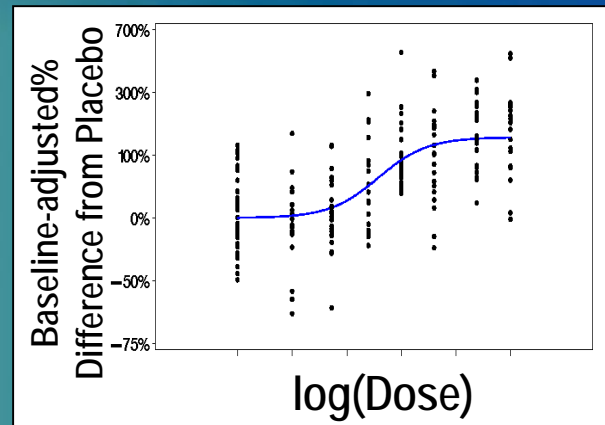
# Example 1: Clinical Utility, or “Not all endpoints are created equal”

We can build models about many of the important drug attributes, and we can ask about many of the others

Efficacy 1



Efficacy 2



Convenience 1

- QD Dosing
- BID dosing

- The Clinical Utility Index is a weighted score assessing the overall value of the treatment

# The CUI index is a linear combination of the attribute utility scores

$$CUI(x_1, x_2, \dots, x_n | treatment) = \sum_{i=1}^n w_i U_i(x_i | treatment)$$

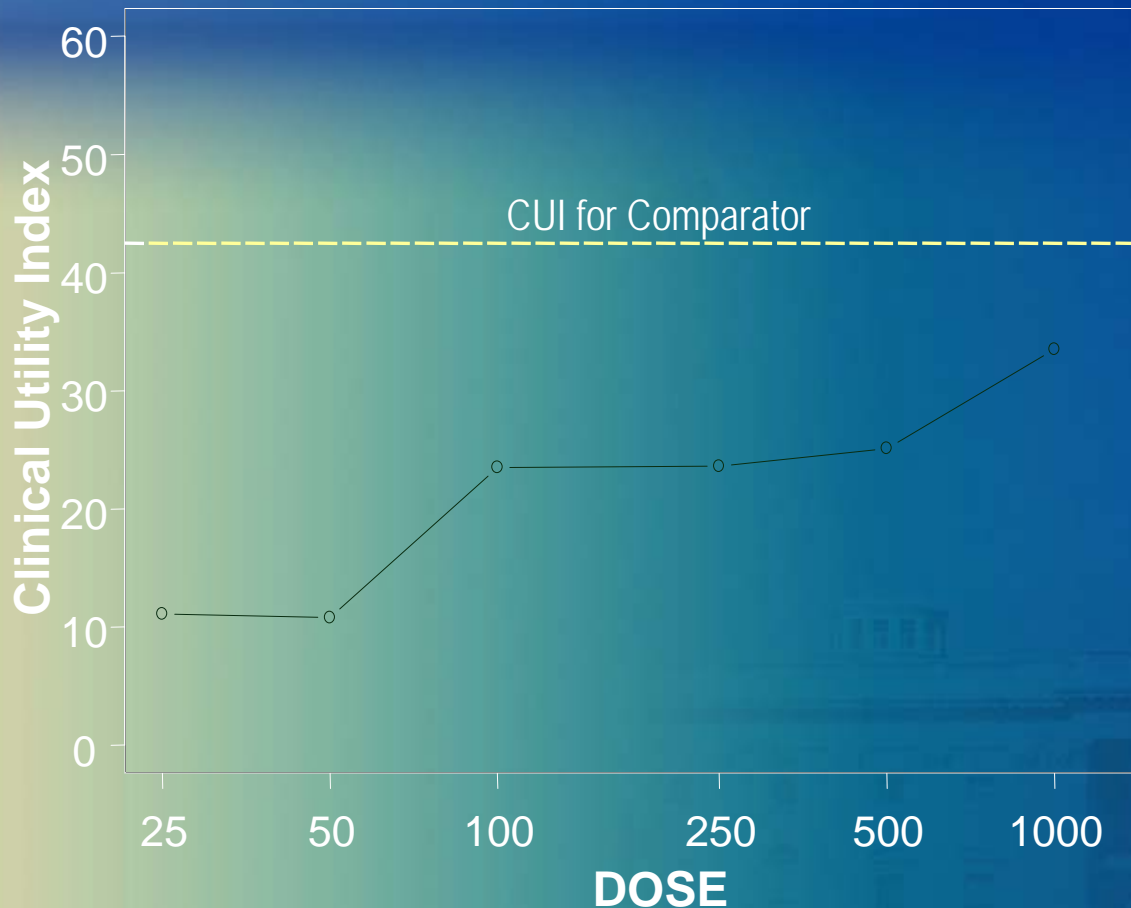
- Weights,  $w_i$ , quantify the relative importance of the various attributes
- The utility score for a particular attribute,  $U_i(x_i | treatment)$ , depends on the probability of the treatment achieving a particular response, and on the relative value of that response
- In this example, the NCE has a somewhat higher utility for Effect 1 efficacy, but a substantially lower utility for AE 1
  - Thus its overall CUI is lower than the comparator

<b>NCE</b>			
Attribute	$U_i$	$w_i$	Contribution
Effect 1	40	0.40	16
AE 1	32.1	0.30	9.6
Effect 2	25	0.30	7.5
Total CUI			33.1

<b>Comparator</b>			
Attribute	$U_i$	$w_i$	Contribution
Effect 1	30	0.40	12
AE 1	61.2	0.30	18.4
Effect 2	25	0.30	7.5
Total CUI			37.9

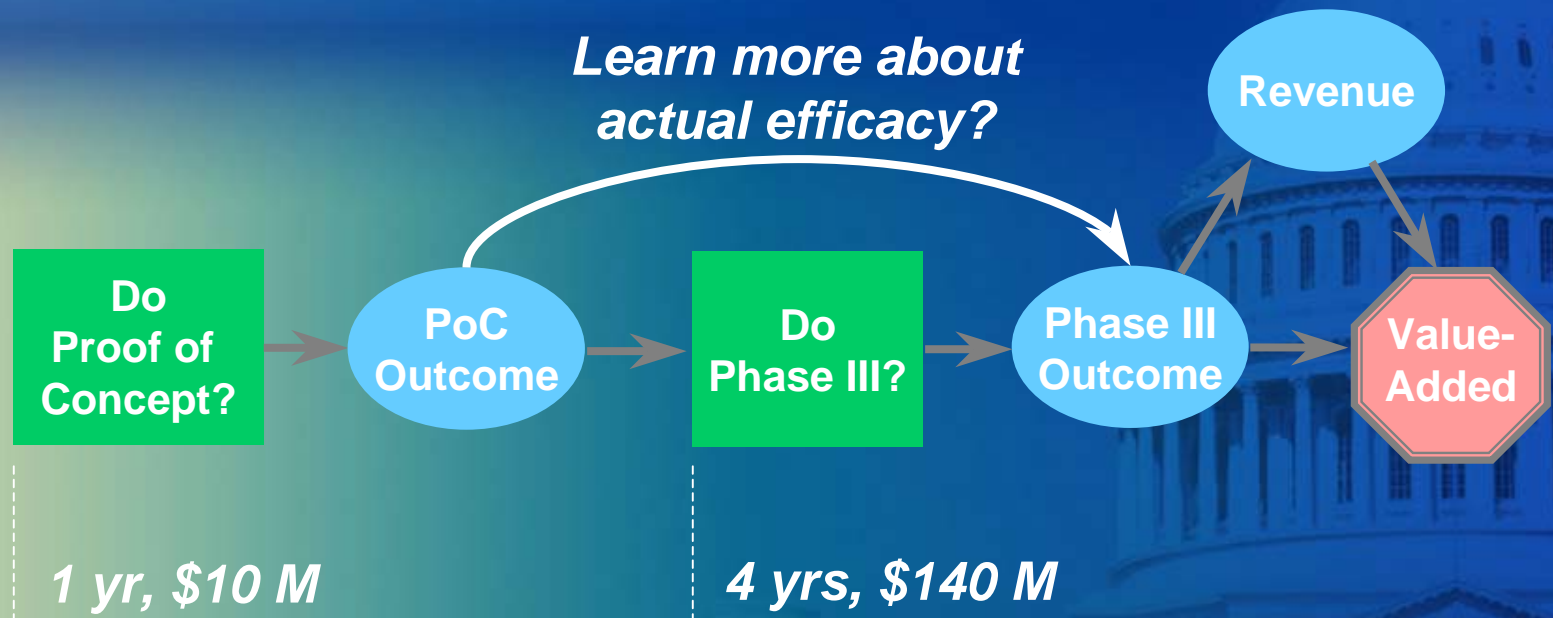
➤ We are now in a position to examine the dose-response for Clinical Utility, and look at sensitivity to particular attributes

# *In this case, there is no dose for which the NCE can be considered equivalent or superior to the Comparator*



- Based on CUI with current attribute ratings and simulated drug responses
- The NCE is unlikely to sell as well as the comparator

# Example 2: Should we do the Proof of Concept trial, or skip it and head straight for Phase III?



*Given what the team already knew, would a PoC trial using the clinical event justify the cost and delay of the trial?*

# *With clinical trial simulation, we could estimate the Probability of Success in Phase III for three development strategies*

*Probability of  
Phase III Success*

## **Strategy 1:**

*Skip Phase II, and do Phase III now*

60%

## **Strategy 2:**

*Do Phase III, only if PoC suggests “winner”  
or “blockbuster”*

74%

## **Strategy 3:**

*Do Phase III, only if PoC suggests  
a “blockbuster”*

86%

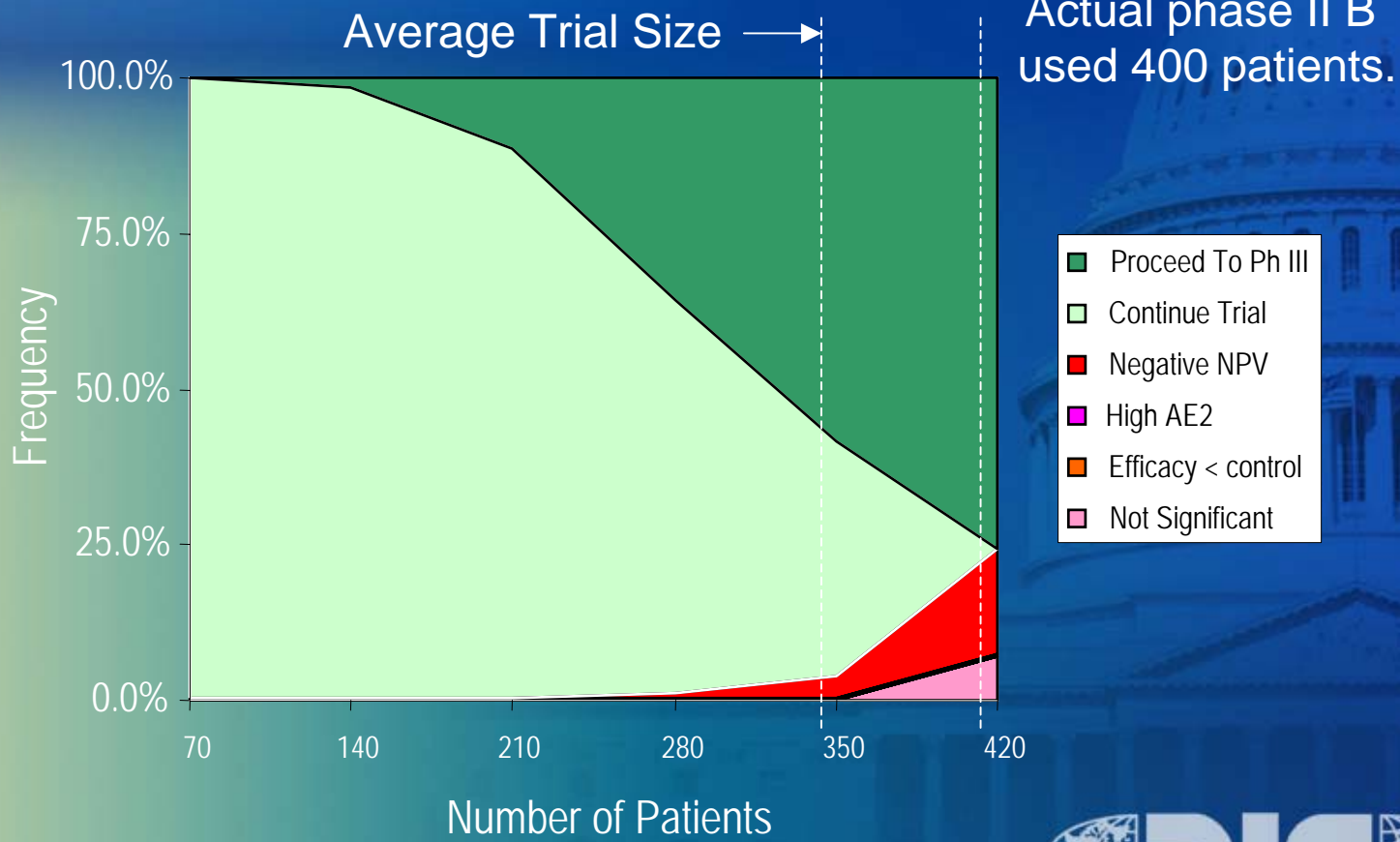
***However, because of the 1 yr delay, the cost of this PoC trial outweighs the value of increased certainty about the Phase III result***

Value of drug if <u>SKIP</u> Proof of Concept trial	<u>\$255 M</u>
Cost of Proof of Concept trial	- \$ 10 M
Cost of delay	- \$ 95 M
<u>Value increase due to better decisions (PoC)</u>	<u>+ \$ 5 M</u>
Value of drug if <u>DO</u> Proof of Concept trial	<u>\$ 155 M</u>

➤ ***In this case, therefore, the better strategy is to skip PoC.***

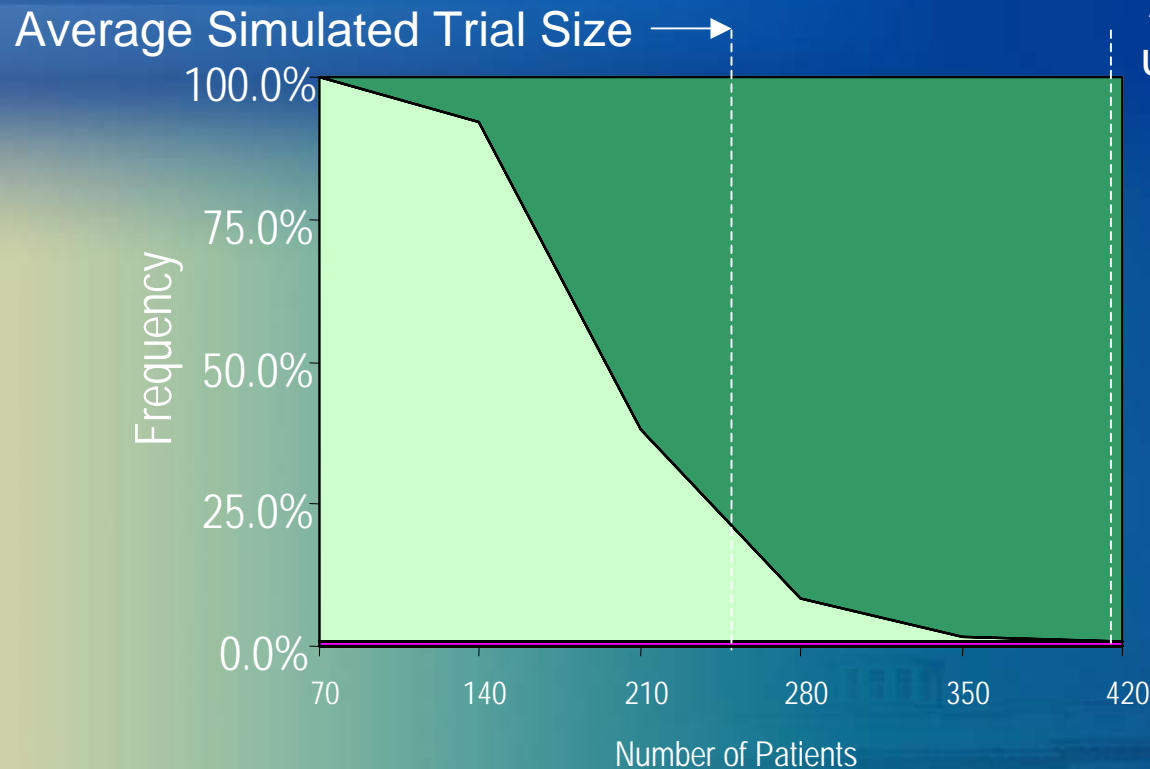
# Example 3: Are we doing the right trial?

Here, a group sequential Phase II design that allows stopping for economic futility recommended proceeding to Phase III 76% of the time for a drug with efficacy profile similar to the positive control.



➤ Average trial accrued 341 patients in ~12 mo.

# ***But with blockbuster efficacy the alternative design trial recommended starting phase III early***



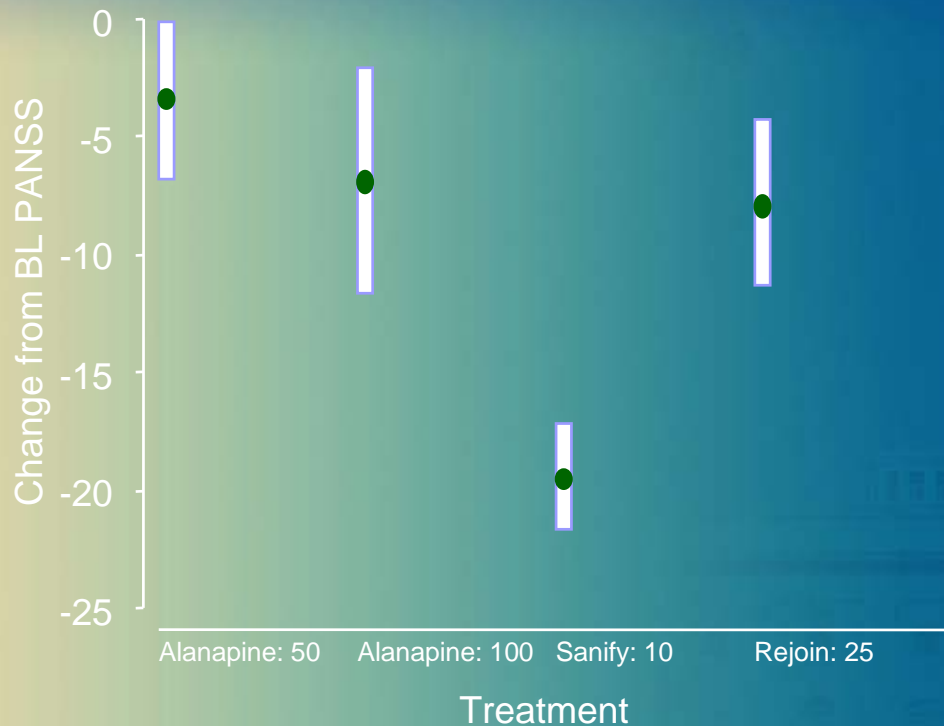
Actual phase II B  
used 400 patients.

- ***Average trial showed significant efficacy after evaluating 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.***

# Example 4: “What about the competing treatments?”

## PANSS vs Treatments

Diagnosis: Population

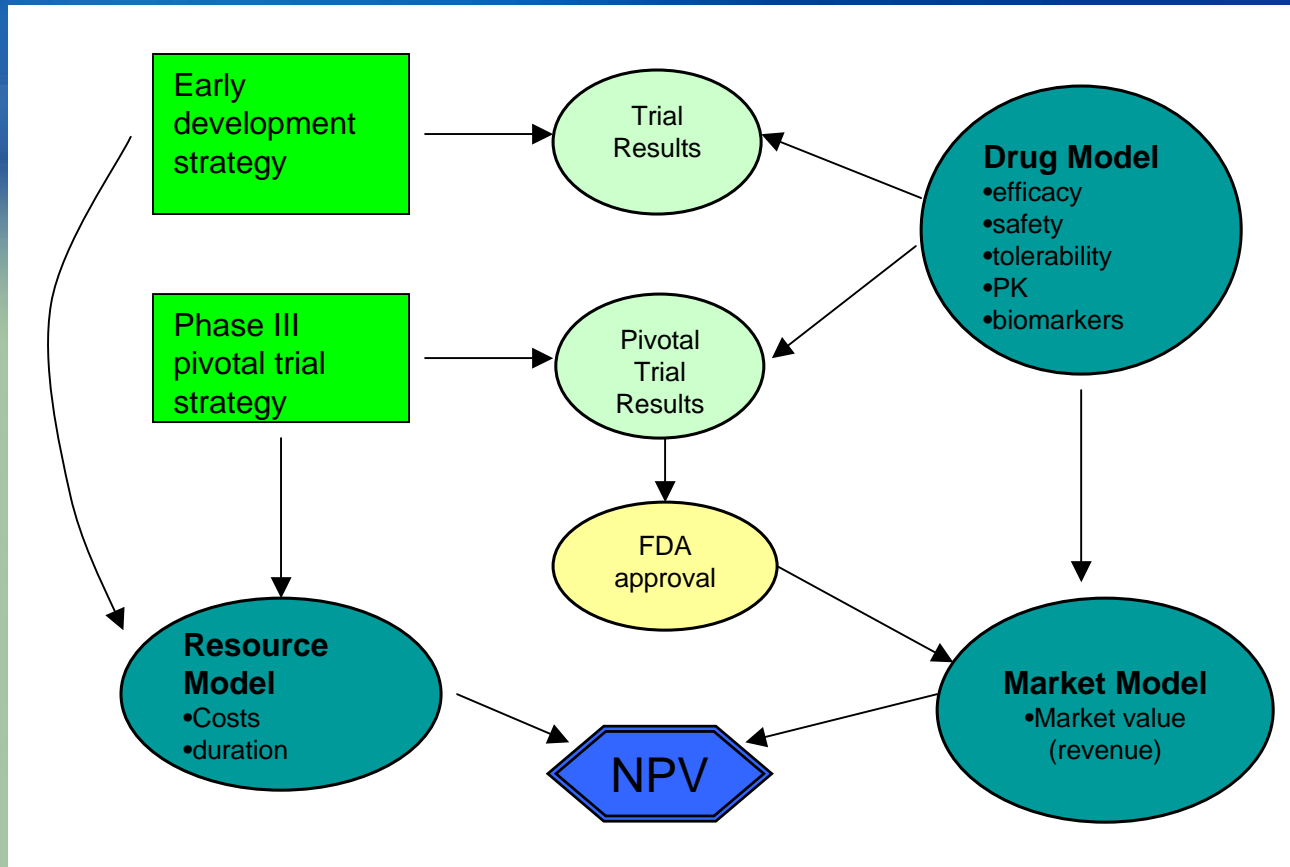


## PANSS vs Treatment

Treatment	5.0%	mean	95.0%
Alanapine: 50	-6.71293	-3.34311	-0.102029
Alanapine: 100	-11.5331	-6.94963	-2.14458
Sanify: 10	-21.6653	-19.5071	-17.1955
Rejoin: 25	-11.232	-7.8887	-4.29936

- Drug Model Explorer® (DMX®) allows facile comparison among treatments

# *Drug Development is complicated; Modeling and Simulation can help capture this complexity and facilitate understanding of its consequences*



*Foster collaboration by providing a common, dynamic, integrated view of the drug and development strategy allowing trade-offs on basis of scientific, clinical, commercial and financial considerations*

# *To summarize: Modeling and Simulation can be used up and down the Clinical Development value pyramid*

## **Portfolio Review**

- Which programs are most likely to succeed?
- At what level of investment?

## **Program Decisions**

- What indications should we pursue?
- When should we stop development?

## **Trial Simulation**

- Which endpoints should we study?
- How many arms, and what size?

## **Drug and Disease Models**

- Safety and efficacy profile?
- Optimal dosing regimen?