

Methods for Developing Differentiated Drug Products



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Kevin Dykstra, Lee Hodge, Bill Poland, & TJ Carrothers

Pharsight

Disclaimer

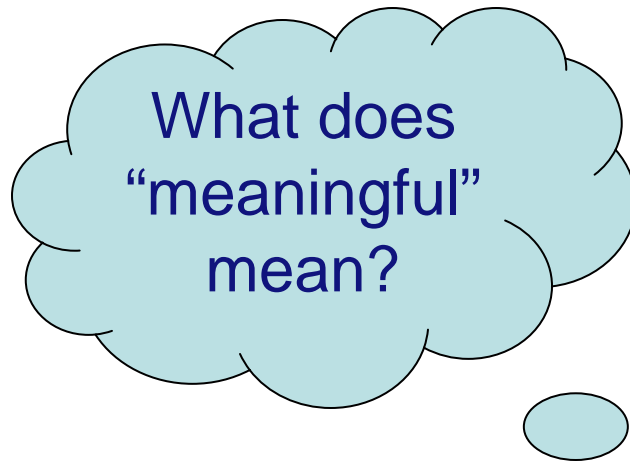
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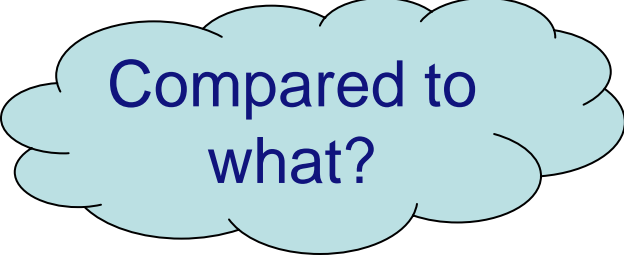
Outline

- What is a differentiated drug product?
- Clinical Utility Index: A methodology for assessing differentiation
- Three examples

**A differentiated drug product
offers a meaningful advantage
over existing treatments for a
given condition**



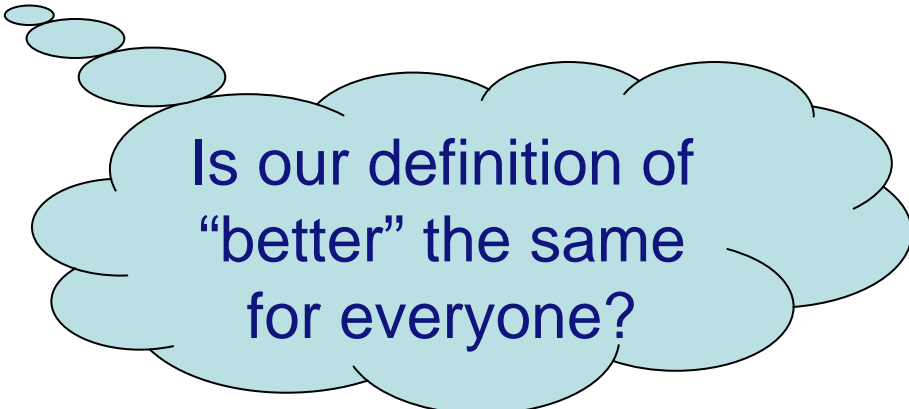
A differentiated drug product offers a meaningful advantage over existing treatments for a given condition



Compared to
what?

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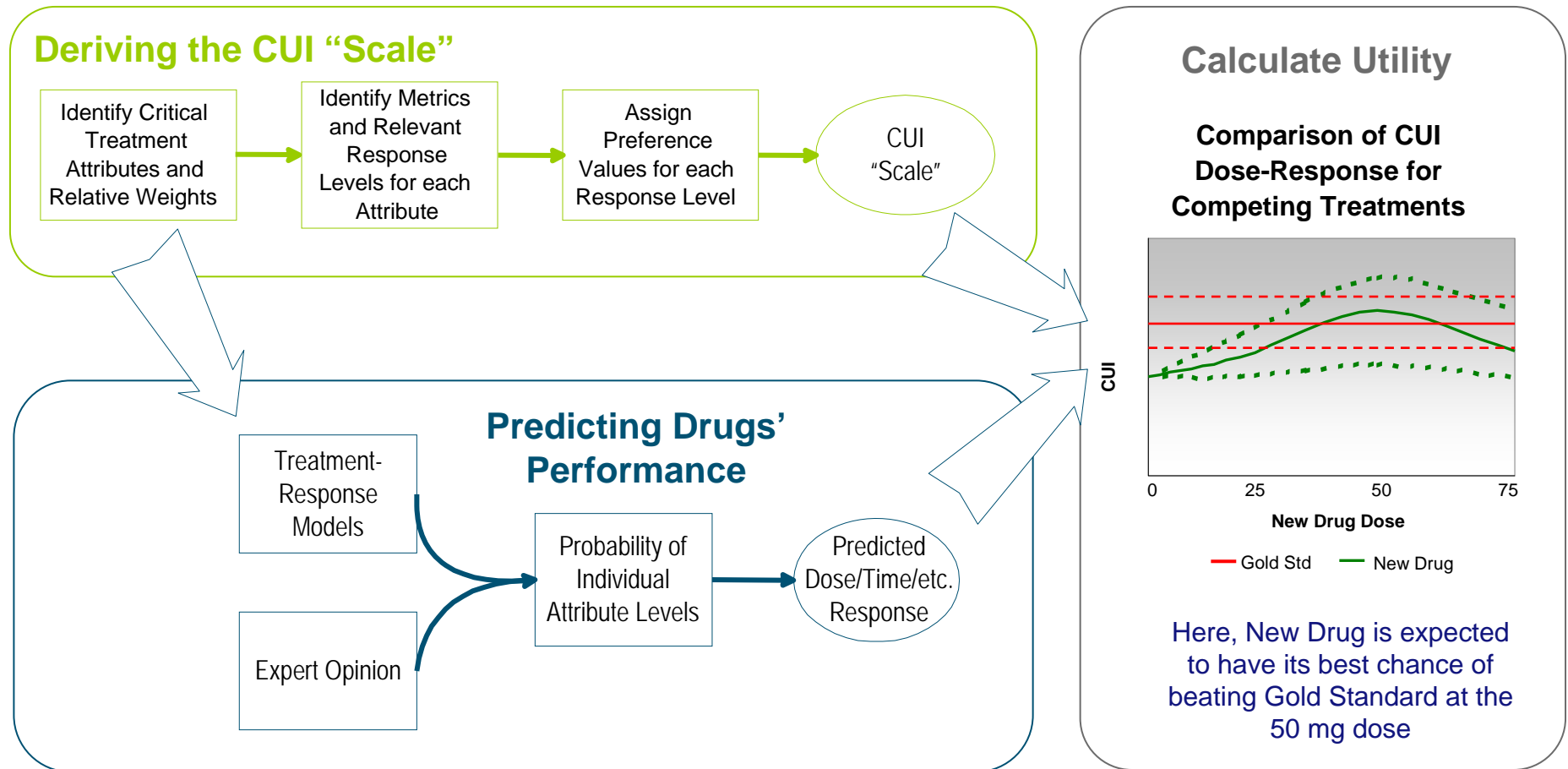


Is our definition of
“better” the same
for everyone?

How useful is a new medicine compared to Placebo or Standard of Care?

- Every drug has benefits and risks.
- The relative importance of these characteristics depends on the disease the drug is intended to treat
- They also change with dosage, patient population, etc.
- Tradeoffs must often be made among the drug effects comprising the product profile, balancing the benefits and risks.
- The **Clinical Utility Index (CUI)** quantifies these tradeoffs by providing a single metric for the multiple dimensions of benefit and risk.
 - It is...a **systematic** approach to understanding **subjective** preferences
a **transparent** way of weighing tradeoffs
knowledge-driven; available data are used; if not, we rely on expert opinion
closely related to the Target Product Profile
a Multi-Attribute Utility Function
 - It is **not** an “**objective**” measure in the sense that a physiological measurement, such as blood pressure, is

To predict CUI, we combine the CUI “scale” with predictions based on models of drug performance



Poland B, Hodge F, Khan A, Clemen R, Wagner JA, Dykstra K, Krishna R. [The Clinical Utility Index as a Practical Multiattribute Approach to Drug Development Decisions](#). Clin Pharmacol Ther 86(1):105-108, July 2009.

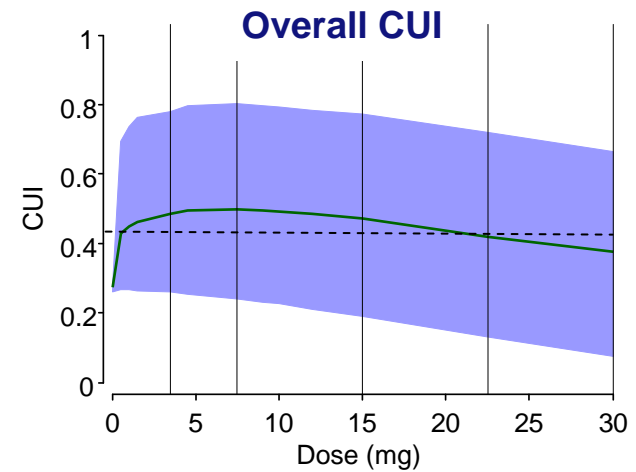
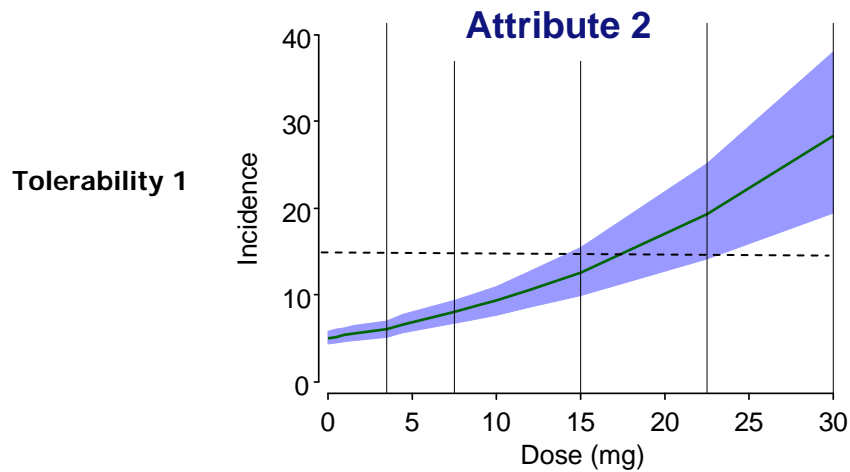
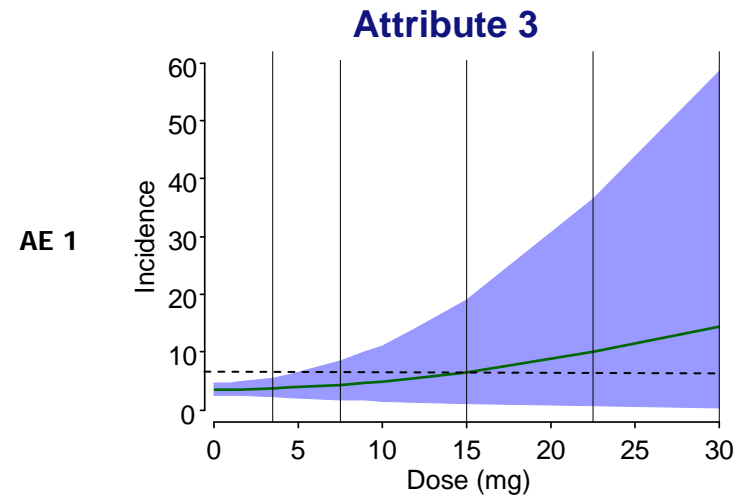
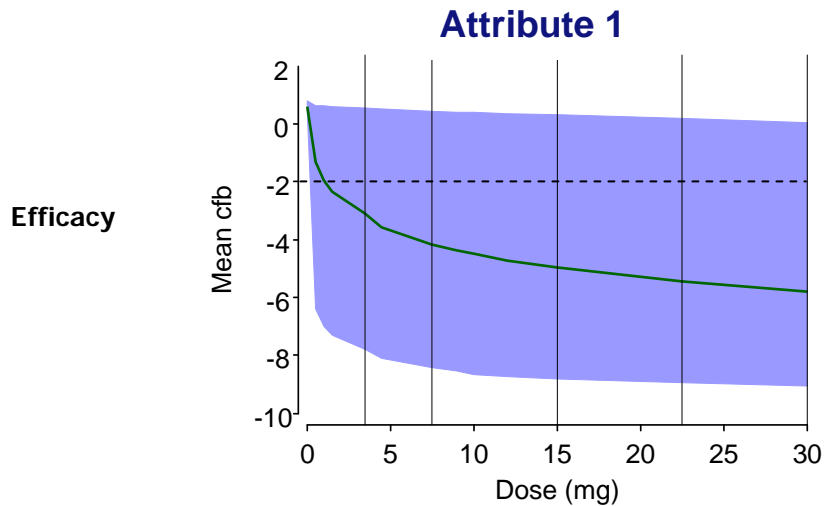
Example 1: Alzheimer's Disease: The team focused on the attributes in green

The following summarizes the endpoints in the Aricept database.

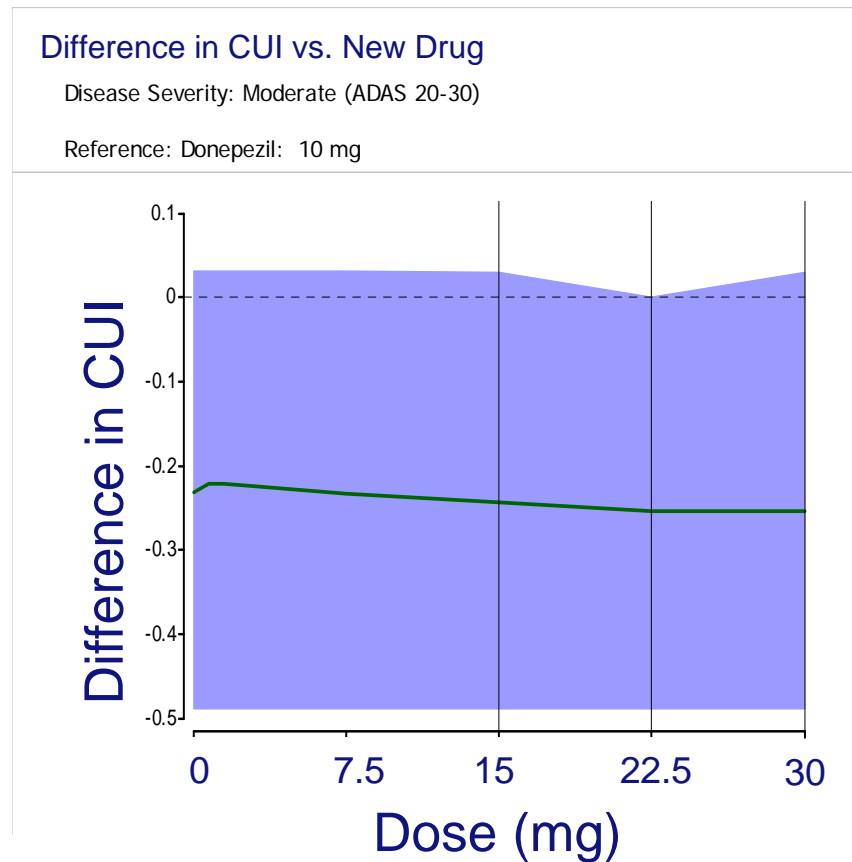
Efficacy	CNS tolerability	GI tolerability	Dropout categories
ADAS-cog	Abnormal dreams	Abdominal disturbances	Dropout due to ineligibility
ADAS-cog/11	Agitation	Abdominal pain	Dropout due to patient becoming asymptomatic/cured
ADAS-cog-mod	Anxiety	Acute abdominal discomfort	Dropouts due to abnormal lab values
ADAS-J cog	Arthralgia	Anorexia	Dropouts due to AE
CDR	Arthritis	Constipation	Dropouts due to all reasons
CDR-SB	Asthenia	Diarrhea	Dropouts due to caregiver request
CGI-2	Back pain	Dyspepsia	Dropouts due to consent
CGIC	Confusion	Fecal Incontinence	Dropouts due to death
CGI-I	Depression	Flatulence	Dropouts due to inter-current illness
CIBIC+	Dizziness	Gastric upset	Dropouts due to investigator decision
DAD	Fatigue	Gastroenteritis	Dropouts due to investigator or patient decision
J-CGIC	Hallucinations	Loose stools	Dropouts due to LOE
MMSE	Headache	Nausea	Dropouts due to LFT
NPI	Hostility	Nausea, Vomiting, Anorexia	Dropouts due to noncompliance
NPI- Delusions	Insomnia	Nausea/vomiting	Dropouts due to nursing home placement
...	Leg cramps	Vomiting	Dropouts due to other
QoL	Muscle Cramps	Weight loss	Dropouts due to PV
SIB	Pain		
SMMSE	Seizures		
	Somnolence		

† The database includes 17 subsets of NPI

Assessment of the impact of multiple attributes was challenging...



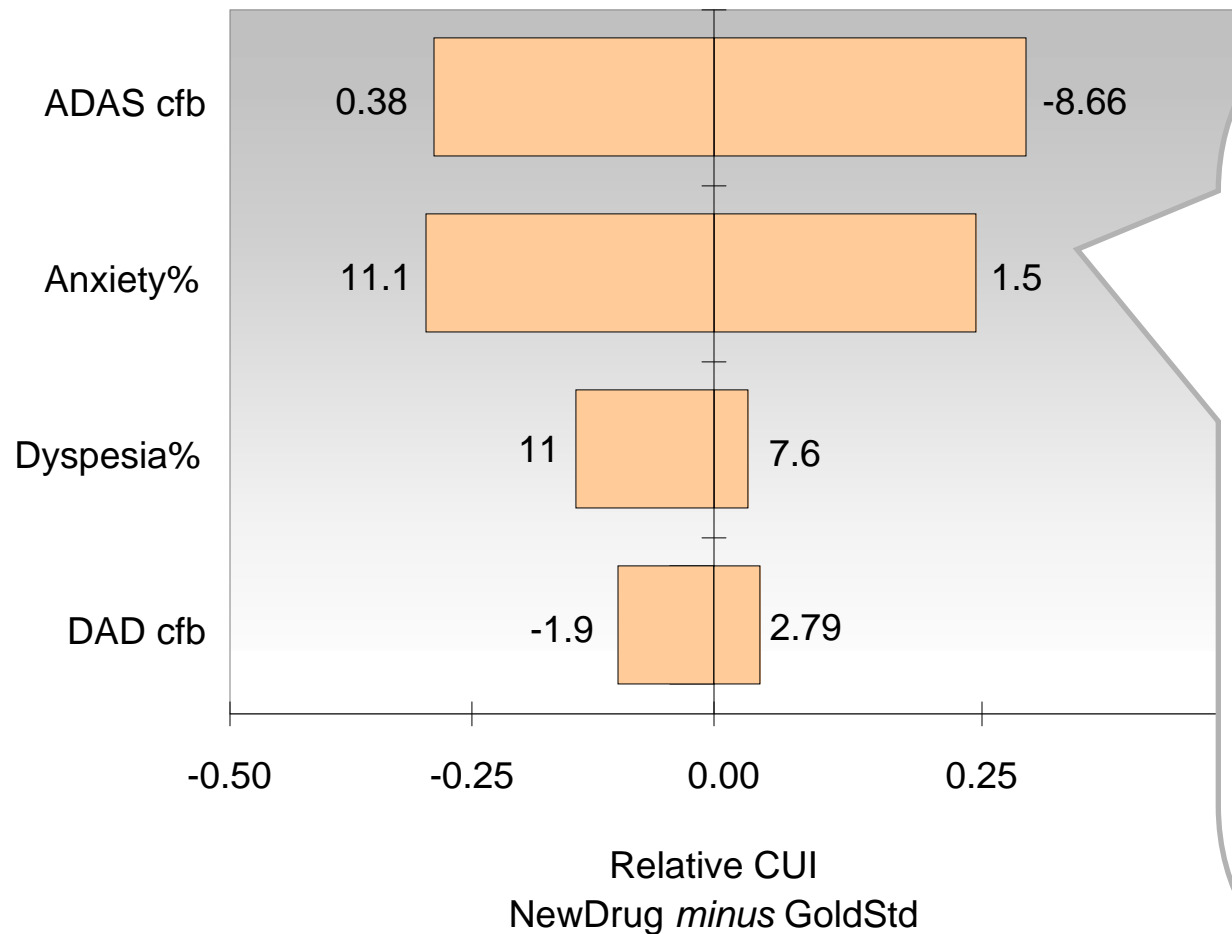
A plot of the difference in CUI between two treatments shows futility of further development



This graph shows the *probability* that any dose of the new drug will beat the SoC

The analysis estimates a less than 10% probability of beating the SoC CUI.

Sensitivity analysis examined “what-if” the assumptions were different



By examining what drives *relative* value, we can see which factors impact the chances of beating the competitor.

This could be used to improve the existing drug NewDrug, or to guide development of a new compound.

Note Relative CUI could also be translated to market share, to a financial metric, etc.

Example 2: A mature drug for a chronic neuromuscular disorder

- Efficacy is closely related to drug levels
 - Measured according to a standard efficacy scale (SES)
- Incidence of adverse events is also related to drug concentration
- Dopahexidine is eliminated quickly
 - To achieve acceptable duration of effect, relatively large doses must be given multiple times daily, i.e. Q6h
 - This means brief exposure to high plasma levels, and increased incidence of concentration-related AEs

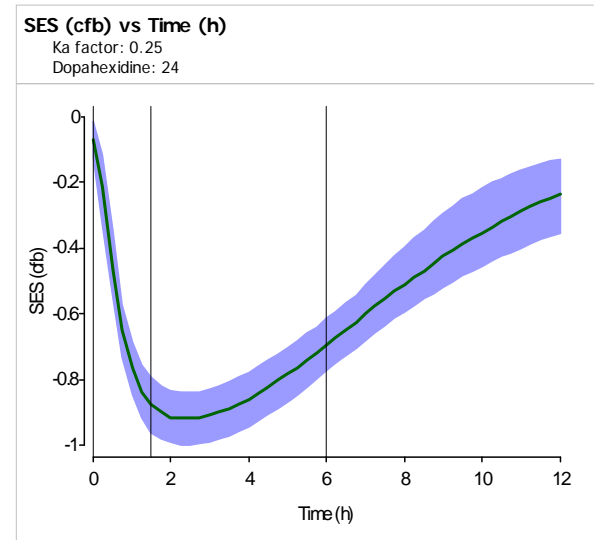
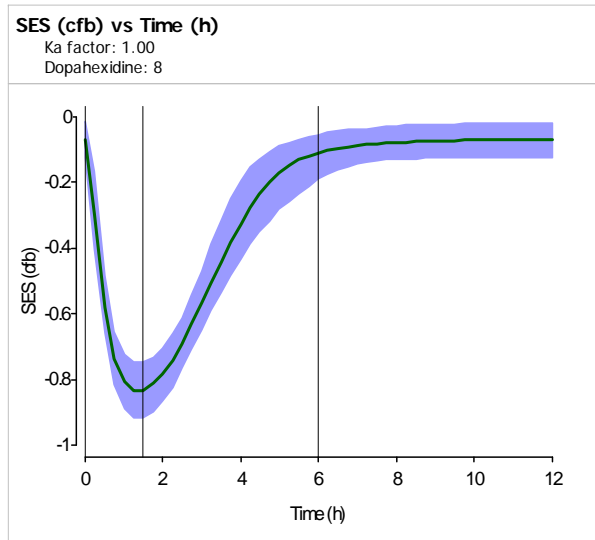
The team identified key treatment attributes— these were tested in a physician survey

Treatment Attribute	Physician Survey		Team	
	Rank	Weight	Rank	Weight
Efficacy (maximal change in SES scale)	1	.228	1	.207
Compliance (%)	2	.169	5	.120
Hypotension (change in mm Hg, systolic BP)	3	.139	4	.140
Drowsiness/Somnolence (% incidence)	4	.135	3	.154
Duration of effect (h)	5	.112	7	.098
Elevated LFTs (incidence over 3x ULN transaminase)	6	.109	2	.182
Dyskinesia (% incidence)	6	.109	6	.101

- Initially, treatment attributes were elicited from the client team
- These choices were later assessed in a small survey of prescribing physicians
 - Rankings changed somewhat, but attribute weights were similar overall
 - Overall results were compared using both sets of weights
- Interestingly, maximal efficacy was important, but not overwhelmingly so
- There were insufficient data to assess incidence of LFT elevation and compliance, so these were considered to be identical in each of the comparisons

We explored the effects of altering PK characteristics

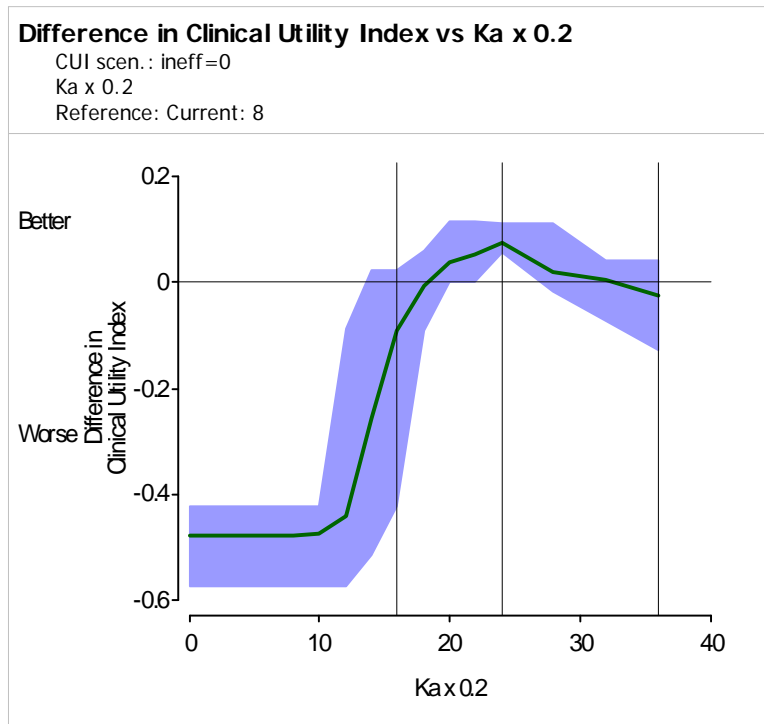
- Graphs show increased duration of effect at a higher dose, with absorption rate decreased by 75%



Time of onset (not mentioned in CUI) and maximal change in SES are similar
Duration of efficacy is substantially increased

We examined the effects of alternative formulations on CUI

Graph and table show compare the best dose of the current formulation to 24 mg dose with absorption rate reduced by 80%



Difference in CUI vs Dose for Ka x 0.2

CUI scen.: ineff=0
 Reference: Current: 8

Ka x 0.2	5.0%	mean	95.0%
16	-0.42	-0.09	0.02
24	0.06	0.07	0.11
36	-0.13	-0.03	0.04

Ask not “How much does this trial cost?”

Ask “How much is this trial worth?!”

Q: Which trial contributes more value to a development program?

- 1) A trial virtually certain to deliver a definitive answer, but requiring 3 yr to complete
- 2) A trial with less power, but requiring half the time

A: I don't know, but it can be estimated

The value can be denominated in terms of the dollar value of the program to the developer (eNPV) or in terms of a reduction in disease burden to the patient (quality-adjusted life year, QALY)

Example 3: A Proposed Phase II Development Strategy in Schizophrenia

A CUI was developed initially, and mapped to financial outcome

Category	Response	Relative Weight	Definition	Category Weight
Decrease in PANSS total	Low	1	<10	41%
	Moderate	2	10-20	
	High	6	> 20	
EPS Symptoms	Negligible		< 33% Incidence	20%
	Moderate		≥ 33% incidence	
QTc Change	Fall Back		> 3 ms	20%
	Acceptable		≤ 3 ms	
Decrease in Negative Symptoms	Acceptable		≤ 3.5	15%
	Outstanding		> 3.5	
Weight Gain	High	1	≥ 5 %	4%
	Moderate	2	2 - 5%	
	Low	3	< 2%	

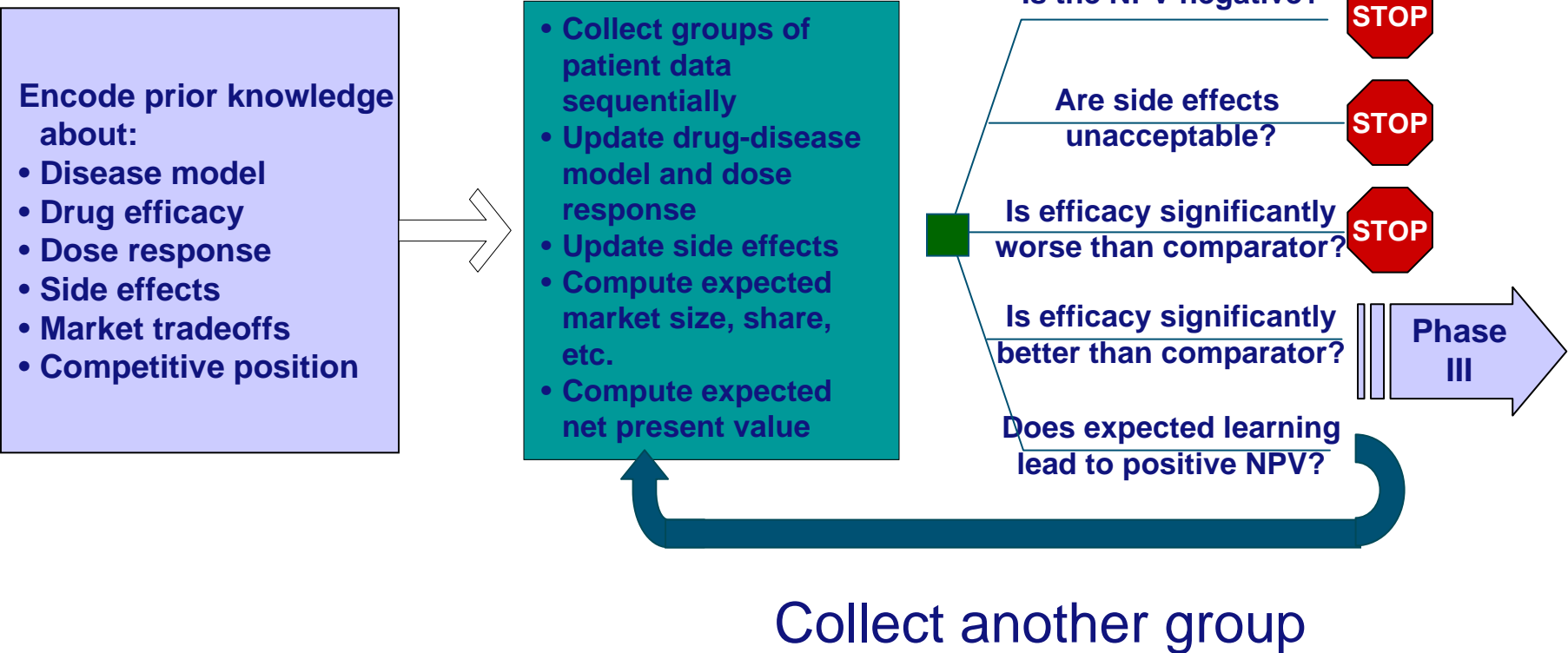
CUI was mapped to expected NPV, and updated based on data collected in the study

Update expected NPV based on:

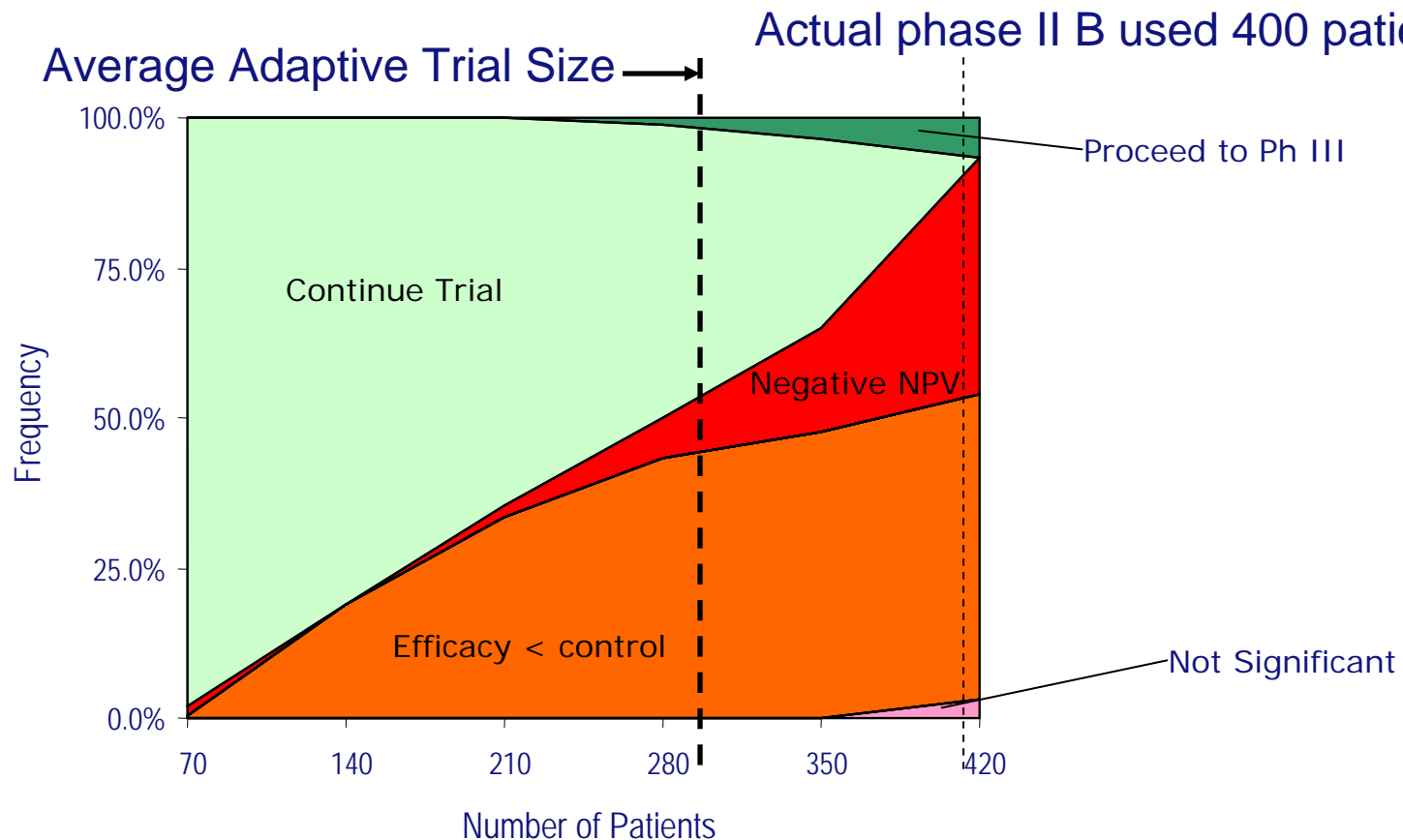
- Expected revenue over life of drug
 - Market life cycle model in which peak market share is a function of a multi-attribute Clinical Utility Index (CUI)
 - CUI is a function of 5 different types of measurements from the study: 2 efficacy and 3 adverse effect
- Cost of continuing Phase II
- Sales and marketing costs
- Cost of manufacturing capacity
- Expected cost and outcome of Phase III

If estimated eNPV acceptable, then continue, otherwise halt development

If estimated eNPV and other characteristics are acceptable, then continue; otherwise halt

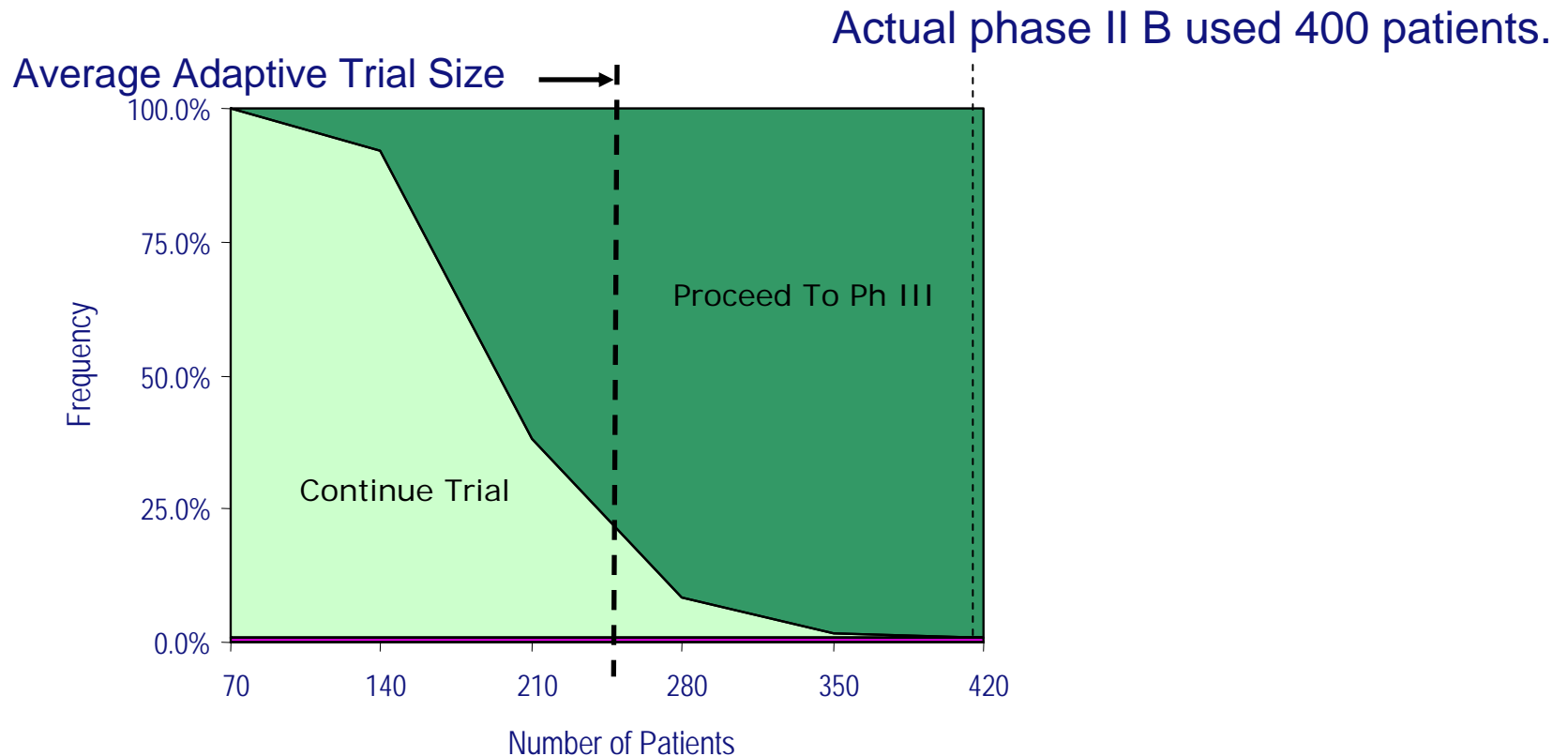


Trial simulation showed that this drug would have failed early due to negative eNPV or lack of efficacy



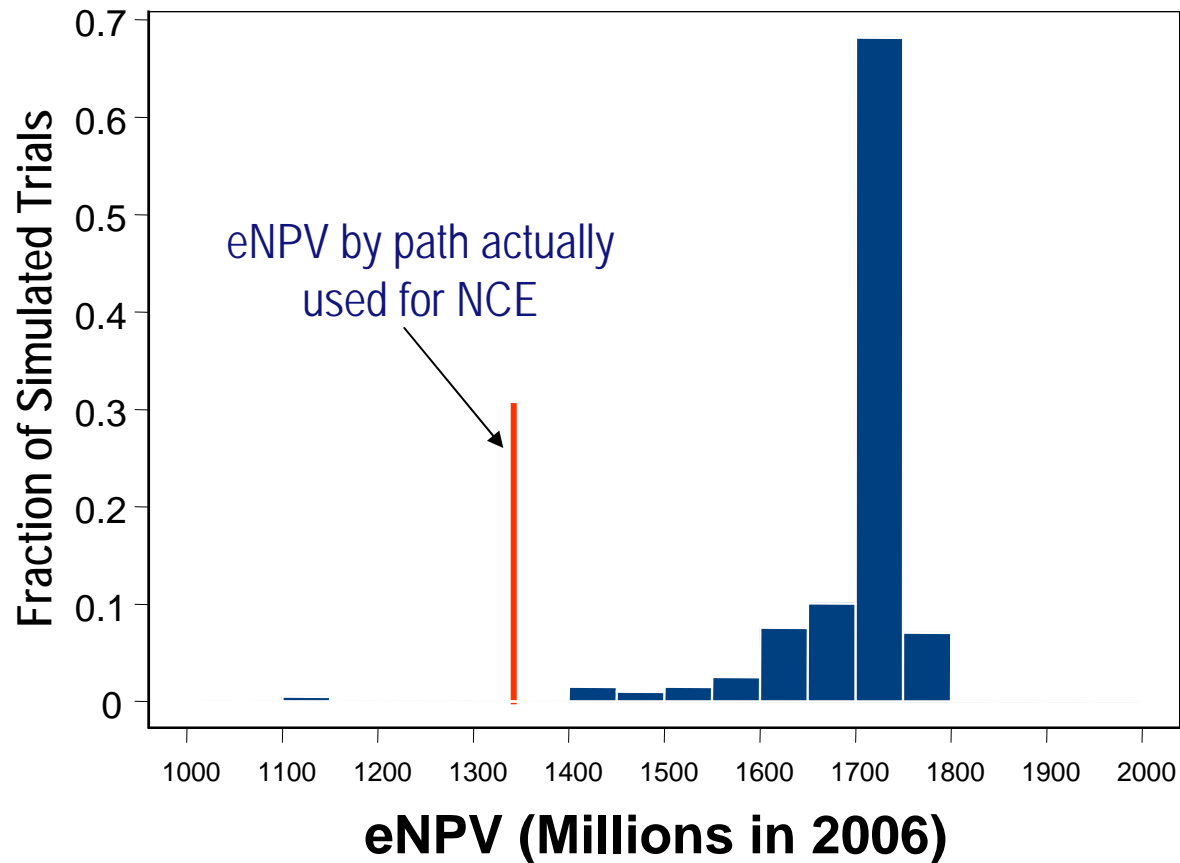
- **Average trial accrued 295 patients in ~10 mo. An erroneous “GO” decision given rarely.**
- **The client had equivocal results and proceeded to phase III.**

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



- **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.**

For an efficacious drug, the time savings results in a significant increase in eNPV



The proposed strategy would save 17 mo, and result in a 26% increase in eNPV

To Summarize...

A quantitative basis for assessing the advantage, or differentiation, of a new drug product over existing treatments can be constructed, even (or especially) in the face of subjective trade-offs

This approach involves explicit enumeration of value of different aspects of drug utility

- In line with recent draft FDA guidance “Target Product Profile – A Strategic Process Tool”, March 2007

These concepts can be extended to financial or health economic valuation to estimate relative value of alternative development scenarios