

The Clinical Utility Index, a Method for Balancing Efficacy and Safety in Drug Development Decision Making

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Clinical Utility Index (CUI) - Outline of Presentation

Motivation

Introduction to the CUI

Nuts and Bolts

- Functional Form
- Elicitation
- Connection to Pharmacometric Workflow

Case Study

Take-Away Points

MOTIVATION

Motivation - We are always balancing benefit and risk.

Every drug has benefits and risks ... balancing them is important throughout the development process.



Typically, however, the conditions by which we see increased efficacy are also associated with increases in side effects.

Motivation - Each drug has a list of relevant attributes

A new product must differentiate itself from existing products in the marketplace.

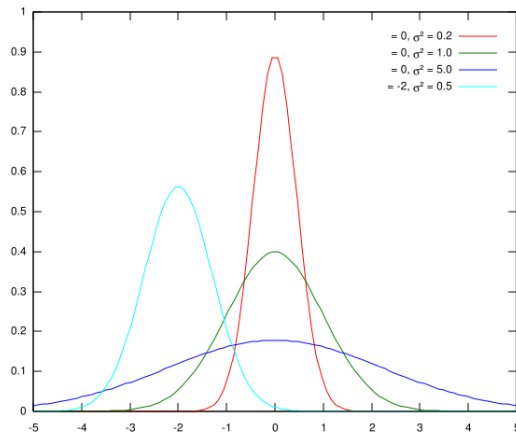
Project teams work with the product profile in its various forms (e.g., target, minimum...) that list the set of attributes (and the levels of attainment thereon) that are relevant when comparing the new product to existing treatments.

Case Study Attribute List

Treatment Attribute
Efficacy (maximal change in SES scale)
Compliance (%)
Hypotension (change in mm Hg, systolic BP)
Drowsiness/Somnolence (% incidence)
Duration of effect (h)
Elevated LFTs (incidence over 3x uln transaminase)
Dyskinesia (% incidence)

Motivation - Most of what we know is uncertain

This audience knows well that project teams face uncertainty regarding the level of achievement that a given treatment will attain on each attribute.



...and that ongoing decisions depend on quantifying what we know, how well we know it, as well as what we do not know.

-> This is the crux of what we do each day.

Motivation - “What is so?” versus “So what?”

We use statistics and pharmacometrics to quantify our knowledge and uncertainties regarding the benefits and risks of a new medicine and existing treatments.

But neither field speaks to how this balancing between benefits and risks should be performed:

- For instance, is a given increase in efficacy (e.g., expected drop in mean arterial pressure) “worth” the associated decrease in safety (e.g., increased incidence of orthostatic hypotension) expected when increasing the dosage?
- Additionally, how can changes in “soft” attributes (e.g., regimen -> convenience) be traded off with changes in “hard” attributes like safety and efficacy?

Thus, we focus a lot on “What is so?” (i.e., Description)

.... and not enough on the “So what?” (i.e., Preference)

Motivation - Decisions must be & are being made, but what is the quality of the decision-making process?

For example, a dominant team member may impose his beliefs regarding the “right” or “acceptable” level of safety.

In other instances, teams may focus on a few best-studied characteristics, such as immediate efficacy and tolerability, while ignoring the true complexity (i.e., likelihood of long-term safety) of the tradeoffs underlying the decision.

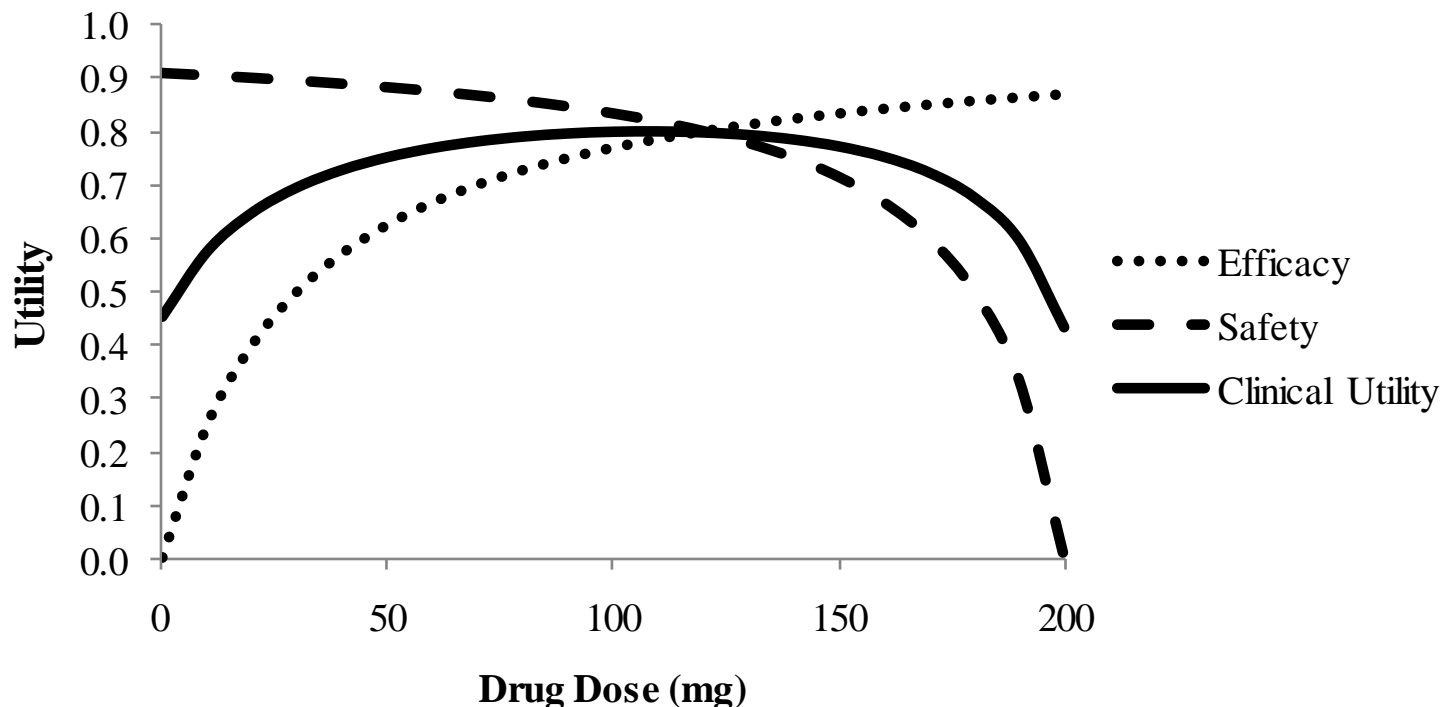
In some cases, typically later in development, the commercial representative on the team may have a market model (e.g., “conjoint analysis”) that calculates commercial viability based on specified levels of attainment on each attribute, but..

- Is it linked to the multivariate simulations produced by other team members? (i.e., Does it fully incorporate uncertainty?)
- Are they modeling the decision at hand?
- This continues the “silo” problem, as the broader project team still may not fully discuss the “preference” side of the problem.

INTRODUCTION TO THE CUI

The Clinical Utility Index has been developed to improve the quality of these drug development decisions.

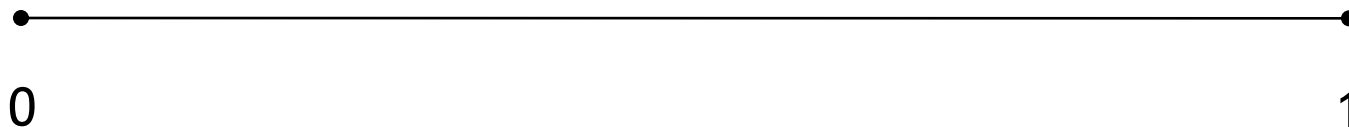
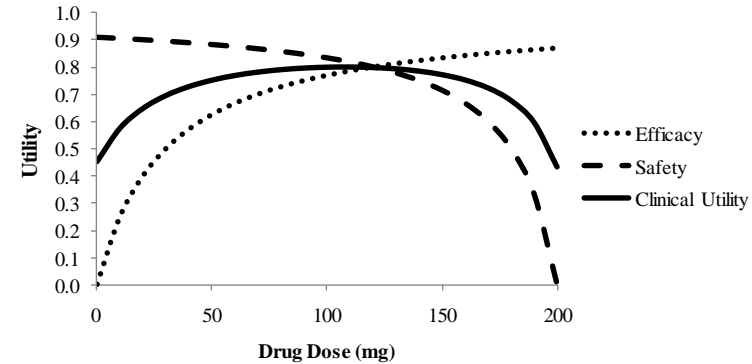
The Clinical Utility Index (CUI) quantifies the tradeoffs between different product attributes by providing a single metric for the multiple dimensions of the product profile.



The Clinical Utility Index is both a tool and a process

As a tool,

- It is a multiattribute utility function with a specific mathematical form.
- Its inputs are the levels of achievement on all of the relevant attributes (with their various respective units).
- Its output is in units of “utility”, where more is better and all things are relative to the problem at hand.



The Clinical Utility Index is both a tool and a process

As a process,

- It is a systematic and transparent approach to understanding subjective preferences for tradeoffs,
- It is knowledge driven and decision-focused,
- It involves the broader project team in thinking about the ‘So what?’s
- It provides a quantitative “bridge” that enables us to utilize our biostat./pharmacometric toolkits in a wider variety of problems.
- And thus, it can elevate the work of the biostat./ pharmacometric representatives by providing a direct and explicit connection to bigger decisions.

The underpinnings of CUI are several decades old, but the application to drug development is relatively new.

“Multiattribute utility functions” have been used for a variety of applications in the private and public sectors:

- Natural gas exploration
- Blood bank operation
- Design of public buildings such as museums and libraries
- Decisions regarding electric power plants (esp. hydroelectric)

Within drug development, CUI has been used in dozens of applications over the last decade, driven primarily by a handful of groups, but interest in it is accelerating.

- Initial academic publication by Erikson and Keller in 1993
- Pioneered by consultants with many clients
- Now incorporated as “part of the toolkit” in technical groups at Pfizer, Merck, and elsewhere.

NUTS AND BOLTS

(DISCLAIMER: I WILL DESCRIBE THE APPROACH IMPLEMENTED BY MYSELF AND MY COLLEAGUES AT PHARSIGHT.)

The CUI is an additive multivariate utility function

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

Each attribute has a utility function, $U_i(x)$, that transforms the attribute from its original scale into the $(0, 1)$ scale of utility.

For a given joint outcome of attributes, we

- Calculate the utility achieved for each attribute $\rightarrow (0, 1)$ scale
- Multiply each attribute's utility by that attribute's weight, w_i
- Add them all together in a weighted sum

→ Thus, the math is easy. Defining the function (cross-attribute weights and individual utility functions) requires a careful and proper process.

Construction of a CUI function takes place in a structured group discussion known as an “elicitation”

First step: Determine the critical attributes affecting the utility of the treatment

Examples: Major efficacy endpoints, adverse effects, compliance-related issues, including those affecting key competitors

Treatment Attribute
Efficacy (maximal change in SES scale)
Compliance (%)
Hypotension (change in mm Hg, systolic BP)
Drowsiness/Somnolence (% incidence)
Duration of effect (h)
Elevated LFTs (incidence over 3x uln transaminase)
Dyskinesia (% incidence)

Construction of a CUI function takes place in a structured group discussion known as an “elicitation”

Second step: Define response levels for each attribute

- The competitive landscape is used to guide this process
- For example: A particular marker could show an effect **Worse, Equivalent, or Superior** relative to the standard of care or a key competitor
- Continuous variables are typically discretized
- Categorical variables fit naturally in this framework
- For each attribute, the most favorable level of achievement within the imaginable competitive space is given a utility of 1.
- For each attribute, the least favorable level of achievement within the imaginable competitive space is given a utility of 0.
- Note that, on any attribute, extreme low levels of achievement are considered “less than zero” and not included in the function if a drug could not be marketed at the level even with full achievement on the other attributes.

Third step: Quantify relative preference for the levels of responses within each attribute.

- This is the construction of utility functions, the $U_i(x)$, for each attribute.
- Well-established decision-analysis methods (such as the standard gamble) are used to define the functions. (See Clemen, *Making Hard Decisions* [1991] in references for more details)

Examples from our case study: meaningful response ranges and their preference values, as assessed by the project team

Endpoint	Range name	Range values		
		Low	High	Value
Efficacy (maximal change in SES)	Not clinically meaningful	-0.3	0	0.00
	Moderately effective	-0.6	-0.3	0.60
	Excellent (super drug)	-1.2	-0.6	1.00
Duration of effect (h)	Worse than competitor	0.00	2.00	0.00
	Effectively the same	2.00	5.00	0.50
	Clearly better	5.00	12.00	1.00

Construction of a CUI function takes place in a structured group discussion known as an “elicitation”

Fourth step: Assign weights to the importance of the attributes relative to each other.

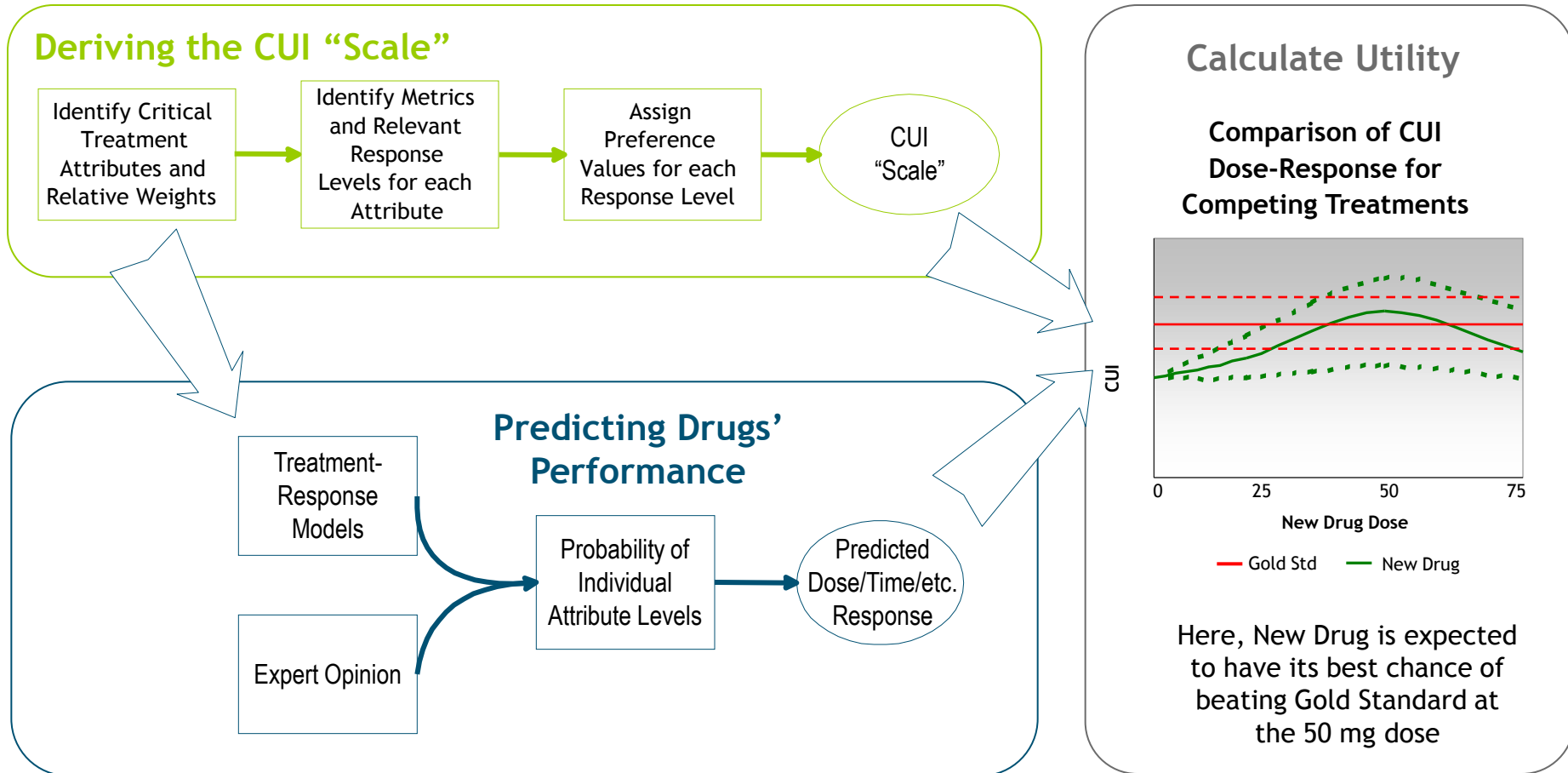
We use a process known as “swing weights,” * whereby the weights represent the relative preference for moving an attribute from its worst level to its highest level. Thus, these weights depend on how the levels of each attribute are defined.

In our case study example, a physician survey was later conducted as a cross-check of the project team’s estimates, with relatively good concordance.

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

* Again, please see Clemen, *Making Hard Decisions* [1991] for further details on the method

How does it all fit together?



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.

CASE STUDY

Dopahexidine is a mature drug for a chronic neuromuscular disorder

Efficacy is closely related to drug levels

- Measured according to a standard efficacy scale (SES)

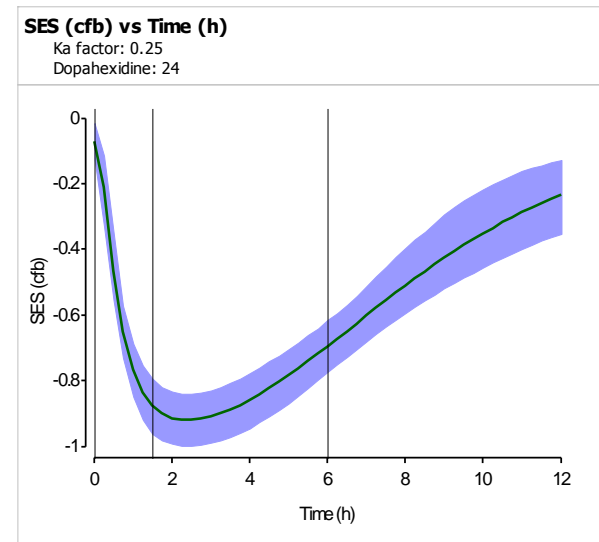
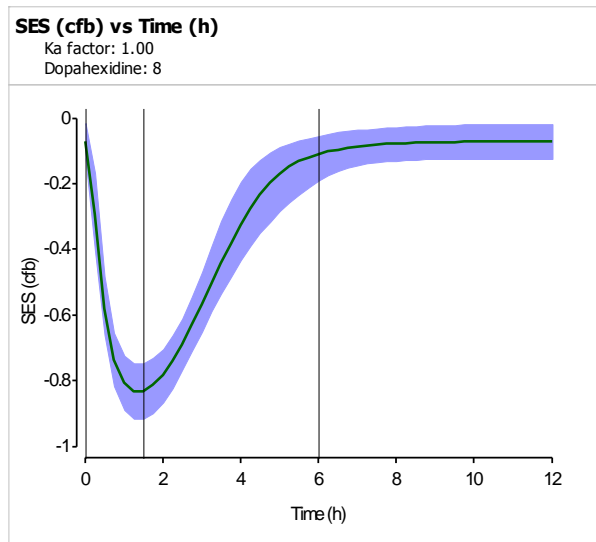
Incidence of adverse events is also related to drug concentration

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

We explored the effects of altering PK characteristics

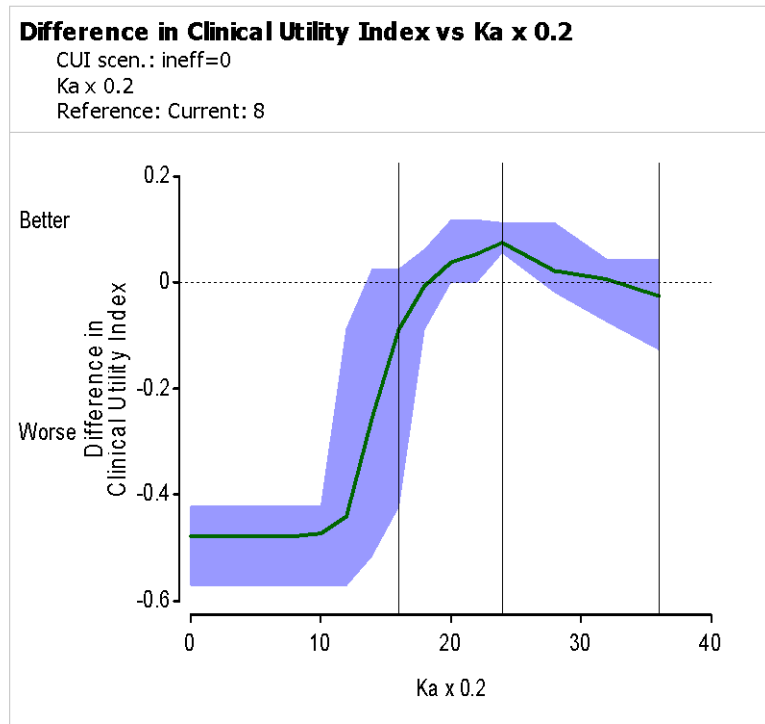
Graphs show increased duration of effect at a higher dose, with absorption rate decreased by 75%



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

CUI allowed us to link our pharmacometric models to address a multiattribute strategic decision.

“Can the main efficacy and tolerability characteristics be predicted from publicly available summary data?”

- We gathered information from a variety of public sources
- Constructed PK/PD models describing the main efficacy and tolerability endpoints
- Gathered input from a variety of internal stakeholders, and integrated this information into a single metric of clinical benefit using the CUI process

“How to reformulate the drug to provide the best mix of net patient benefit?”

- Simulated outcomes for a variety of drug absorption scenarios
- Explored the expected outcomes with the project team
- *Identified specific, actionable recommendations for a reformulated drug that is likely to have superior benefit to the current formulation*

Supported by these insights, this project continued development

TAKE-AWAY POINTS

The Clinical Utility Index reduces a multi-dimensional problem to a single number, called “utility”.

CUI can be applied to a variety of decisions, including

- Product differentiation
- Futility (i.e., no-go decisions) analyses
- Design of clinical trials, including
 - Patient characteristics
 - Selection of dose range
 - Sample size needed to show differentiation
- Where to focus to improve a drug in the eyes of the marketplace? In the eyes of regulators?
- Exploration of alternative formulations to alter drug kinetics and thus optimize the “mix” of efficacy and safety

CUI picks up where biostat./PM currently leave off...

While biostat./PM provide methods to quantify the levels of knowledge and uncertainty surrounding drug attributes, the CUI provides a quantitative model describing the preferences for tradeoffs between competing attributes.

It is both a tool and a process; many project teams have reported great benefits for simply “going through the CUI process.”

- A CUI cannot make a bad drug good, although it can help project teams to realize that it’s bad.
- Likewise, it cannot change the amount of uncertainty that exists, but it can help to remove ambiguity, resulting in a clear statement of how much uncertainty there is and how to manage it.

The CUI process can be extended to model market share and linked to traditional pharmaceutical decision analysis (i.e., “NPV”), if desired.

Putting CUI into Practice

A relatively new application of a well-tested process

Implementation is often a joint effort (decision analysis, pharmacometrics, and biostatistics)

The math is simple, but proper use requires careful education in the process and underlying assumptions (as with any of our tools)

In conclusion, CUI is an important new and broadly applicable tool that will help to elevate the work of this audience by more directly linking it to the decision-making process at all levels.

Thanks for your attention!

I encourage you to consult the growing list of publications in the area.

Carrothers TJ, Hodge FL, Korsan RJ, Poland WB, and Dykstra KH (2010) Decision-making in drug development - application of a clinical utility index, Ch 5 in Clinical Trial Simulations: Applications and Trends, Kimko H and Peck C, eds., Springer. [forthcoming]

Eriksen S and Keller LR (1993) A multiattribute-utility-function approach to weighting the risks and benefits of pharmaceutical agents. Med Decis Making 13: 188-125.

Khan AA, Perlstein I and Krishna R (2009) The use of clinical utility assessments in early clinical development. AAPS J 11: 33-38.

Korsan B, Dykstra K and Pullman W (2005) Transparent tradeoffs: a clinical utility index openly evaluates a product's attributes and chance of success. Pharmaceutical Executive, March.

Ouellet D, Werth J, Parekh N, Feltner D, McCarthy B and Lalonde RL (2009) The use of a clinical utility index to compare insomnia compounds: a quantitative basis for benefit-risk assessment. Clin Pharm Ther 85: 277-282.

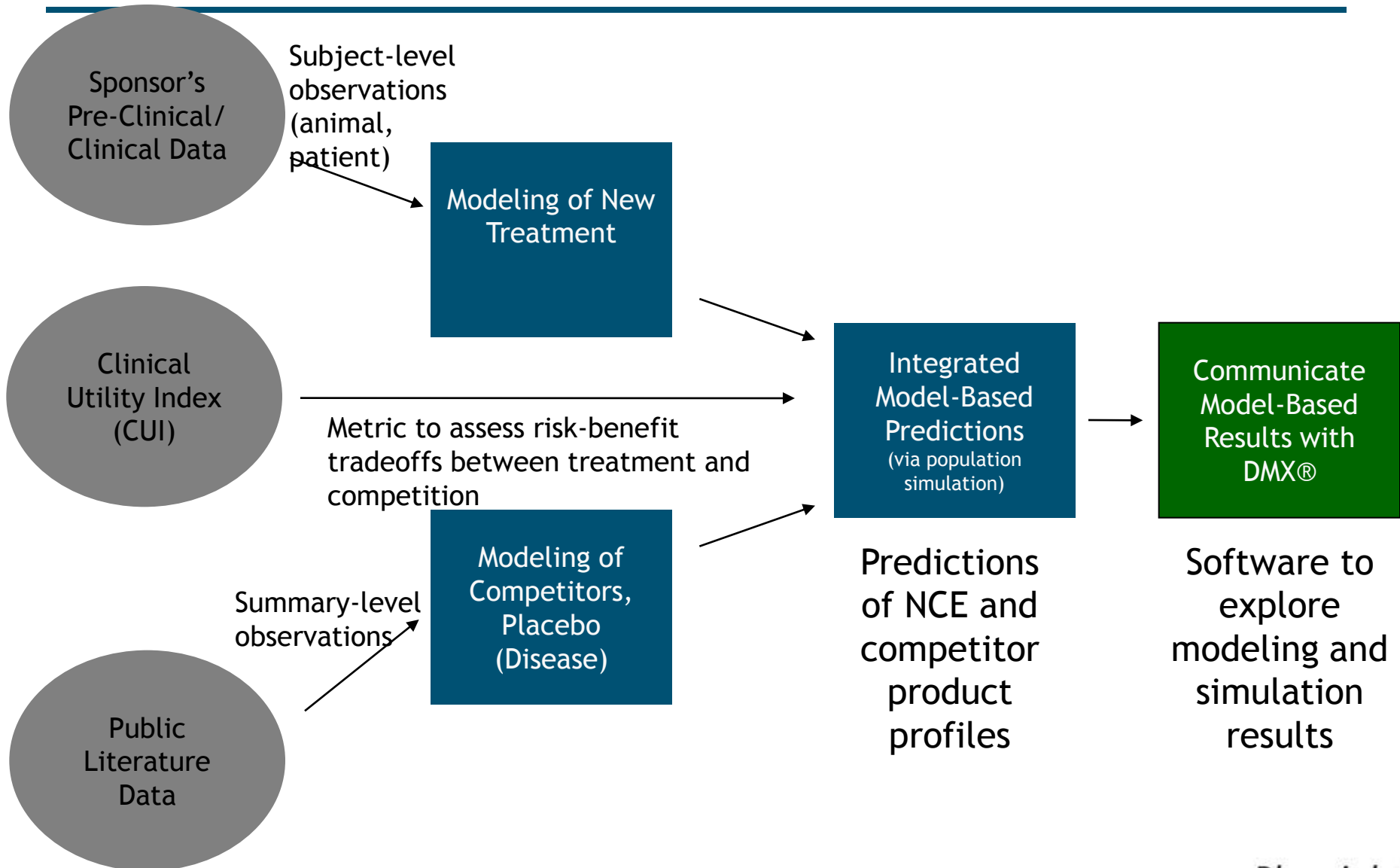
Poland B, Hodge FL, Khan A, Clemen RT, Wagner JA, Dykstra K and Krishna R (2009) The clinical utility index as a practical multiattribute approach to drug development decisions. Clin Pharm Ther 86: 105-108.

and an introductory source text for the underlying methodology:

Clemen RT (1991) Making Hard Decisions: An Introduction to Decision Analysis. Duxbury Press, Belmont, CA.

BACKUP

Model-Based Approach for Competitive Product Positioning



Extensions of CUI

- Reveal path that best mitigates Phase III failure risk → **Integrate with decision analysis techniques**
- Make trial / program design decisions by examining their risk of false-positives and negatives → **Combine with clinical trial simulation**
- Consider dimensions beyond safety and efficacy → **Extend the CUI**
- e.g., target population, product formulation, third-party payer acceptance, and patient adherence
- Evaluate and screen in-licensing candidates → **Use CUI as first-order valuation tool, or extend with financial-based decision analysis**
- Explain and understand differences in clinical daily doses and value drivers across geographies (US, EU, Japan)? → **Evaluation of CUIs**