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Trans- parent Trade- Offs

A clinical utility index (CUI) openly evaluates a product's attributes—and chance of success

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■ IN DESIGNING CLINICAL TRIALS, THE PHARMA INDUSTRY has been primarily concerned with a drug's efficacy, and therefore, modeling and simulation technologies used for those designs have also focused on efficacy. But the clinical utility and economic worth of a compound depends on many dimensions beyond efficacy, including important influences such as target population, product formulation, and patient compliance. To enhance market share and value to patients, pharma companies must consider those dimensions earlier in the drug development process.

One way to do that is with the use of a clinical utility index (CUI), which quantifies factors like a product's efficacy, safety, cost, and contribution to quality of life—and makes trade-offs transparent to decision makers. A CUI provides a single metric for multiple dimensions of benefit and risk and captures expert opinion on the therapeutic importance of various product characteristics. It also enhances communication between discovery, development, and the commercial side. >>

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Multiple Dimensions

Getting the right information to physicians about the best clinical use of a drug becomes more challenging as the number of available therapies grows. In his article "Choosing Which Drug to Prescribe" (*Medscape General Medicine*, 6 August 2003), Tomas Kramer, MD pens: "Recently, a great deal has been written urging clinicians to practice 'evidence-based medicine,' in which clinical decision making is based on scientifically derived data. The problem with this, of course, is there is very little evidence upon which to practice evidence-based medicine."

Treatment choices A prescribing physician must choose a therapy that gives the best balance of efficacy, side effects, safety, ease-of-use, and quality-of-life benefits for a given patient. Analytic tools developed in pharmacological science and operations/market research can organize knowledge from different sources into a decision making framework. (See "CUI

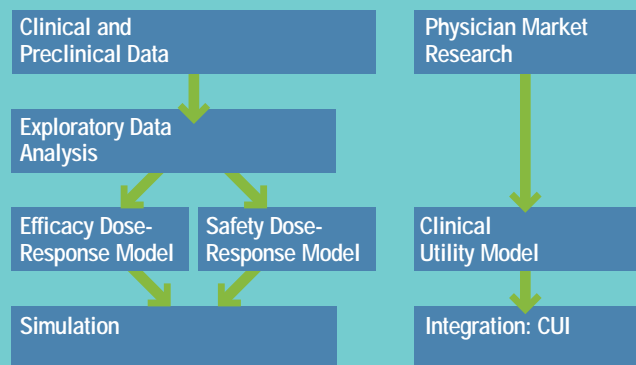
Model" below.) First, modeling is used to predict, design, and learn. A drug candidate's likely clinical performance is modeled using information from related therapies as well as pre-clinical and early clinical data. Next, the predicted product profile(s) are evaluated using the CUI.

Clinical utility Every medical therapy has benefits and risks. The relative importance of these characteristics depends on the disease, patient, and how the drug is used (for example, dosage or concomitant therapy). A CUI is a transparent means of weighing and quantifying a compound's trade-offs. It provides a scale to compare product profiles and measure the impact of scientific and market assumptions. It can be used at low cost (a small amount of time and effort on the part of the drug development team) and early in a clinical program (Phases I and II). »

Clinical utility is defined as the net benefit of treatment to the patient as perceived by the prescribing physician or a surro-

CUI Model

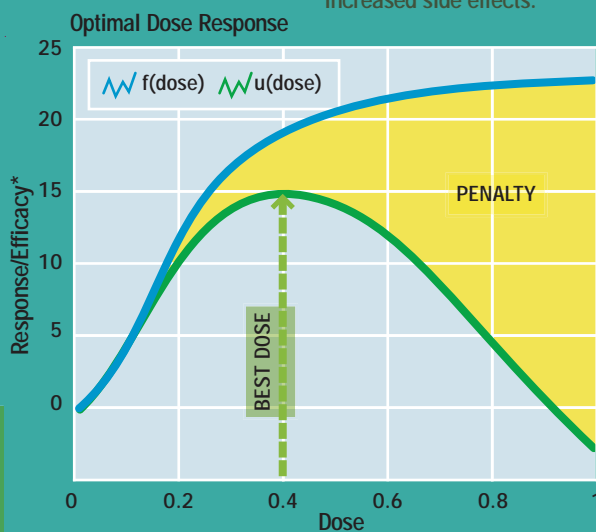
A model-based approach to decision making, integrating scientific and market information, is the basis of the clinical utility index (CUI).



Overall, a clinical utility index can be used to assess a product's chance of success in the marketplace.

Dose Benefit Model

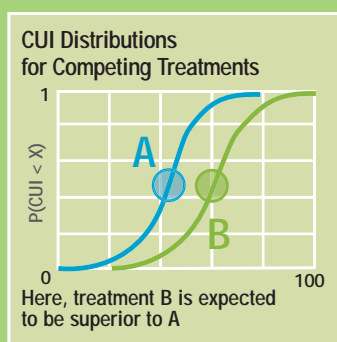
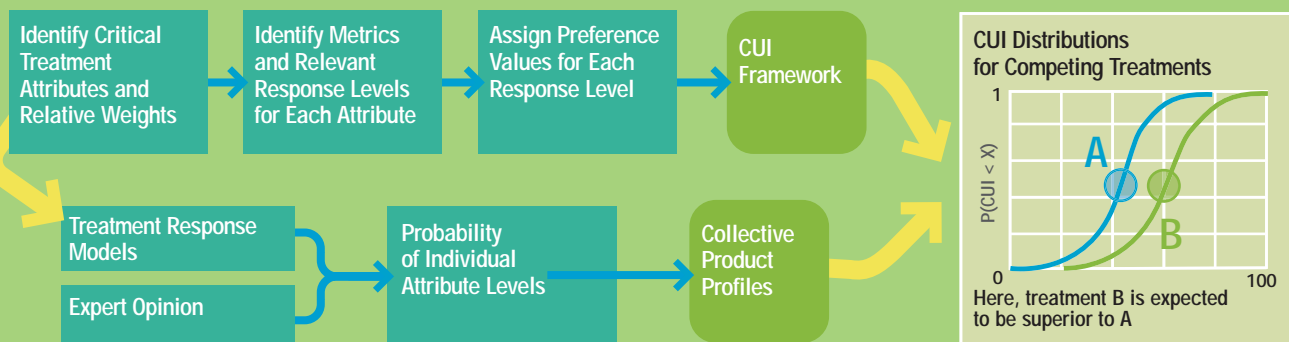
In this dose benefit model, the optimal dose emerges at the point before efficacy begins to be penalized by increased side effects.



*Definition: Improvement in efficacy score from baseline relative to placebo

Information Flow

The CUI uses various sources of information to assess competing treatments' benefits.



gate decision maker such as an HMO making formulary decisions. A CUI quantifies the contribution of each attribute in the product profile (label) using physician preference data, if available, or by relying on clinical advisors and other internal expertise. The latter is less expensive, and may be more appropriate early in a development program.

Metrics and methods When modeling prescribing physician behavior, a CUI is similar to models used in later clinical development (Phases III and IV). Both CUI and conjoint analysis attempt to weigh the relative value of treatment attributes and to capture that information in a single metric for comparison of competing treatment options. A CUI differs from conjoint and discrete choice analyses in its source of information and cost. Tools such as discrete choice analysis actually survey a large number of physicians asking them to choose between hypothetical product profiles. The trade-offs among elements of the competing product profiles are inferred from physician responses. A similar tool goes by the name of “conjoint analysis.” Both tools use slightly different methodologies to arrive at the same empirical result and a large number of physicians must be interviewed to obtain a meaningful model, leading to high cost.

Product position CUI, in addition to lower cost, offers specific benefits when used in lieu of or as an early measure of physician prescribing behavior. Construction of a CUI leads the development team to identify those product attributes critical to the patient. A CUI focuses development team efforts on exploring the most valuable region of treatment—not necessarily the most efficacious—and the best market position. Further, CUI can be used to examine differences between internal team opinion and outside physician input. Multiple CUIs can explore the potential influence of non-prescriber decision makers, such as the FDA or third-party payers.

Practical Tool

In clinical practice, the patient’s decision maker is generally the prescribing physician. Ideally, the development process will result in drugs that are just what the prescribing physician ordered. The framework for the CUI is elicited from the project team. Attribute utilities and weights are determined based on physician preference data, if available, or internal expert opinion. When combined with models of what the body does to the drug (pharmacokinetics) and what the drug does to the body (pharmacodynamics), the CUI is a tool for understanding the benefit of the drug to the patient, relative to competing therapies.

Because these models also include the uncertainty in the drugs effects, they can also be used to predict the outcomes of proposed development trials. As a development program progresses, ongoing or completed trial results provide learning and models are updated. Model output can be broken into categories that show the chance of achieving a given product profile and CUI, given what is known about the drug. The chances of different product profiles can, in turn, be linked to financial models for decision making.

Such models have been used successfully to support better choices in clinical development, as illustrated in the following case studies. Each is derived from a real project conducted for a

client in the pharmaceutical industry. Indications and other information may have been blinded to protect confidentiality.

Case Study: Efficacy vs Side Effects

CUIs needn’t be complex to prove useful. A simple index, constructed using a penalized dose-response model, was used to explicitly value trade-offs between increased efficacy and side effects for a new chemical entity (NCE) with a novel mechanism of action. This index formed the basis for the choice of best dose, which was in turn used in simulations to optimize trial strategy for a phase II dose-ranging trial.

The compound was a psychiatric medication with a novel mechanism of action and little prior information was available to inform expectations for efficacy or side effects. Phase I safety trials and one inconclusive Phase IIa trial had been completed, leaving high uncertainty in efficacy and dose-response for the NCE.

A modeling project was undertaken to improve efficiency and informativeness of Phase II trial strategies, and to optimize the treatment regimen. First, drug and disease models were developed to quantify expectations and uncertainties about efficacy and side effects. This formed the basis for a penalized dose-response model, developed to provide a utility criterion for choosing best dose. (See “Dose Benefit Model,” page 90.)

A model of various dosing strategies was developed. Simulations assessed each design’s performance compared to fixed-dose dose-ranging. The criteria for trial quality were: closest estimate of best dose (Dbest) and minimum effective dose (MED), as measured using the penalized dose function (utility index). The simulations indicated an advantage to particular designs because the uncertainty in safety and efficacy was understood and a utility index provided a single, quantitative measure of that best dose.

Case Study: Identifying No-Gos

Evaluating a potential next-in-class drug against successful predecessors requires close comparison of risk–benefit profiles. A CUI is ideal for the job.

A new selective estrogen receptor modulator (SERM) was in early human trials. Concern had risen over a possible side effect, endometrial hypertrophy, which could lead to cancer if unchecked. Further trials posed not only financial risk but possible health risks for hundreds of women if this side effect proved troublesome. To explore whether any dose of the new candidate could be expected to perform acceptably against the popular first-in-class drug, Evista (raloxifene), Aventis Pharmaceuticals turned to modeling and simulation.

Dose–response models for efficacy versus side effects were developed from early trials of the new SERM and prior information on related compounds. An initial version of the CUI was elicited from project team members. They identified 10 critical attributes of the product profile. For each attribute, possible attribute levels and their clinical value were defined using a preference ratio. The attributes were ranked and their impor-

The use of a CUI leads development efforts to explore the most valuable region of treatment—not necessarily the most efficacious.

Clinical Impact

Trial designs based on modeling and simulation can eliminate Phase IIa/IIb trials, saving time and money.

	Preclinical	I-IIa	IIb	III	Submission
Phase duration	Same	Same	Large decline	Same or decline	Decline
Phase cost	Increase	Increase	Decline	Decline (fewer failed trials)	Decline
Phase PoS	Same	Higher attrition	Increase	Increase	Increase

SOURCE: Pharsight

analysis made it clear that the drug could have performed well except for the key side effect; an identical drug without the risk of endometrial proliferation would surpass the competition. The upcoming trial would have been quite expensive and those funds could be used more effectively on other compounds. Consequently, it was decided to progress a more promising back-up compound that did not appear to have this liability in preclinical testing.

Quicker Wins

In early drug development, a CUI makes optimal use of internal expertise and minimizes the cost of focusing development on the best product profile—not the most efficacious one. By using comparisons to current competitors and new entries under development, drugs that have no differentiation can be weeded out earlier from a crowded marketplace, providing more resources for R&D. It can substantially lower the cost of delivering a beneficial drug to the marketplace.


Additional benefit is gained by the use of modeling and simulation analyses in Phases II and III. By investing in these more intensive and adaptive early phase analyses, developers can spot poor drug candidates earlier and improve positioning of those going into Phase III. The use of a CUI can optimize the trade-offs in speed, cost, and learning during these phases, leading

tance weighted. The team reviewed the attributes to ensure that they described all important and relevant clinical issues, captured the range of outcomes for each attribute, and reflected the expected clinical value of possible outcomes.

Simulation produced a distribution of likely patient outcomes for each attribute. Each distribution was parsed into categories, each of which had a known likelihood of occurrence. Every unique combination of attribute levels yielded one possible CUI score. The probabilities of the attribute levels for a given CUI score yielded the likelihood of that score being the “true” product CUI. The combined set of possible CUI scores and their likelihoods were characterized as a probability distribution, describing the expected CUI values for the new SERM and its primary competitor.

Simulations revealed that the new SERM, as reflected in its CUI distribution, was expected to perform worse than the established competition at all doses. Sensitivity

A CUI can optimize the trade-offs in speed, cost, and learning, helping developers spot poor candidates early.

to quicker wins. The end result is a label that supports the best therapeutic use of a new therapy, and offers the best patient benefit. Thus, the CUI is a valuable communication, decision making and optimization tool. 

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