Using desirability indices for decision making in drug development

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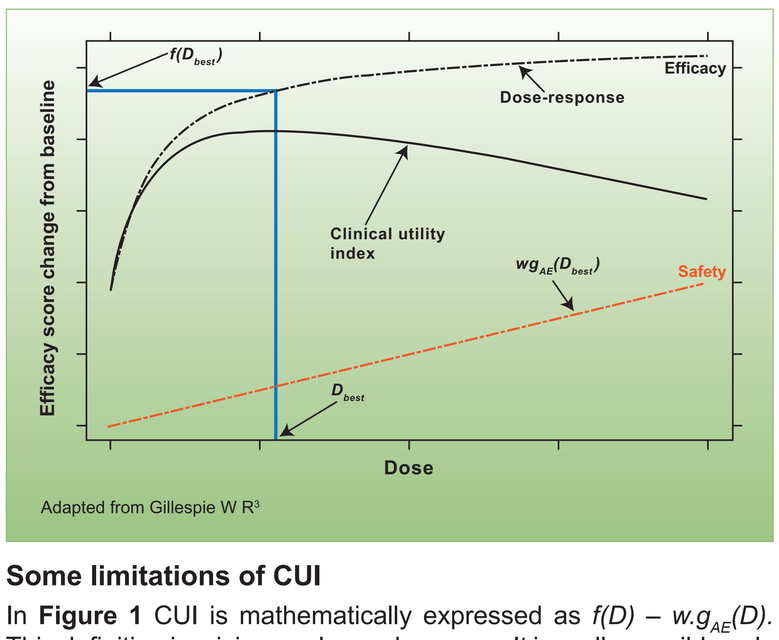
Background

The clinical utility index (CUI) has been proposed as an integrated measure of clinical benefit/risk.[1, 2] Its usage has focused on:

- Determination of optimal doses, reflecting the efficacy and safety outcomes (**Figure 1**).
- Comparison of competing compounds when decisions are based on multiple attributes (*e.g.,* safety and efficacy outcomes, quality-of-life benefits, drugability properties, *etc.*).

Various formulations of CUI have appeared depending on its usage. CUI is typically expressed as a weighted sum and requires defining (implicitly or explicitly) utility functions to represent expected clinical value of possible outcomes.

Figure 1. *Illustration of clinical utility index*



Some limitations of CUI

In **Figure 1** CUI is mathematically expressed as $f(D) - w.g_{AE}(D)$. This definition is mixing apples and oranges. It is really sensible only when the efficacy and safety outcomes are measured on the same scale (*e.g.* probability). This can be circumvented by calibrating versus some reference value in order to normalize each attribute to a common scale.[4]

CUI can result in a poor dose selection when efficacy compensates for the unacceptable safety. Finally, CUI can raise Issue when dose–response curves have similar shapes. An extreme example is when both curves are identical. In this case CUI is uniformly zero, hence useless for dose selection. However, intuitively there should be an optimal dose choice made possible, too.

Desirability

We borrow ideas from the field of multi-criteria optimization (MCO) that has been developed for optimizing industrial production processes (*e.g.* to improve the quality of a product). The root of the problem is to identify factor settings, which optimize simultaneously a number of possibly competing properties.

Desirability functions[5] are used to quantify how desirable certain outcomes are on an absolute scale (0,1). **Figure 2** shows examples of elicited desirability functions. Any functions yielding values into (0,1) could be used here.

Desirability values are combined using some kind of mean value, the Desirability Index (DI). The weighted geometric mean has desirable properties which carry over to drug development applications:

$$DI(d) = D_{Eff}(f_{Eff}(d))^{w1} \times D_{Saf}(f_{Saf}(d))^{w2}$$

"If one of the product's properties is completely unacceptable, the product as a whole is unacceptable."

Other indices (*e.g.* weighted sum) could be used as well. DI can serve as an absolute measure for decisions of interest here. Its use for dose selection is illustrated in **Figure 3**.

Figure 2. *Example of elicited desirability functions*

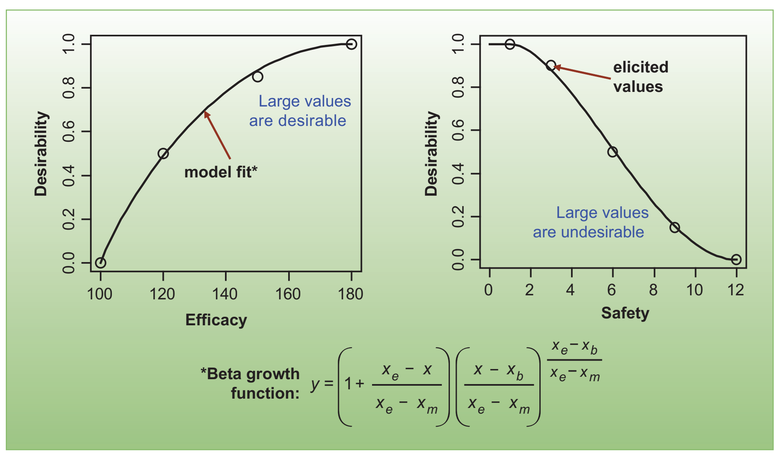
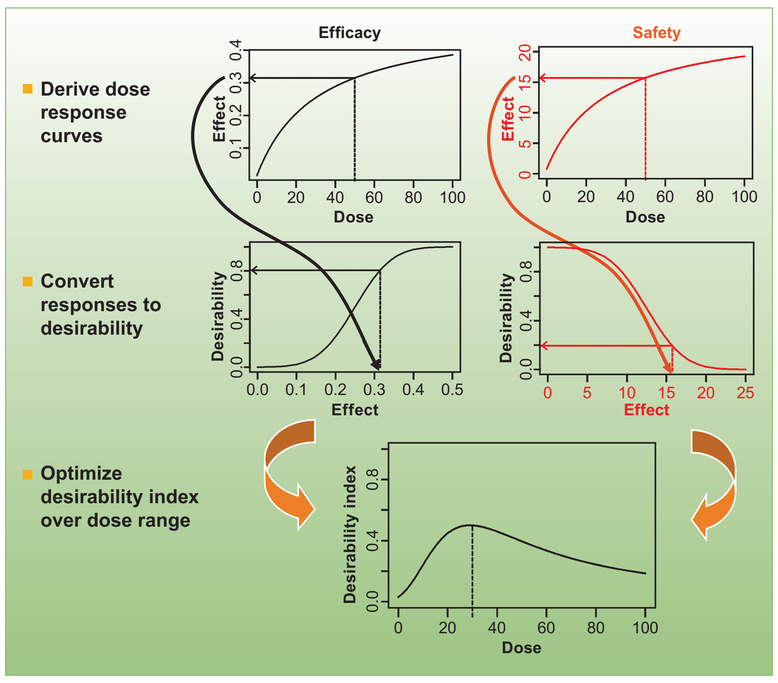


Figure 3. *Desirability for dose selection in 3 steps*



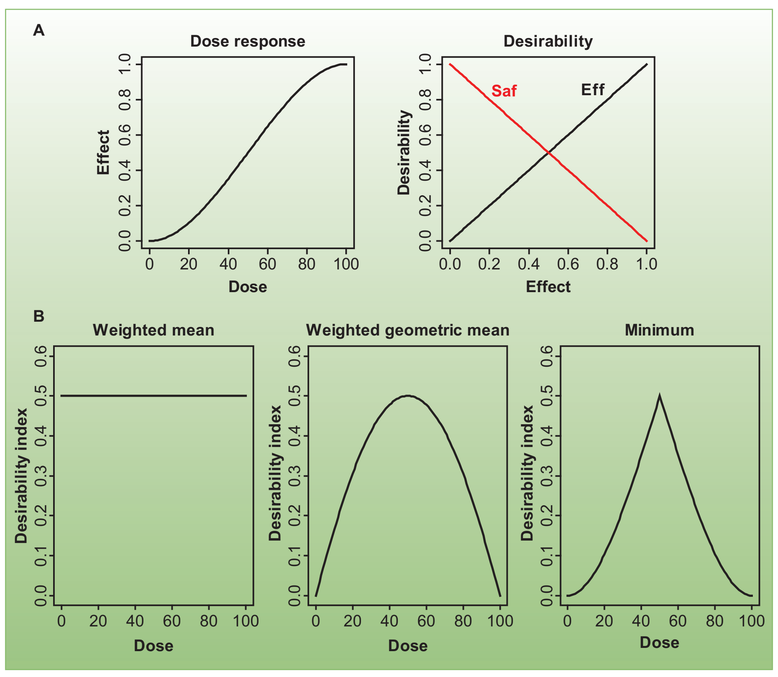
Utility and desirability

CUI=$f(D) - w.g_{AE}(D)$ can be observed as a particular example of desirability index with the following assumptions:

- Both outcomes are normalized.
- Respective weights are $1/(1+w)$ and $w/(1+w)$ for the efficacy and safety.
- $D_{Eff}(x) = x$, $D_{Saf}(x) = 1-x$
- A weighted sum is specified to combine desirabilities.

Figure 4 compares three indices when the efficacy and safety dose–response curves are identical (panel A) and the above desirability functions are assumed (panel B). The Standard CUI definition does not allow the determination of an optimal dose in that case.

Figure 4. *Utility and desirability: importance of summary measure*



Integrating sources of uncertainty

Two sources of uncertainty are integrated in the analysis:

- Variability in estimated dose–response curves.
- Desirability functions are inherently subjective and random variation is added to achieve a more robust assessment (**Figure 5**). This can be motivated by a multi-rater elicitation procedure.

Uncertainty propagation can take place using either simulation-based or Bayesian modeling approaches. The distribution of DI and derived quantities can then easily be obtained. This is illustrated in **Figure 6** for the simulation-based approach.

Figure 5. *Random variation in desirability functions*

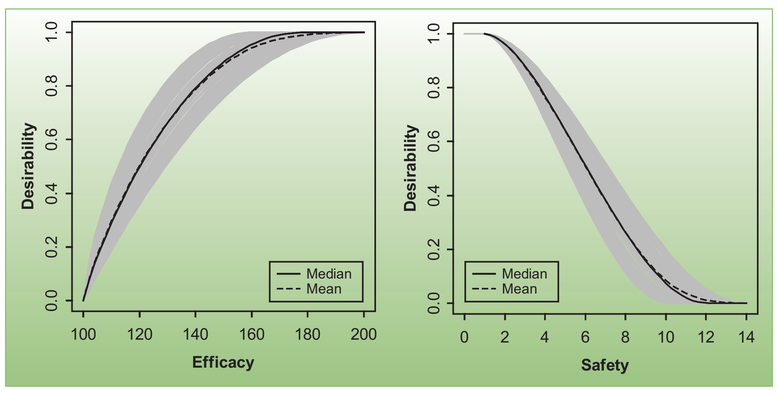
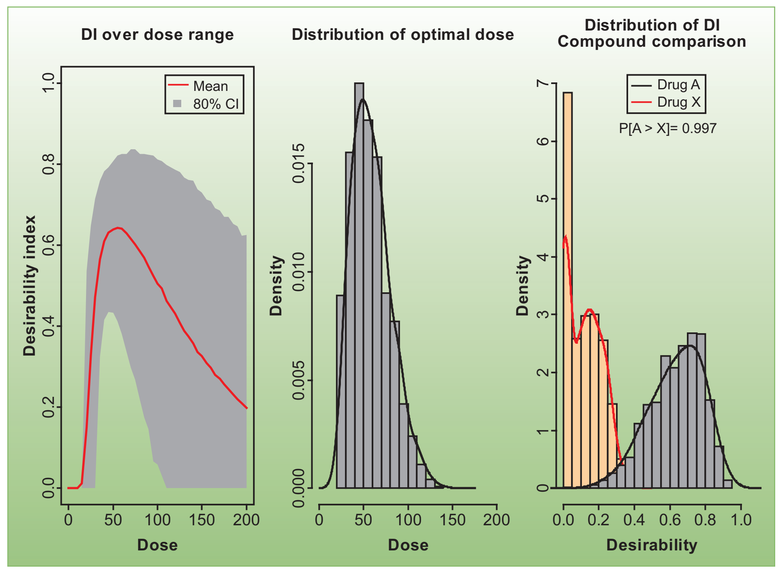


Figure 6. *Inference for DI*



Representation of benefit–risk assessment

Desirability functions are defined separately for each attribute, which does not convey the full benefit–risk evaluation. The resulting desirability surface should, therefore, be investigated to verify assumptions. This is exemplified in **Figure 7** based on the previous elicited desirability functions.

Another useful view is given by equidesirable contours. Those can be used in a second stage to validate the desirability functions, example by identifying new, equally desirable points on the surface. This is illustrated in **Figure 8** (right panel) showing adjustment in weighting to have red points lie on the same contour. Weights could take values outside the unit interval for a more flexible adjustment.

Figure 7. *Desirability surface*

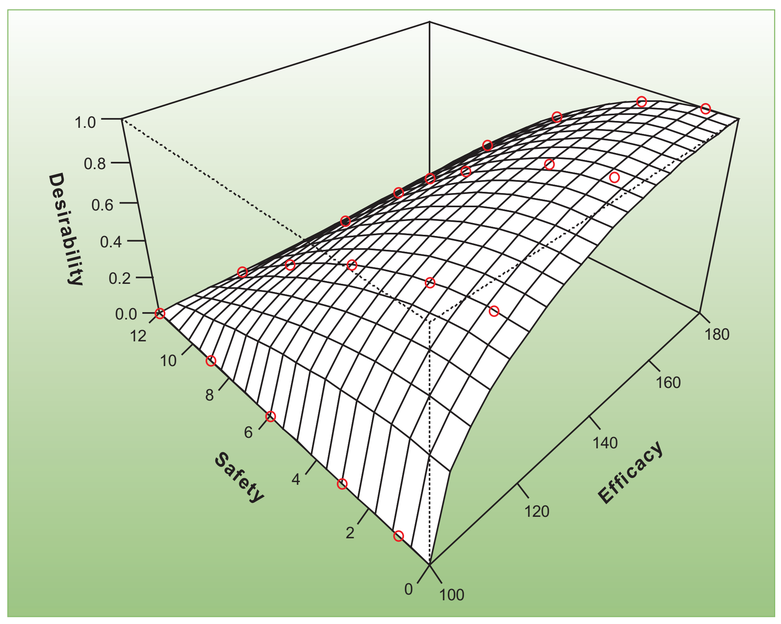
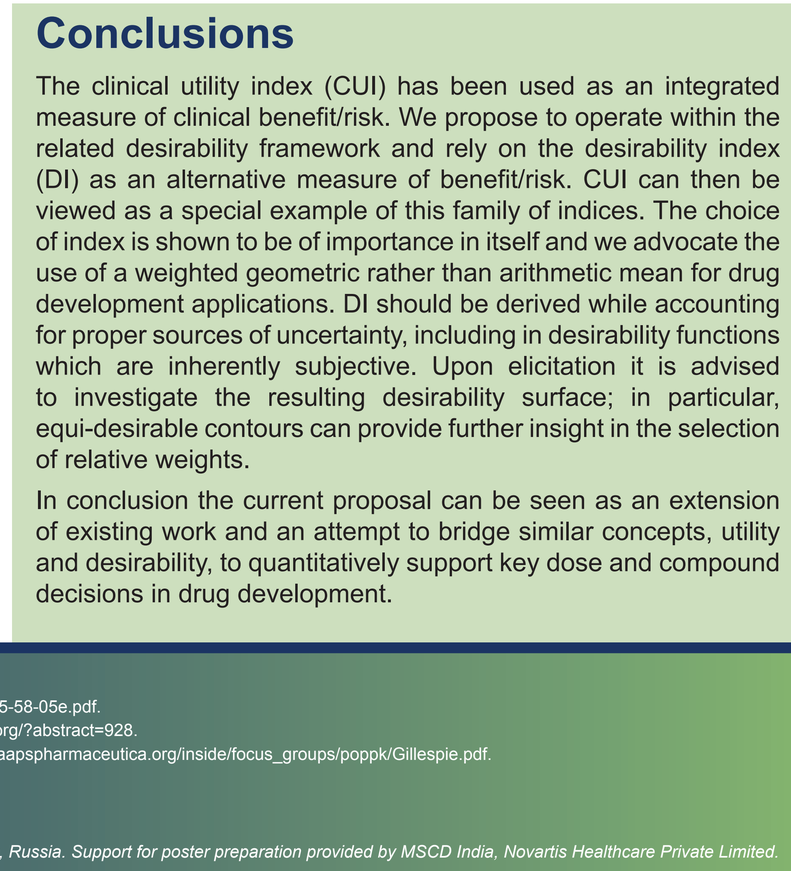


Figure 8. *Using equi-desirable contours to adjust weighting*



Conclusions

The clinical utility index (CUI) has been used as an integrated measure of clinical benefit/risk. We propose to operate within the related desirability framework and rely on the desirability index (DI) as an alternative measure of benefit/risk. CUI can then be viewed as a special example of this family of indices. The choice of index is shown to be of importance in itself and we advocate the use of a weighted geometric rather than arithmetic mean for drug development applications. DI should be derived while accounting for proper sources of uncertainty, including in desirability functions which are inherently subjective. Upon elicitation it is advised to investigate the resulting desirability surface; in particular, equi-desirable contours can provide further insight in the selection of relative weights.

In conclusion the current proposal can be seen as an extension of existing work and an attempt to bridge similar concepts, utility and desirability, to quantitatively support key dose and compound decisions in drug development.

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