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 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, druggability 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.

Some limitations of CUI
In Figure 1 CUI is mathematically expressed as \( f(D) = \sum w_i f_i(D) \). The effect of 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 issues 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 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.

Desirability values are combined using some kind of mean value, 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 mean 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.

Figure 1: Illustration of clinical utility index

Figure 2: Example of elicited desirability functions

Figure 3: Desirability for dose selection in 3 steps

Figure 4: Utility and desirability: two important summary measures

Figure 5: Random variation in desirability functions

Figure 6: Inference for DI

Figure 7: Representation of benefit–risk assessment

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 mean 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.

References