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ON THE PROPERTIES OF STOCHASTIC MULTIPLE-CRITERIA COMPARISON METHODS IN HEALTH TECHNOLOGY ASSESSMENT

Abstract

To ensure the optimal usage of scarce resources in the assessment of health technologies two criteria are used: costs and effectiveness of available options. For each treatment the evaluations of these criteria are obtained from clinical trials, cost and utility studies and therefore are given as random variables. In our research we compare the decision theoretic properties of expected net benefit, cost-effectiveness acceptability curve and expected value of perfect information methods of choosing the optimal treatment.

Keywords

Cost-effectiveness acceptability curves; net benefit; willingness to pay; uncertainty.

Introduction

In the paper we consider the problem of comparing a given finite set of available therapies (cf. [9], [16]). We assume that the decision maker bases her decision on two criteria: the expected costs and effects of the therapies, but she is not able to measure these parameters with certainty (cf. 6). Instead, she has some estimates available, e.g. results of clinical trials, cost studies or utility of health state evaluations (cf. 20).

It is usually assumed that the decision maker compares the therapies *incrementally*, i.e. calculates the ratio of increment of the expected cost to the increment of the expected effect when switching from a worse and cheaper therapy to a more effective and expensive one (dominated and extendedly--dominated therapies are excluded). This ratio is called the incremental cost-effectiveness ratio (henceforth $ICER$). When both the numerator and denominator are positive, $ICER$ is interpreted as expected additional cost that needs to be incurred to obtain an additional unit of expected effect. It is then compared with the threshold value, named willingness-to-pay, henceforth WTP (cf. [3]), representing societal preferences. If $ICER$ is below this value then therapy switch is recommended. For the theoretical foundation of this approach see Garber and Phelps [8].

As the decision maker knows only the estimates of expected costs and effects, the $ICER$ is also given with uncertainty. Analyzing this uncertain $ICER$ presents statistical difficulties due to several causes. When expected costs and effects estimates are normally distributed, so are their increments, and the ratio is vulnerable to a so-called Hodgson paradox, i.e. it can have a Cauchy distribution without any mean value or variance defined (cf. [12]). Moreover, for some data and methods (e.g. Fieller's method) the calculated confidence intervals can be empty, constitute a set of disconnected intervals, or encompass the whole real line (cf. [2], [13]). Another problem is that the negative $ICER$ loses its interpretation (can mean that the therapy is either dominated or dominant), so confidence intervals containing negative values are meaningless.

The solution to the above problems proposed in the literature and analyzed in this paper is to analyze the so-called net benefit, i.e. the difference between the expected effect expressed in monetary terms (using WTP as the monetary value of a unit of effect) and the expected cost (cf. [18], [19], [16]). Then the decision maker can compare the net benefits of all available therapies and choose the therapy offering the biggest net benefit; we shall call this therapy to be *cost-effective*. The uncertainty of expected cost and effect results in the uncertainty of net benefit. However, as the calculation of net benefit involves only multiplication and addition, this parameter has better statistical properties than $ICER$, while remaining equivalent in terms of decision making process when no uncertainty is present (cf. [15]).

The expected net benefit (ENB) approach does not directly take into account the stochastic nature of expected cost and effect estimate. Therefore two additional measures have been proposed in the literature: cost-effectiveness acceptability curve ($CEAC$) and expected value of perfect information ($EVPI$).

The $CEAC$ approach gives the probability that the true net benefit of the therapy is the highest among all alternatives considered (cf. [20]), and, therefore, the probability that the therapy is cost-effective. The $EVPI$ criterion measures the expected value of removing uncertainty from the decision making problem – in other words, how much at maximum should a decision maker be willing to pay for perfect information about the true expected costs and effects of the options compared (cf. [3], [5]).

The objective of the paper is to analyze the decision-theoretic properties of maximization of ENB and $CEAC$ and minimization of $EVPI$ criteria for the selection of optimal therapy in health technology assessment. This paper continues the work of Jakubczyk and Kamiński [14] formalizing some of their ideas, developing the properties of $EVPI$ criterion and introducing uncertainty of WTP assessment.

In the next section we present the notation used throughout the paper, introduce the choice rules used in health technology assessment and present the properties of choice rules usually demanded in decision analysis. In the third section we analyze the properties of choice criteria introduced for a given value of societal willingness-to-pay. In the fourth section we present the analysis in the case of random value of willingness-to-pay (representing the uncertain elicitation of societal preferences). The last section is a summary.

1. The model of therapy comparison

In this section we present a general notation used in the paper. First we describe the set of alternatives and decision maker's uncertainty. Then we formalize the decision making process by defining the choice function – a method of choosing one of the alternatives and some often required properties. Finally we introduce three choice functions based on the ENB, $CEAC$ and $EVPI$ criteria.

Throughout the whole paper we analyze the decision maker's choosing from a given set of n therapies represented by the set $I = \{1, 2, \ldots, n\}$. Each therapy i is associated with its expected cost and effect. The true values of these are not known; instead, the decision maker knows their distributions (resulting from the estimation procedure) defined for cost and effect, respectively, by the random variables C_i and E_i. We assume that these random variables are independent across therapies, i.e. any subset of $\{C_1,\ldots,C_n,E_1,\ldots,E_n\}$ with random variables of different indices (e.g. not containing simultaneously variables C_i and E_i) is independent. We do not assume that C_i is independent from E_i.

For each i we define a probability space (Ω_i, F_i, P_i) that describes the distribution of the two-dimensional random variable (C_i, E_i). We also define a probability space (Ω, F, P) that is a product space for all i. Thus it represents the whole uncertainty present in the problem.

In this paper we analyze the choice based on the comparison of net benefit, where the equivalent of a unit of effect in monetary terms (WTP) is denoted for brevity by k. Therefore, throughout most of the paper we do not directly analyze C_i and E_i, but define a new random variable $NB_{i,k} = kE_i - C_i$ denoting the expected net benefit of the therapy i given that the value of WTP is equal to k.

We assume that all random variables are continuously distributed and denote cumulative distribution function of $NB_{i,k}$ as $\Phi_{i,k}(\cdot)$ and its density function as $\phi_{i,k}(\cdot)$. Notice that $\{NB_{1,k}, NB_{1,k}, \ldots, NB_{n,k}\}$ is the set of independent random variables.

We now define ENB, $CEAC$ and $EVPI$ measures for the therapy i:

$$
\begin{aligned}
&ENB_{i,k} = E(NB_{i,k}),\\
&CEAC_{i,k} = \Pr(NB_{i,k} = \max_{t\in I}\{NB_{t,k}\}),\\
&EVPI_{i,k} = E(\max_{t\in I}\{NB_{t,k}\} - NB_{i,k}).
\end{aligned} \tag{1}
$$

Let us notice that $CEAC$ and $EVPI$ methods are related to the concept of Savage's regret criterion – that is the difference between the selected therapy i net benefit $NB_{i,k}(\omega)$ and the optimal therapy net benefit $\max_{t\in I}\{NB_{t,k}(\omega)\}$ averaged out over all $\omega \in \Omega$. They differ in the measure of regret. The $CEAC$ criterion assumes constant regret (equal to 1) if the therapy is not optimal and the $EVPI$ criterion assumes that regret is proportional to the expected net benefit loss. Both of these can be rationalized for the decision maker in specific situations. If the decision maker cares only to make a decision that will be confirmed to be optimal *a posteriori* when enough evidence is gathered to remove uncertainty from the problem then she should use the $CEAC$ approach. When the decision maker is mostly concerned not with probability but the expected monetary value of making sub-optimal decision then she should use the $EVPI$ approach.

Before moving to the definition of choice functions based on the on ENB, $CEAC$ and $EVPI$ criteria we outline the desired properties of such functions in a decision-theoretic approach.

We formalize the decision making process by introducing a *choice function* as a representation of a method of making a choice. For a given set of alternatives $I \neq \emptyset$ let us define a regular choice function T following Hammond [10]:

$$T : 2^I \to 2^I ,$$
$$\forall \emptyset \neq I' \subset I : \emptyset \neq T(I') \subset I .$$

Therefore a regular choice function selects a non-empty subset of the given set of alternatives. Henceforth we consider only regular choice functions, and call them simply choice functions.

Regularity does not imply that the choice function have the intuitive properties usually required. One of these properties is *coherence*. We will call a choice function T coherent, if:

$$\forall \emptyset \neq I'' \subset I' \subset I : I'' \setminus T(I'') \subset I' \setminus T(I').$$

Coherence means that if an alternative is not selected out of a smaller subset of alternatives (I''), it will not be selected when additional alternatives are available (and the bigger set I' is considered). It is often required that a “nice” choice function be coherent as otherwise it is open to manipulation – adding irrelevant (not chosen) alternatives can change the outcome. This property is also referred to as α-property or basic contraction consistency, cf. Sen [17].

If choice function T is coherent then it generates a pre-order $\leq$ in I, such that $\forall I' \subset I : T(I') = \{x \in I' : \forall y \in I' : y \leq x\}$ (cf. [11]).

Additionally we will call choice functions T' and T'' equivalent if $\forall \emptyset \neq I' \subset I : T'(I') = T''(I')$.

Now using those definitions let us introduce choice functions stemming from ENB, $CEAC$ and $EVPI$ measures in health technology assessment given a set of therapies $I' \subset I$.

Table 1

Health technology evaluation measures and choice functions associated with them

Measure	Choice function
ENB	$T_k^{ENB}(I') = \arg\max_{i \in I'} \{ENB_{i,k}\}$
$CEAC$	$T_k^{CEAC}(I') = \arg\max_{i \in I'} \{CEAC_{i,k}\}$
$EVPI$	$T_k^{EVPI}(I') = \arg\min_{i \in I'} \{EVPI_{i,k}\}$

In the next section we will analyze the properties of the choice functions introduced above.

2. Properties of choice functions for fixed *WTP*

In this section we first analyze the coherence properties of ENB, $CEAC$ and $EVPI$ and their conditions for their equivalence for fixed WTP (k parameter). Let us start with the comparison of the of ENB and $EVPI$ criteria.

Proposition 1.

The choice functions T_k^{ENB} and T_k^{EVPI} are coherent and equivalent.

Proof

First we will show the equivalence of those two choice functions. Notice that for $I' \subset I$:

$$EVPI_{i,k} = E\left(\max_{t \in I'}\{NB_{t,k}\} - NB_{i,k}\right) = E\left(\max_{t \in I'}\{NB_{t,k}\}\right) - ENB_{i,k}.$$

But this implies that:

$$T_k^{EVPI}(I') = \arg\min_{i \in I'}\{EVPI_{i,k}\} = \arg\min_{i \in I'}\left\{E\left(\max_{t \in I'}\{NB_{t,k}\}\right) - ENB_{i,k}\right\}.$$

Notice that $E\left(\max_{t\in I'}\{NB_{t,k}\}\right)$ is constant given I' so:

$$T_k^{EVPI}(I') = \arg\min_{i\in I'}\{-ENB_{i,k}\} = \arg\max_{i\in I'}\{ENB_{i,k}\} = T_k^{ENB}(I').$$

This implies that these choice functions are equivalent. Hence, to prove their coherence it is enough to check that $T_k^{ENB}(I')$ is coherent. To show this consider any $I'' \subset I' \subset I$. Assume that $i \in I'' \setminus T(I'')$. This implies that there exists $j \in I''$ such that $ENB_{i,k} < ENB_{j,k}$. However $i, j \in I'$, so i will not be an element of $T(I')$, as ENB does not depend on a set of available alternatives. This implies that T_k^{ENB} is coherent.

Although the $CEAC$ criterion, similarly to $EVPI$, is also based on the regret concept, it has different properties than the ENB and $EVPI$ approaches. Jakubczyk and Kamiński ([14]) showed that the choice function T_k^{CEAC} is not coherent and therefore not equivalent to T_k^{ENB} and T_k^{EVPI}. The following example illustrates this issue.

Example 1

Consider the following three distributions of ENB:

$$ENB_{1,k} \sim N(0,10);$$

$$ENB_{2,k} \sim N(1,1);$$

$$ENB_{3,k} \sim N(1,1).$$

Let us consider the following sets $I'' = \{1,2\}$ and $I' = \{1,2,3\}$. Using the properties of normal distribution we can calculate that for the set I'': $CEAC_{1,k} \cong 46\%$ and $CEAC_{2,k} \cong 54\%$. Therefore $T_k^{CEAC}(I'') = \{2\}$. However, for the set I' we get: $CEAC_{2,k} = CEAC_{3,k} \cong 28\%$ and $CEAC_{1,k} \cong 44\%$. Therefore $T_k^{CEAC}(I') = \{1\}$. So T_k^{CEAC} is not coherent.

But if T_k^{CEAC} is not coherent then it is also not equivalent to T_k^{ENB} and T_k^{EVPI} that are coherent.

□

Fenwick *et al.* ([7]) show that $CEAC$ and ENB methods are equivalent for two therapies if the distributions of NB_i are symmetric. The above--presented proof shows that this property does not hold for more than two therapies.

We have shown that in general $CEAC$ method can give different results than ENB and $EVPI$ criteria. However, there are cases when those methods give the same recommendations. Jakubczyk and Kamiński ([14]) postulated that if one option dominates the other in the sense of first-order stochastic dominance, then this option has a greater probability of being cost-effective (even in the case of a choice from more than two options). We prove this assertion in the following proposition.

Proposition 2.

If there exists such $i \in I$ that $NB_{i,k}$ first order stochastically dominates $NB_{j,k}$ for $j \neq i$ then T_k^{CEAC}, T_k^{ENB} and T_k^{EVPI} are equivalent.

Proof

Define random variables X_t that have the same distribution as $NB_{t,k}$ but are independent from all $NB_{t,k}$ variables. We have for all $j \in I \setminus \{i\}$:

$$CEAC_{j,k} = \Pr\left(NB_{j,k} > \max_{t \in I \setminus \{j\}}\{NB_{t,k}\}\right) =$$

$$= \Pr\left(X_j > \max\left\{X_i, \max_{t \in I \setminus \{i,j\}}\{NB_{t,k}\}\right\}\right) <$$

$$< \Pr\left(X_i > \max\left\{X_j, \max_{t \in I \setminus \{i,j\}}\{NB_{t,k}\}\right\}\right) <$$

$$< \Pr\left(NB_{i,k} > \max_{t \in I \setminus \{i\}}\{NB_{t,k}\}\right) = CEAC_{i,k}$$

Therefore $T_k^{CEAC}(I) = \{i\}$.

However, first order stochastic dominance of $NB_{i,k}$ over $NB_{j,k}$, $j \neq i$ implies that $\forall j \neq i : E(NB_i) > E(NB_j)$ [1]. Therefore also $T_k^{ENB}(I) = T_k^{EVPI}(I) = \{i\}$.

□

In the above analysis we have shown that for fixed WTP approaches using ENB and $EVPI$ are coherent and equivalent. On the other hand $CEAC$ criterion is not coherent and not equivalent to the above two. Therefore one can conclude that $CEAC$ method should not be used as a basis for decision support in health technology assessment.

Setting the value of WTP is rather a matter of consensus than estimation (even though theoretical models have been proposed – e.g. [8]). Some methods encompass using the price of a referential therapy (usually dialysis) or referring to gross domestic product *per capita* (e.g. setting WTP to be three times greater). Due to these informal methods in applied research the value of WTP is treated as given approximately, and therefore can be analyzed as a randomly distributed variable. The next section explores these issues.

3. Properties of choice functions for random *WTP*

Now let us assume that the decision maker does not know k (WTP) with certainty, but assumes that it has a continuous random distribution (independent from C_i and E_i). In this section we abandon the analysis of $CEAC$ method as not recommended and concentrate on ENB method only ($EVPI$ method is also not analyzed as it was shown in Section 2 to be equivalent to ENB).

We will consider two approaches of the decision maker. In the first one we assume that the decision maker prefers the option with the highest probability of being chosen by the ENB criterion given the uncertainty of the evaluation k. Formally, we define the evaluation of *probability of the expected net benefit* ($PENB$) maximization of the alternative i as follows:

$$PENB_i = \Pr\left(i \in T_k^{ENB}(I)\right), \tag{2}$$

where the probability is taken over the distribution of k. The choice rule associated with this criterion is $T_k^{PENB}(I') = \arg\max_{i \in I'} \{PENB_{i,k}\}$.

In the second approach we assume that the decision maker maximizes the expected value of net benefit including the uncertainty of k. Formally, we define the evaluation of the *total expected net benefit* ($TENB$) of the alternative i as follows:

$$TENB_i = E\left(NB_{i,k}\right), \tag{3}$$

where the expectation is taken over the distribution of k, C_i and E_i. The obvious choice rule associated with this criterion can be defined as $T_k^{TENB}\left(I'\right) = \arg\max_{i \in I'}\left\{TENB_{i,k}\right\}$.

We will show that the $TENB$ choice rule is coherent while $PENB$ is not (which also implies that they are not equivalent).

Proposition 3.

The choice function T^{TENB} is coherent, while the choice function T^{PENB} is not.

Proof

First we show the coherence of T^{TENB}. Consider any $I'' \subset I' \subset I$. Assume that $i \in I'' \setminus T\left(I''\right)$. This implies that there exists $j \in I''$ such that $E\left(NB_{i,k}\right) < E\left(NB_{j,k}\right)$. However $i, j \in I'$, so i is not an element of $T\left(I'\right)$, as $E\left(NB_{i,k}\right)$ does not depend on the set of available alternatives. This implies that T^{TENB} is coherent.

To prove the second part of the proposition consider the following counterexample:

$E\left(C_1\right) = 1$ and $E\left(E_1\right) = 1$;

$E\left(C_2\right) = 2$ and $E\left(E_2\right) = 2$;

$E\left(C_3\right) = 3.5$ and $E\left(E_3\right) = 3$;

and assume that k has uniform distribution over the set $[0.1;2]$.

Let us consider the sets $I'' = \{1,2\}$ and $I' = \{1,2,3\}$ (all the calculations are illustrated in Figure 1).

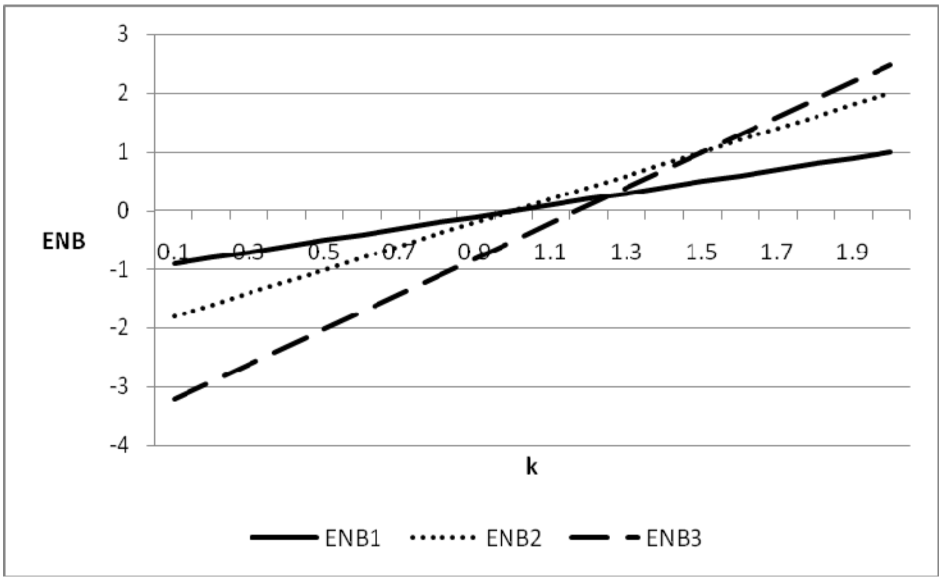

Figure 1. Presentation of $ENB_{i,k}$ as a function of k

We start with the analysis of the set I''. Notice that $E(E_1 - kC_1) > E(E_2 - kC_2)$ for $k \in [0.1;1]$. Therefore in this case $E(E_1 - kC_1)$ and $PENB_2 \cong 53\%$ and consequently $T^{PENB}(I'') = \{2\}$.

Now let us move on to the analysis of the set I'. Notice that $E(E_1 - kC_1)$ is optimal for $k \in [0.1;1]$, but $E(E_2 - kC_2) > E(E_3 - kC_3)$ for $k \in [1;1.5]$. Therefore in this case $E(E_1 - kC_1)$ and $PENB_2 = PENB_3 \cong 26.5\%$ and, consequently, $T^{PENB}(I') = \{1\}$. This implies that T^{PENB} is not coherent.

□

Summing up, the criterion of maximal fraction of good choices ($PENB$) again proves not to be coherent. Therefore it is recommended to use the criterion of averaging out the uncertainty of k ($TENB$).

4. Discussion

In this paper we analyzed the formal properties of methods of comparison used in the applied health technology assessment taking into account cost, effectiveness and willingness-to-pay criterions. These methods encompassed expected net benefit, cost-effectiveness acceptability curves and expected value of perfect information.

The basic conclusion from the paper is that, for given societal willingness-to-pay, minimizing the expected value of perfect information is equivalent to maximizing the expected net benefit of an option. Both of these methods are coherent and therefore robust to manipulation through adding irrelevant alternatives. Conversely, maximizing the probability of making the best choice, i.e. using the cost-effectiveness acceptability curves, do not yield coherent choices. These properties hold when we consider indeterminacy in WTP valuation. Again, maximizing the probability of making the best choice is a non-coherent method, while maximizing the expected net benefit of a choice is coherent.

In general, the choice method used in decision making should, on one hand, result from the preferences of the decision maker, but on the other, from the verification of statistical properties. Otherwise the decision making process may be prone to (possibly unintended) manipulation. It should be required that the decision maker is aware of the properties of the choice criterion so that she can structure her decision problem properly, i.e. choose the set of options compared in some preceding phase.

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