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Stochastic Cost-Effectiveness Analysis on Global Benefits

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Abstract: Dealing with randomness is a crucial aspect that cost-effectiveness analysis (CEA) tools need to address, but existing stochastic CEA tools have rarely examined risk and return from the perspective of global benefits. This paper proposes a stochastic CEA tool that supports medical decision-making from the perspective of global benefits of risk and return, the risk-adjusted incremental cost-effectiveness ratio (ICER). The tool has a traditional form of ICER but uses the risk-adjusted expected cost. Theoretically, we prove that the tool can provide marginal medical decisions that promote the risk-return level on global benefits within any intervention structure and can also serve as a discriminating condition for the optimal intervention structure. Numerical simulations within a framework of mean-variance support the conclusions in this paper.

Keywords: cost-effectiveness analysis; global benefits; risk-adjusted ICER

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1. Introduction

The classical cost-effectiveness analysis framework is of high importance in deterministic medical decision-making, and it has been widely applied in both theoretical and practical problems. Moreover, accounting for uncertainty has recently gained much attention. Both the cost-effectiveness acceptability curve (CEAC, see Stinnett and Mullahy [1]) based on probabilistic dominance analysis and the net monetary benefit (NMB) theory based on risk-adjusted performance measurement (RAPM), e.g., cost-effectiveness risk-aversion curve (CERAC, see Sendi [2]), present effective approaches for making medical decisions under uncertainty (see Al [3]). However, Sendi et al. [4] shows that the most frequently used CEACs still have many weak points, such as insensitivity and lack of risk appetite.

Besides, challenges such as risk correlation (as noted in Barton et al. [5]), asymmetry (as highlighted by Jakubczyk et al. [6]), and the sub-optimality of a unique intervention (as mentioned in Sendi et al. [7]) confront the existing stochastic CEA methods. The challenges arising from correlation structures and the constraints from unique interventions can be addressed through the application of global benefits analysis tools. For the correlation structure problem, global benefits analysis can effectively differentiate the correlation of benefits for different patients within the same intervention and the correlation between different interventions. Also, for the problem of the constraint of the unique intervention, a patient cannot choose to receive two interventions simultaneously, but a patient group can choose to combine different interventions proportionally.

Furthermore, specific choices and assumptions in some methods have also been challenged in practical applications. Elbasha [8] compared the risk-adjusted performance measure of CERAC with other methods and found that choosing the Sortino ratio as a RAPM implies a highly risk-averse assumption, which causes the method to fail when the real level of risk aversion is not high. Kim et al. [9] also show that most studies lack proper considerations when selecting broader evaluation perspectives. Lomas [10] directly points out the non-marginality issue of existing methods, which may cause seemingly cost-effective interventions to be rejected in actual applications. Paulden [11] challenges the function of traditional ICER as a "distance" by pointing out its impossibility on intervention ranking. These findings collectively suggest that a global marginal risk-adjusted ICER needs to be developed.

To this end, this paper proposes a stochastic cost-effectiveness analysis tool aiming at enhancing global benefits. We also present a discriminant tool for judging whether a medical decision would

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contribute to this goal. Furthermore, we propose the analytical expressions for the discriminant measure in a traditional ICER form with good economic interpretation. Also, the properties and superiority of the proposed approach are shown with numerical simulations in the mean-variance framework.

2. The Optimization Problem of Global Benefits

Global benefits refer to the total level of benefits for a specific group of patients. Different from the classical individual benefits problem, global benefits assess the total benefit level for all patients in the group. In a global prospect, each patient may be with high heterogeneity, as they may have different natural conditions, different interventions, and different individual benefits within one intervention. Therefore, global benefits analysis should be introduced to allow for the coexistence of different medical interventions and also takes the correlation structure between patients into account. The stochastic optimization problem aimed at global benefits forces maximizing the overall risk-return levels of global benefits by solving for the optimal structure of medical interventions.

2.1. Model Settings

Consider a specific group of patients, and the number of patients in the population is denoted as M. There are N optional interventions that may be effective for this group, with each intervention possessing potential or existing feasibility. Let M^i represent the number of patients in the group who have received the i-th intervention, where $i \in \{1, 2, ..., N\}$. Every patient requires an intervention, hence $\sum_{i=1}^{N} M^i = M$. The vector $\boldsymbol{M} = \{M^1, M^2, ..., M^N\}$ composed of all M^i values represents the intervention structure adopted by this patient population.

The net monetary benefit (NMB) is a measurement used to determine an individual's benefit level in monetary. This calculation employs a monetization coefficient λ to convert the quality-adjusted life-year (QALY) that a patient receives through a given intervention to a monetary value and forms a monetization return measure in summary. For the m^i-th patient who receives the i-th intervention, their level of NMB, $X^i_{m^i}$, is defined as:

$$X^i_{m^i} := \lambda \text{QALY}^i_{m^i} - \text{Cost}^i_{m^i}, \ \forall m^i \in \{1, 2, ..., M^i\}, i \in \{1, 2, ..., N\}. \tag{1}$$

As the costs incurred by patients during the intervention and their QALY outputs are stochastic, each $X^i_{m^i}$ represents a random variable. These random variables representing NMB levels belong to a random space, $(\Omega, \mathcal{F}, \mathbb{P})$. For any i, the expected value of $X^i_{m^i}$ is denoted as $\mathbb{E}[X^i_{m^i}] = \mu^i$. It is generally assumed that $\{X^i_{m^i}\}$ has cross-moments of any order.

Under a given intervention structure $\boldsymbol{M}$, the global benefits $S(\boldsymbol{M})$ of the studied population can be determined by summing up the NMB of each case. Therefore, the following definition is proposed:

Definition 1. ***Global Benefits:*** *We define the global benefits as a function $S(\cdot) : R^N \mapsto R$ that is N-dimensional, representing a specific studied population. Specifically, if we assume a given intervention structure $\boldsymbol{M}$, we express $S(\boldsymbol{M})$ as:*

$$S(\boldsymbol{M}) = \sum_{i=1}^{N} \left(\sum_{m^i=1}^{M^i} X^i_{m^i} \right). \tag{2}$$

2.2. Optimization Problem

The stochastic optimization problem for global benefits is to find the optimal intervention structure $\boldsymbol{M}^*$, which balances the expectation and risk level of the global benefits. Typical stochastic CEA studies use specific risk-adjusted performance measures, such as the Sharpe ratio and the Sortino ratio, to measure such trade-offs. This article employs a more generalized family of risk-adjusted performance measures, $\mathbb{E}[\cdot]/\rho(\cdot)$, as the target of global benefits in risk-return trade-offs, where $\rho(\cdot)$ is a one-dimensional non-negative functional used to represent the risk measure applied to the random

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variable of the global benefits (see Artzner et al. [12]). The risk measures commonly utilized in typical stochastic CEA research include variance (such as in the case of deterministic equivalence under the Constant Absolute Risk Aversion framework), standard deviation (such as in the case of the Sharpe Ratio), and downside deviation (in the case of the Sortino Ratio). Additionally, other risk measures such as Value at Risk (VaR) and Tail Conditional Expectation (CTE) are employed in more generalized research of risk.

Under these risk-adjusted performance measures, the target function of the stochastic optimization problem in this paper, which represents the risk-return ratio of global benefits, can be expressed as

$$\mathbb{U}(\boldsymbol{M}) = \frac{\mathbb{E}(S(\boldsymbol{M}))}{\rho(S(\boldsymbol{M}))}. \tag{3}$$

With this objective, subject to the constraint $\sum_{i=1}^{N} M^i = M$, the stochastic optimization problem can be represented as:

$$\max_{\boldsymbol{M}} \mathbb{U}(\boldsymbol{M}), \quad s.t. \quad \frac{\|\boldsymbol{M}\|_1}{M} = 1. \tag{4}$$

Similar to the discussion in Buch et al. [13], when M is sufficiently large, the risk measure is subadditive, and given that $\rho^{ij} \in (0,1), \forall i,j$, the optimization problem equation (4) has a unique positive inner solution, denoted as $\boldsymbol{M}^*$. This inner solution represents the optimal intervention structure that maximizes the risk-return ratio of global benefits.

2.3. The Necessary Conditions for the Optimal Solution of the Problem

Assuming that M is sufficiently large, we can assert that $\mathbb{U}(\boldsymbol{M} + \boldsymbol{e}^i) - \mathbb{U}(\boldsymbol{M})$ can be approximated by $\partial\mathbb{U}(\boldsymbol{M})/\partial M^i$, where $\boldsymbol{e}^i$ is an N-dimensional basis vector with the i-th element being 1 and the remaining elements being 0. Under this assumption, the optimization problem equation (4) can be solved using the Lagrange method. Specifically, the following theorem specifies the necessary conditions that the optimal intervention structure should satisfy.

Theorem 1. *Assuming that M is sufficiently large, the inner solution for the optimization problem expressed in formula (4) , which is the optimal intervention structure $\boldsymbol{M}$, must satisfy the following necessary conditions:*

$$\mu^i \rho(S(\boldsymbol{M})) - \mathbb{E}[S(\boldsymbol{M})] \frac{\partial \rho(S(\boldsymbol{M}))}{\partial M^i} = \gamma \rho^2(S(\boldsymbol{M})), \ \forall i \in \{1, 2, ..., N\}, \tag{5}$$

where γ is a non-zero constant.

Proof of Theorem 1. For Equation (4), We construct the Lagrange function,

$$\mathcal{L}(\boldsymbol{M}, \gamma) = \frac{\mathbb{E}(S(\boldsymbol{M}))}{\rho(S(\boldsymbol{M}))} - \gamma \left(\sum_{i=1}^{N} M^i - M \right), \tag{6}$$

where γ is the Lagrange parameter, which must be non-zero due to the nature of the constraints.

Thus, the inner solution must satisfy the condition $\partial\mathcal{L}(\boldsymbol{M}, \gamma)/\partial M^i = 0$ for any i, resulting in equation

$$\frac{\mu^i}{\rho(S(\boldsymbol{M}))} - \frac{\mathbb{E}[S(\boldsymbol{M})]}{\rho^2(S(\boldsymbol{M}))} \frac{\partial \rho(S(\boldsymbol{M}))}{\partial M^i} - r = 0, \ \forall i, \tag{7}$$

moreover, the properties of risk measurement functions stipulate that $\rho(S(\boldsymbol{M})) \neq 0$, then we get Equation (5). □

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Theorem 1 shows that under certain conditions, the optimal intervention structure can be obtained by solving the system of equations composed of Equation (5) and $\sum_{i=1}^{N} M^i = M$. For medical decision-making problems with adequate decision independence, selecting the intervention structure derived from solving these equations can lead to the maximum risk-return ratio of the global benefits of the patient population.

3. Stochastic Cost-Effectiveness Analysis

In general, the freedom of medical decision-making is often limited by various internal and external factors. It is challenging for decision-makers to fully reconstruct the optimal intervention structure of the group within a single decision-making period. To face this situation, we introduce the stochastic cost-effectiveness analysis criterion for global benefits in which any two interventions could be taken into comparison. This also provides comparability with the traditional CEAs.

From a global perspective, the superiority of one intervention over another can be understood as a form of marginal contribution. In other words, if the intervention for a unit patient switches from one to another and the switch results in an increase in the risk-return ratio of global benefits, then the latter intervention can be considered to be marginally superior to the former. Leveraging the model framework and theorem presented earlier, we can obtain the global marginal optimization theorem, which enables us to determine whether one of any two interventions satisfies the superiority criterion for stochastic CEA over the other.

3.1. Global Marginal Optimization Theorem

The marginal criterion for stochastic CEA on global benefits can be expressed through the following theorem.

Theorem 2. ***Global marginal optimization theorem:*** *The equivalence criterion for an intervention to dominate another in a global marginal sense is that the addtional risk-adjusted expected cost to obtain a unit increase in expected QALY is less than the monetization factor λ.*

Mathematically, for any $i, j \in \{1, 2, ..., N\}$, if $\mathbb{E}[\mathrm{QALY}^j] - \mathbb{E}[\mathrm{QALY}^i] > 0$, then

$$\lim_{c \to 0^+} \frac{\mathbb{U}(\boldsymbol{M} - ce^i + ce^j) - \mathbb{U}(\boldsymbol{M})}{c} > 0 \Leftrightarrow \frac{\mathbb{E}^{\mathbb{Q}}[\mathrm{Cost}^j] - \mathbb{E}^{\mathbb{Q}}[\mathrm{Cost}^i]}{\mathbb{E}[\mathrm{QALY}^j] - \mathbb{E}[\mathrm{QALY}^i]} < \lambda, \tag{8}$$

where $\mathbb{E}^{\mathbb{Q}}[\mathrm{Cost}^j]$ is the risk-adjusted expected cost under the intervention j, defined as

$$\mathbb{E}^{\mathbb{Q}}[\mathrm{Cost}^j] = \mathbb{E}[\mathrm{Cost}^j] + \alpha(\boldsymbol{M}) \frac{\partial \rho(S(\boldsymbol{M}))}{\partial M^j}, \tag{9}$$

and $\alpha(\boldsymbol{M}) = \mathbb{E}(S(\boldsymbol{M}))/\rho(S(\boldsymbol{M}))$ is the current level of risk-return for global benefits.

Proof of Theorem 2. First, the substitution definition, $D(c) = \mathbb{U}(\boldsymbol{M} - ce^i + ce^j)$, denotes the risk-return of global benefits after transferring patients in unit c from intervention i to intervention j. By the definition of partial derivatives, $D(\cdot)$'s continuity for c and the uniform integrability of $S(\boldsymbol{M})$, there is

$$\lim_{c \to 0^+} \frac{\partial D(c)}{\partial c} = \lim_{c \to 0^+} \lim_{\Delta c \to 0^+} \frac{D(c + \Delta c) - D(c)}{\Delta c} = \lim_{c \to 0^+} \frac{\mathbb{U}(\boldsymbol{M} - ce^i + ce^j) - \mathbb{U}(\boldsymbol{M})}{c}, \tag{10}$$

and thus only the equivalence condition of $\lim_{c \to 0^+} \frac{\partial D(c)}{\partial c} > 0$ needs to be examined.

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Since we have

$$\frac{\partial D(c)}{\partial c} = \frac{\mathbb{U}(\boldsymbol{M} - ce^i + ce^j)}{\partial M^i}\frac{\partial(M^i - c)}{\partial c} + \frac{\mathbb{U}(\boldsymbol{M} - ce^i + ce^j)}{\partial M^j}\frac{\partial(M^j + c)}{\partial c}, \tag{11}$$

we can obtain

$$\begin{aligned}
\lim_{c\to 0^+}\frac{\partial D(c)}{\partial c} &= -\frac{\partial \mathbb{U}(\boldsymbol{M})}{\partial M^i} + \frac{\partial \mathbb{U}(\boldsymbol{M})}{\partial M^j} \\
&= -\frac{\mu^i}{\rho(S(\boldsymbol{M}))} + \frac{\mathbb{E}[S(\boldsymbol{M})]}{\rho^2(S(\boldsymbol{M}))}\frac{\partial\rho(S(\boldsymbol{M}))}{\partial M^i} + \frac{\mu^j}{\rho(S(\boldsymbol{M}))} - \frac{\mathbb{E}[S(\boldsymbol{M})]}{\rho^2(S(\boldsymbol{M}))}\frac{\partial\rho(S(\boldsymbol{M}))}{\partial M^j} \\
&= \frac{1}{\rho(S(\boldsymbol{M}))}\left(\mu^j - \mu^i - \frac{\mathbb{E}[S(\boldsymbol{M})]}{\rho(S(\boldsymbol{M}))}\left(\frac{\partial\rho(S(\boldsymbol{M}))}{\partial M^j} - \frac{\partial\rho(S(\boldsymbol{M}))}{\partial M^i}\right)\right) \\
&= \frac{1}{\rho(S(\boldsymbol{M}))}\left(\mu^j - \mu^i - \alpha(\boldsymbol{M})\left(\frac{\partial\rho(S(\boldsymbol{M}))}{\partial M^j} - \frac{\partial\rho(S(\boldsymbol{M}))}{\partial M^i}\right)\right).
\end{aligned} \tag{12}$$

Since $\rho(S(\boldsymbol{M})) > 0$, the equivalence condition for $\lim_{c\to 0^+}\frac{\partial D(c)}{\partial c} > 0$ can be expressed as

$$\mu^j - \mu^i - \alpha(\boldsymbol{M})\left(\frac{\partial\rho(S(\boldsymbol{M}))}{\partial M^j} - \frac{\partial\rho(S(\boldsymbol{M}))}{\partial M^i}\right) > 0, \tag{13}$$

and there is $\forall i, \quad \mu^i = \lambda\mathbb{E}[\text{QALY}^i] - \mathbb{E}[\text{Cost}^i]$, which is substituted to express the equivalence condition as

$$\lambda\mathbb{E}[\text{QALY}^j] - \lambda\mathbb{E}[\text{QALY}^i] - \mathbb{E}[\text{Cost}^j] + \mathbb{E}[\text{Cost}^i] - \alpha(\boldsymbol{M})\left(\frac{\partial\rho(S(\boldsymbol{M}))}{\partial M^j} - \frac{\partial\rho(S(\boldsymbol{M}))}{\partial M^i}\right) > 0. \tag{14}$$

Noting that

$$\mathbb{E}^Q[\text{Cost}^j] = \mathbb{E}[\text{Cost}^j] + \alpha(\boldsymbol{M})\frac{\partial\rho(S(\boldsymbol{M}))}{\partial M^j}, \tag{15}$$

there is

$$\lambda\left(\mathbb{E}[\text{QALY}^j] - \mathbb{E}[\text{QALY}^i]\right) > \mathbb{E}^Q[\text{Cost}^j] - \mathbb{E}^Q[\text{Cost}^i], \tag{16}$$

then the theorem is proved with $\mathbb{E}[\text{QALY}^j] - \mathbb{E}[\text{QALY}^i] > 0$. □

It can be seen that Theorem 2 provides a way of comparing the marginal cost-effectiveness of any two interventions when considering uncertainty. The expression on the left-hand side of Equation (8) measures the change in the risk-return ratio of global benefits when switching from intervention i to intervention j for a small unit of patients under uncertainty. The expression on the right-hand side of Equation (8) measures the incremental risk-adjusted expected cost required to achieve one unit of incremental QALY gain relative to intervention i for intervention j. In other words, under the current intervention structure, an intervention switch in which the incremental risk-adjusted expected cost for gaining incremental QALY is less than λ is beneficial to the risk-return ratio of global benefits.

It is worth noting that although the criterion in Theorem 2 has a form similar to that of traditional ICER, the main difference lies in the measurement of "expected costs". Here, the incremental expected cost needs to be measured from the perspective of risk adjustment, that is, considering the "implicit" cost corresponding to risk in the cost measurement. In the definition formula, equation (9), of the risk-adjusted expected cost, $\alpha(\boldsymbol{M})$ is the risk-return level for global benefits under the current intervention structure, which can be understood as the current globally risk-cost rate. The $\partial\rho(S(\boldsymbol{M}))/\partial M^j$ is a risk allocation method (often called a marginal allocation, see Denault [14]) and can be understood as the risk level allocated to one unit of patients receiving intervention j when distributing the global risk $\rho(S(\boldsymbol{M}))$. Furthermore, the risk-adjusted expected cost can be understood as the sum of the traditional expected cost and the risk cost allocated to the intervention. And then, the criteria are constructed using such risk-adjusted expected costs.

3.2. Risk-Adjusted ICER

The criterion in Theorem 2 uses a specific form of ICER as a measure to discriminant the superiority of any two intervention measures under the consideration of stochasticity. Such a criterion is defined as risk-adjusted ICER due to the utilization of risk-adjusted expected costs.

Definition 2. ***Risk-adjusted ICER:*** *Under the intervention structure $\boldsymbol{M}$, if $\mathbb{E}[\mathrm{QALY}^j] - \mathbb{E}[\mathrm{QALY}^i] > 0$, the risk-adjusted ICER, $\mathrm{ICER}^{\mathbb{Q}}_{i,j}(\boldsymbol{M})$, of switching intervention i to j is defined as:*

$$\mathrm{ICER}^{\mathbb{Q}}_{i,j}(\boldsymbol{M}) = \frac{\mathbb{E}^{\mathbb{Q}}[\mathrm{Cost}^j] - \mathbb{E}^{\mathbb{Q}}[\mathrm{Cost}^i]}{\mathbb{E}[\mathrm{QALY}^j] - \mathbb{E}[\mathrm{QALY}^i]}, \tag{17}$$

where $\mathbb{E}^{\mathbb{Q}}[\mathrm{Cost}^j]$ is the Risk-Adjusted Expected Cost under intervention j, defined as:

$$\mathbb{E}^{\mathbb{Q}}[\mathrm{Cost}^j] = \mathbb{E}[\mathrm{Cost}^j] + \alpha(\boldsymbol{M})\frac{\partial\rho(S(\boldsymbol{M}))}{\partial M^j}, \tag{18}$$

and $\alpha(\boldsymbol{M}) = \mathbb{E}(S(\boldsymbol{M}))/\rho(S(\boldsymbol{M}))$ is the risk-return level of the current global benefits.

It can be seen that risk-adjusted ICER is an incremental cost-effectiveness ratio based on the risk-adjusted expected cost. Therefore, risk-adjusted ICER is also applicable in situations where traditional ICER applies. Compared with other CEA methods that consider stochasticity, risk-adjusted ICER has several typical advantages. First, from the perspective of the risk-return ratio of global benefits, risk-adjusted ICER allows different interventions to coexist, solving the "either black or white" challenge faced by traditional individual CEA. Second, risk-adjusted ICER is a marginal discriminant condition that incorporates the current intervention structure into the decision of optimality, allowing medical decision-makers to gradually adjust interventions. Third, risk-adjusted ICER accommodates the degree of risk aversion in the risk measure selection, allowing medical decision-makers to select any risk measure for CEA analysis without the need for special discriminant tools for each measure. Finally, risk-adjusted ICER retains the classic ICER form, and the monetization constant λ remains unchanged from the original setting, avoiding the problem of mixing costs and QALYs in individual RAPMs.

Technically, it is worth adding that the condition of $\mathbb{E}[\mathrm{QALY}^j] - \mathbb{E}[\mathrm{QALY}^i] > 0$ actually only requires a specified order of intervention i and intervention j according to their $\mathbb{E}[\mathrm{QALY}]$ values when comparing the two interventions. That is to say, in the continuous sense, excluding interventions that are exactly equivalent, the set of cases with superiority of j over i and i over j are complementary sets. The decision result can be obtained by comparing in any determined order. Therefore, both Theorem 1 and Theorem 2 are stated under a specified order, and they also have equivalent dual forms in the other order, which will not be repeated here.

4. A Numerical Example in the Mean-Variance System

In order to further clarify the properties of the method proposed in this paper and demonstrate its association and difference with classical CEA tools, we perform numerical simulations to calculate the results, differences, and effectiveness of various types of uncertain CEA tools under the classical mean-variance system.

4.1. Mean-Variance System Settings

In the mean-variance system, it is assumed that the joint distribution of the costs and QALY outcomes of individuals receiving various interventions follows an overall joint normal distribution. Therefore, characterizing all the stochasticity can be accomplished by setting the means, standard

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deviations, and the matrix of the correlation coefficient. For each intervention subgroup, it is assumed that the costs and QALY outcomes of each patient within the subgroup are identically distributed but not independent and that there is a certain correlation between the costs and QALY outcomes of individual patients. The correlation between patient costs of different interventions is only related to their group, without distinguishing individuals, and the same assumption applies to QALY outcomes. In addition, it is assumed that the cost of any patient is independent of the QALY outcome of any other patient.

Specifically, for each intervention group, the costs and QALY outcomes of each patient have unique mean and variance values. For any i and m^i, we have

$$\begin{aligned} \mathbb{E}[\text{QALY}^i_{m^i}] &= \mu^i_Q, \quad \text{Var}[\text{QALY}^i_{m^i}] = (\sigma^i_Q)^2 \\ \mathbb{E}[\text{Cost}^i_{m^i}] &= \mu^i_C, \quad \text{Var}[\text{Cost}^i_{m^i}] = (\sigma^i_C)^2. \end{aligned} \tag{19}$$

And for the correlation coefficient of each cost, there is

$$\forall i,j,\ \text{Corr}[\text{Cost}^i_{m_1}, \text{Cost}^j_{m_2}] = \begin{cases} 1, & i=j,\ m_1=m_2 \\ \rho^{ii}_C, & i=j,\ m_1 \neq m_2 \\ \rho^{ij}_C, & i \neq j, \end{cases} \tag{20}$$

and for each QALY there is a similar equation

$$\forall i,j,\ \text{Corr}[\text{QALY}^i_{m_1}, \text{QALY}^j_{m_2}] = \begin{cases} 1, & i=j,\ m_1=m_2 \\ \rho^{ii}_Q, & i=j,\ m_1 \neq m_2 \\ \rho^{ij}_Q, & i \neq j. \end{cases} \tag{21}$$

In addition, the cross-sectional relationship between cost and QALY output is assumed as

$$\forall i,j,\ \text{Corr}[\text{Cost}^i_{m_1}, \text{QALY}^j_{m_2}] = \begin{cases} \rho^i_{QC}, & i=j,\ m_1=m_2 \\ \rho^{ii}_{QC}=0, & i=j,\ m_1 \neq m_2 \\ \rho^{ij}_{QC}=0, & i \neq j. \end{cases} \tag{22}$$

The structure of each correlation is schematically shown in the following Figure 1:

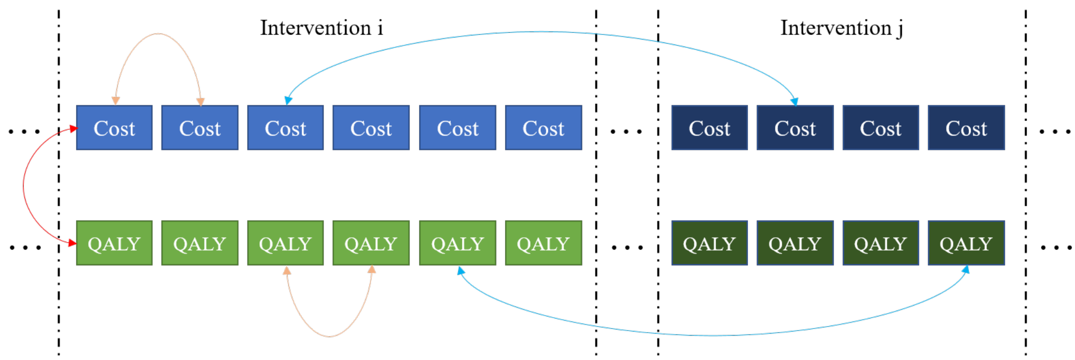

Figure 1. source of correlation.

4.2. Simulation Methods and Settings

The numerical simulation uses Monte Carlo sampling to form a column vector that combines the costs and QALY outputs of each patient with selected intervention structure and parameters. A sufficient number of samples are generated and the statistical features of the overall results (such as global benefits and total costs) are calculated. Then, the results of the objective function for the

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corresponding intervention structure are obtained. Following this, different stochastic CEA methods are compared and analyzed for optimal interventions, and simulations are performed again for each method's recommended intervention structure modification, resulting in different outcomes for different stochastic CEA methods' decisions. Some key intermediate results are also recorded and presented.

4.2.1. Simulation Process

The purpose of simulation mainly lies in three aspects. Firstly, illustrating through numerical examples that in terms of global benefits, the mixture of different interventions could have a better risk-return level than an absolutely unique intervention. Secondly, under different intervention structures, calculating the risk-adjusted expected cost and risk-adjusted ICER proposed in this paper, and verifying the process of inducing the optimal risk-return ratio of global benefits in a marginal sense. Thirdly, comparing the decision using different stochastic CEA methods in the same environment, testing the accuracy of different methods' performance on global benefits, and checking their direction of optimization.

Specifically, the simulation first selects two interventions from all optional interventions, calculates their risk-return level in terms of global benefits separately, and then mixes them in different proportions to form intervention structures. Secondly, under different intervention structures, the risk-adjusted expected cost and risk-adjusted ICER of the two interventions are calculated, along with the corresponding decisions. Then, to evaluate the effectiveness of each method, a specific intervention structure is selected, and different stochastic CEAs are used for determinations between any two interventions, with the change in the risk-return level of global benefits being measured after adjusting the intervention structure according to the corresponding determination results.

In the simulation process, it is necessary to simulate the QALY outcomes and costs under the selected intervention and evaluate the global benefits quantitatively. In detail, under each selected intervention structure $\boldsymbol{M}$, the evaluation of the risk-return ratio of the global benefits level consists of the following steps in the simulation process:

1. Divide the M simulated patients into N groups, where the i-th group has M^i patients according to the structure of $\boldsymbol{M}$.
2. Combine the cost and QALY output of each patient into a random vector and calculate the mean and covariance matrix of the random vector.
3. Generate 10000 samples of the group using the calculated mean and covariance matrix as the parameters of a high-dimensional normal distribution.
4. Measure the global benefits level of each sample of the group.
5. Summarize the global benefits level of each sample and measure their statistical characteristics and risk-return ratios.

Since the simulation can only generate a limited number of samples, selecting relatively tailed risk measures may cause the simulation results to be affected by this limit. Therefore, we repeat the evaluating steps of the risk-return ratio of global benefits level 100 times independently and use the average value as the final result, and use empirical probability to estimate the accuracy of different CEAs for the effectiveness assessment.

4.2.2. Parameter Setting and Reference Methods Selection

To balance the adequacy of alternative interventions and the interpretability of results, we select a total of $N = 5$ interventions and assume that the patient population consists of $M = 100$ individuals. The number of samplings of the outcome results of the patient group is chosen to be 10000, and the number of repeated random experiments for the risk-return evaluation results of global benefits is chosen to be 100 times.

The distribution parameters within the intervention groups are assumed as shown in Table 1:

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Table 1. Assumptions of distribution parameters within intervention groups.

ID (i)	μ_Q^i	μ_C^i	σ_Q^i	σ_C^i	ρ_Q^{ii}	ρ_C^{ii}	ρ_{QC}^{ii}
1	7.5	6000	0.1	100	0.03	0.04	0.02
2	9	8000	0.05	200	0.04	0.04	0.02
3	10	10000	0.1	300	0.03	0.03	0.02
4	12	12000	0.15	400	0.03	0.03	0.02
5	14	15000	0.2	200	0.03	0.03	0.02

In addition, the correlation coefficients between different individual outcomes among different groups are set to $\forall i \neq j$, $\rho_C^{ij} = 0.005$, $\rho_Q^{ij} = 0.002$, and the monetary constant, λ, is set to $\lambda = 2000$ \$/QALY unless specifically mentioned.

Besides the method proposed in this paper, we select four different stochastic CEA methods as reference methods to participate in the simulation together. The first is the traditional ICER method, where the measurement standard is

$$\text{ICER}_{i,j}(\boldsymbol{M}) = \frac{\mathbb{E}[\text{Cost}^j] - \mathbb{E}[\text{Cost}^i]}{\mathbb{E}[\text{QALY}^j] - \mathbb{E}[\text{QALY}^i]}.$$

The second is the Sortino ratio method (see Elbasha2022) based on NMB, which compares the Sortino ratios of different interventions, $\mathbb{E}[X^i_{m^i}]/\text{DD}[X^i_{m^i}]$, to determine their priority. The third and fourth methods are the probabilistic methods based on CEAC, which determine the superiority of the methods by judging whether the α percentile of the ICER distribution, $Q_\alpha(\frac{\text{Cost}^j - \text{Cost}^i}{\text{QALY}^j - \text{QALY}^i})$, is within the range of the willing-to-pay level (λ). The third method is relatively aggressive, using $\alpha = 5\%$, while the fourth method is relatively conservative, using $\alpha = 95\%$. Comparisons are made between the method proposed in this paper and these four reference methods.

4.3. Simulation Results

The simulation results are mainly presented in three parts. The first part shows the advantage of mixed intervention compared to unique intervention from the perspective of risk-return of global benefits. The second part displays the regularity of changes in the risk-adjusted expected cost and the risk-adjusted ICER with the variation of intervention structures and demonstrates the marginal optimality under different intervention structures. The third part shows the preference decision of different interventions by different stochastic CEA methods under a specific intervention structure and compares and demonstrates the accuracy of the decisions.

4.3.1. Benefits of Diversification with Mixed Intervention

In this subsection, we evaluate the level of global benefits under different intervention structures through simulation calculations and assess the influence of intervention structures on the risk-return ratio of global benefits. We also verify the initial claim in this paper that mixed interventions may lead to better risk returns. Specifically, intervention 4 and intervention 5 are chosen as the objects of this simulation, while the first three interventions have proportions of 0 in the structure, i.e., $M^1, M^2, M^3 = 0$. Then, the level of M^4/M gradually varies in the $[0, 1]$ range, and the corresponding risk-return ratio of the global benefits is calculated. The results are shown in Figure 2.

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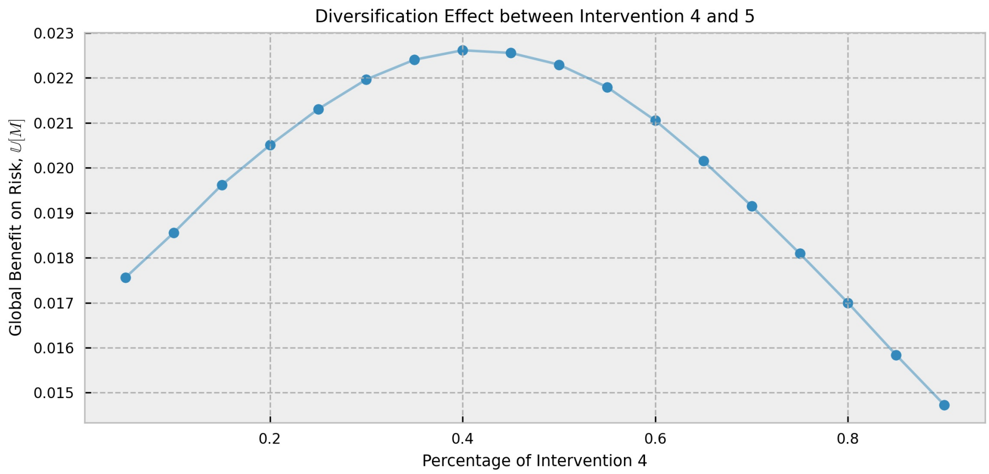

Figure 2. Effects on the global benefits of different intervention structures.

From Figure 2, it can be seen that as the proportion of intervention 4 gradually increases from 0 to 1, the risk-return level of global benefits shows a pattern of first increasing and then decreasing, reaching its optimum at around $M^4/M = 0.4$. The optimum level of 0.0227 is significantly higher than the risk-return ratios of 0.0173 at $M^4/M = 0$ and 0.0127 at $M^4/M = 1$. This suggests that if considering the medical decisions with intervention 4 and intervention 5, using a 4:6 structure to mix both interventions is more risk-efficient in a global sense than using either intervention alone. This validates the claim that better risk returns may be obtained through mixed interventions.

4.3.2. Risk-Adjusted Expected Cost and Risk-Adjusted ICER

With the same settings as in the previous subsection, we calculate the risk-adjusted ICER for switching marginal from intervention 4 to intervention 5, and the level of the risk-adjusted expected cost of both interventions as we gradually adjust the level of M^4/M in the $[0, 1]$ range. Through the simulation results, we monitor how the risk-adjusted ICER changes lead the intervention structure to achieve the optimum risk-return of global benefits. The simulation results are shown in Figure 3.

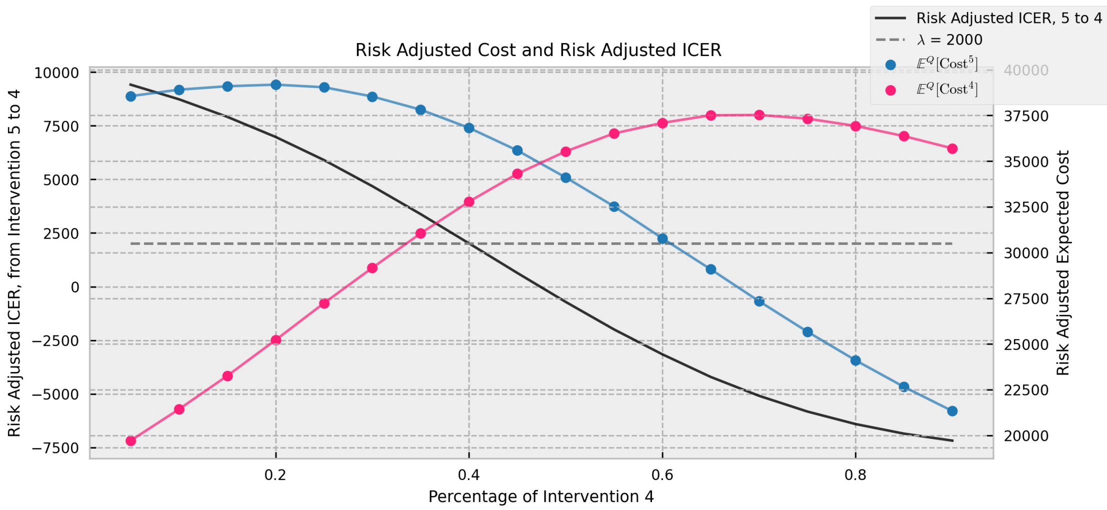

Figure 3. Risk-adjusted expected cost and risk-adjusted ICER.

In Figure 3, the red curve represents the risk-adjusted expected cost of intervention 4, and the blue curve represents that of intervention 5. It can be seen that as the proportion of intervention 4 in the intervention structure increases, the risk-adjusted expected cost of intervention 5 relative to

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intervention 4 changes from much higher to much lower. This is due to changes in the diversification structure. Specifically, when the proportion of intervention 4 is small, there are many cases using intervention 5 in the system. At this time, increasing one unit of intervention 5 cases is equivalent to adding a highly correlated risk to the total risk pool, resulting in a relatively high level of risk allocated to the newly added intervention 5. This makes the risk-adjusted expected cost of the new unit of intervention 5 high at this stage. In contrast, the risk-adjusted expected cost of intervention 4 is relatively low because it is relatively independent of the risk pool. This pattern validates that the risk-adjusted expected cost does indeed take into account the marginal impact of intervention restructuring on the risk pool in the cost modification.

In addition, the black curve in Figure 3 represents the evaluation results of the risk-adjusted ICER obtained in switching one unit of intervention 4 to intervention 5. It can be seen that the curve intersects with the $\lambda = 2000$ threshold at around $M^4/M = 0.4$, the optimal structure point. To the left of the intersection point, the level of the risk-adjusted ICER is higher than the monetized constant, indicating that switching from one unit of intervention 4 to intervention 5 is not cost-effective and has a negative impact on the risk-return of global benefits. Therefore, the proportion of intervention 5 needs to be reduced. On the contrary, to the right of the intersection point, the opposite is true. It is worth noting that the intersection point of the black curve in Figure 3 and $\lambda = 2000$ coincides perfectly with the position where the risk-return of global benefits reaches its optimum in Figure 2. This also confirms that the risk-adjusted ICER can induce changes in the intervention structure to achieve the optimal risk-return of global benefits.

4.3.3. Comparison of Methods

In this subsection, we selected a specific intervention structure (equal-weighted) as the starting point to examine the decisions of different stochastic CEAs for adjusting interventions and quantified the corresponding impact on the distribution of the risk-return of global benefits. We demonstrate the results and validate the effectiveness of different stochastic CEAs. These results are shown in Figure 4.

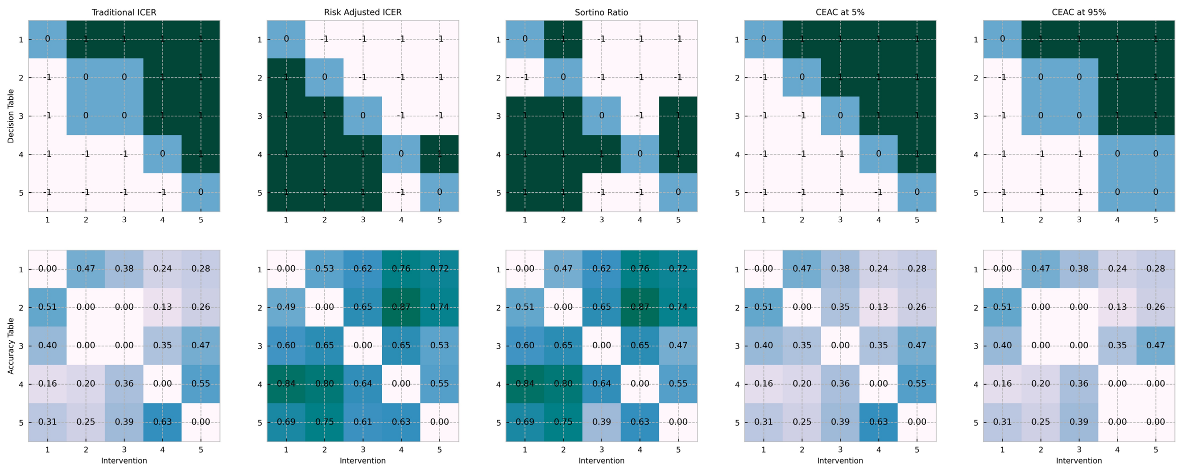

Figure 4. Decisions and accuracy of various stochastic CEAs. "Traditional ICER" represents the results of the traditional ICER tool, "Risk-adjusted ICER" represents our proposed method, "Sortino Ratio" represents the decision made using the Sortino ratio tool, "CEAC at 5%" represents the aggressive CEAC method, and "CEAC at 95%" represents the conservative CEAC method.

In Figure 4, each sub-plot presents the information in a 5×5 matrix, where the grid in the i-th row and j-th column represents the decision and its effectiveness of the corresponding stochastic CEA for the replacement of intervention i with intervention j. The decision is shown in the sub-plots in the first row, where $+1$ represents a decision to replace, -1 represents a decision in reverse, and 0 represents no modification. The accuracy of the decision results is displayed in the sub-plots in the

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second row, where the number in each grid represents the percentage of scenarios where the risk-return ratio of global benefits is improved after adjustment based on that decision, within the 100 times of Monte Carlo simulations. Additionally, the cells on the diagonal of each sub-plot do not contain any information.

From the comparison of the decisions, it can be seen that the decisions of the traditional ICER and CEAC methods differ to some extent from our proposed method and the Sortino method in the current scenario. Specifically, the traditional ICER does not consider the stochasticity and only requires the ICER to be below the monetized constant in an expected sense for each accepted intervention replacement. And, the CEAC method, similar to the traditional ICER, does not use the information contained in the current intervention structure under the mean-variance framework. The Sortino Ratio method obtained a similar decision to our proposed method, which can be attributed to the similarity in risk-adjusted measures between the two methods. However, the Sortino Ratio method still does not consider the current intervention structure, so there are still differences from our proposed method, but these differences are not very significant due to the low level of correlation coefficient selected in the simulation.

From the comparison of the accuracy of the decisions, it can be found that only our proposed method can almost perfectly ensure that the decisions between each pair of interventions can achieve an accuracy rate of over 50% and reaches the highest level among all methods in expectation (The magnitude of the accuracy rate is related to the number of simulations, so the relative level of each method is mainly compared.). In addition, except for the scenario [1] where intervention 2 replaces intervention 1, our proposed method achieved the highest accuracy rate among all methods for any pair of comparisons. This also validates the effectiveness of our proposed method.

5. Conclusions and Discussion

This paper proposes a stochastic CEA tool that considers uncertainty from the perspective of global benefits. The tool can evaluate the effectiveness of different interventions within the current intervention structure. In theory, we present the necessary conditions for achieving the optimal intervention structure that maximizes the risk-return of global benefits. Furthermore, we introduce the risk-adjusted ICER as a discriminant tool to compare any two interventions within the current intervention structure. Theoretical analysis confirms that the discriminant tool is effective in promoting the risk-return levels of global benefits. Results from numerical simulations under the mean-variance framework also provide support for these findings.

It is worth noting that the risk-return analysis of global benefits breaks the constraints of traditional CEA analysis for unique intervention. This may have a high practical value in avoiding the high concentration risk and the potential monopolies that may be introduced by traditional CEA. Specifically, a single intervention may have some systematic risks that cannot be diversified in a global sense, such as some long-term adverse effects that have not yet been discovered by clinical trials (such as the example of Thalidomide). Unique intervention may expose all patients to such risks and result in significant adverse consequences on a global scale once these losses occur. Meanwhile, the risk-adjusted ICER retains the same expression format as the traditional ICER, with high comparability with previous evaluation conclusions and lower tool substitution costs. The risk-adjusted expected cost used in the numerator also has clear economic implications. The adjustment item added to the expected cost is obtained by multiplying the cost rate of risk by the allocated risk level, which is consistent with the economic logic of risk premium.

In addition, the analysis tool proposed in this paper can use different risk measures and does not make too many assumptions about the distribution family and correlation structure. This means that

[1] The bias in the comparison results of this pair of interventions is a random result with a small probability due to the limited number of samples.

the methodhas high generality and can also be used in scenarios with special tail risks, correlation structures, and risk appetites.

Overall, the risk-return of global benefits is a measure that considers the impact of different interventions on benefits from a holistic perspective and is a valuable measurement tool that takes stochasticity and diversity into consideration. The risk-adjusted ICER, as the discrimination tool under this perspective, can effectively induce the optimization of risk-return of global benefits and has clear economic implications. The conclusions obtained by the method proposed in this paper in the CEA analysis with uncertainty should be provided as decision reference to medical decision-makers.

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