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METHODOLOGICAL ARTICLES

Two Approaches to Incorporate Clinical Data Uncertainty into Multiple Criteria Decision Analysis for Benefit-Risk Assessment of Medicinal Products

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ABSTRACT

Background: The Problem formulation, Objectives, Alternatives, Consequences, Trade-offs, Uncertainties, Risk attitude, and Linked decisions (PrOACT-URL) framework and multiple criteria decision analysis (MCDA) have been recommended by the European Medicines Agency for structured benefit-risk assessment of medicinal products undergoing regulatory review. **Objective:** The objective of this article was to provide solutions to incorporate the uncertainty from clinical data into the MCDA model when evaluating the overall benefit-risk profiles among different treatment options. **Methods:** Two statistical approaches, the δ-method approach and the Monte-Carlo approach, were proposed to construct the confidence interval of the overall benefit-risk score from the MCDA model as well as other probabilistic measures for comparing the benefit-risk profiles between treatment options. Both approaches can incorporate the correlation structure between clinical parameters (criteria) in the MCDA model and are straightforward to implement. **Results:** The two proposed approaches were applied to a case study to evaluate the benefit-risk profile of an add-on therapy for rheumatoid arthritis (drug X) relative to placebo. It demonstrated a straightforward way to quantify the impact of the uncertainty from clinical data to the benefit-risk assessment and enabled statistical inference on evaluating the overall benefit-risk profiles among different treatment options. **Conclusions:** The δ-method approach provides a closed form to quantify the variability of the overall benefit-risk score in the MCDA model, whereas the Monte-Carlo approach is more computationally intensive but can yield its true sampling distribution for statistical inference. The obtained confidence intervals and other probabilistic measures from the two approaches enhance the benefit-risk decision making of medicinal products.

Keywords: multiple criteria decision analysis (MCDA), probabilistic sensitivity analysis, regulatory decision making, structured benefit-risk assessment of medicinal products.

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Introduction

A structured benefit-risk assessment of medicinal products is not a new concept. It was initially proposed or appeared in the scientific literature more than 20 years ago [1–3]. During the past decade, however, a structured framework for benefit-risk assessment, as well as various qualitative and quantitative methods, has become an emerging research topic among both regulatory and pharmaceutical industries around the world. In 2005, the Pharmaceutical Research and Manufacturers of America initiated the Benefit-Risk Action Team (BRAT) and proposed the BRAT framework for structured benefit-risk assessment. The BRAT framework was finalized in 2010, and several global pharmaceutical member companies in Pharmaceutical Research and Manufacturers of America have piloted the BRAT framework since then [4–6]. At the end of 2011, the work of the BRAT was transferred to the Center for Innovation in Regulatory Science, an independent research-based institution in the United Kingdom, whose objective is to promote scientific making and best practice in global regulatory affairs [7]. Currently, the Center for Innovation in Regulatory Science is devoted to developing the Unified Methodologies for Benefit-Risk Assessment framework and piloting its structured benefit-risk assessment proforma template among regulatory authorities and pharmaceutical companies [8,9]. The Center for Drug Evaluation and Research of the U.S. Food and Drug Administration initiated its own effort on a structured benefit-risk framework in 2009. In 2010, the Food and Drug Administration/Center for Drug Evaluation and Research proposed a five-grid benefit-risk framework that includes five decision factors—Analysis of Condition, Unmet Medical Need, Benefit, Risk, and Risk Management—and an overall Benefit-Risk Summary and Assessment. This framework will be incorporated into Center for Drug Evaluation and Research Standard Operating Procedures and is planned to be rolled out in the upcoming Prescription Drug User Fee Act V [10–12].

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Among all the efforts from different regulatory authorities toward structured benefit-risk assessment, the European Medicines Agency (EMA), in particular, started a large research project in 2008 called the Benefit-Risk Methodology Project. The main objective of this project is the development and testing of tools and processes for balancing multiple benefits and risks, which can be used as an aid to informed, science-based regulatory decisions about medicinal products [13]. As of January 1, 2014, four out of five work packages (WPs) in this EMA Benefit-Risk Methodology Project have been published. These work packages summarized the current practice of benefit-risk assessment in the European Union regulatory network (WP1), reviewed more than 20 qualitative and quantitative benefit-risk assessment methods (WP2), recommended the eight-step Problem formulation, Objectives, Alternatives, Consequences, Trade-offs, Uncertainties, Risk attitude, and Linked decisions (PrOACT-URL) framework as well as the multiple criteria decision analysis (MCDA) for structured benefit-risk assessment with several field tests (case studies) (WP3, WP4). The overall experience from the field tests demonstrated the usefulness of the MCDA approach and the PrOACT-URL framework in determining the benefit-risk balance of a medicinal product. As an extension to the EMA Benefit-Risk Methodology Project, the Innovative Medicines Initiative - Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (IMI-PROTECT), a multinational consortium consisting of 34 public and private partners coordinated by the EMA, has conducted its research stream (IMI-PROTECT Work Programme 5) and published its final recommendation report for the methodology and visualization techniques to be used in the assessment of benefit and risk of medicines [14,15]. Among the PROTECT benefit-risk final report and case studies, the MCDA approach is perhaps one of the most popular quantitative benefit-risk assessment tools [16].

The MCDA, first introduced in 1976 by Keeney and Raiffa, has been used recently by both regulatory authority and pharmaceutical companies to perform benefit-risk assessment of medicines [17–25]. It naturally fits into the PrOACT-URL framework but is independent with any qualitative benefit-risk assessment or decision-making framework. The MCDA brings together evaluations of different decision options on multiple criteria into one overall evaluation through scoring and weighting [13, EMA WP2]. Scoring is to quantify each criterion into a common scale (called preference value, preference score, or simply utility) for measuring the value of decision options. Weighting is to ensure that the units of value on all the criteria are comparable so that they can be combined into one overall scale (called overall benefit-risk score). For our benefit-risk assessment of medicinal products setting, the decision options usually refer to the medical treatment options under evaluation/comparison (e.g., control vs. investigational/experimental drug) and the criteria usually refer to the benefits (favorable effects) and risks (unfavorable effects) of taking the treatments, such as the improvement in the health condition and the rate of serious adverse events.

The MCDA addresses the problem of comparing benefits and risks of different decisions (i.e., different treatment options or medicinal products in our setting) by providing a common unit of value so that the added value of favorable effects can be compared with the loss of value from unfavorable effects. The obtained overall benefit-risk score from a deterministic analysis, however, usually reflects only the average scenario (a point estimate) without quantifying the variability of such quantity. Because many uncertainties may be involved in the benefit-risk assessment, it is important to understand the variability of the overall benefit-risk score, namely, how sensitively the overall benefit-risk profile will be affected by underlying uncertainties. There are generally two types of uncertainty in MCDA modeling when assessing the benefit-risk balance of different treatment options. One is from the MCDA model itself and is usually subjective in nature. For instance, different value functions, weights, or criteria selections will certainly have an impact on the comparison of the overall benefit-risk profiles of different treatment options. The other type of uncertainty arises from the clinical data and is usually objective. For instance, given a fixed MCDA model in which the criteria, the value functions of each criterion, and the weights of each criterion are settled, the variability of the overall benefit-risk profile can be affected by the data extracted from clinical trials and the variation in the clinical data [26]. For instance, the instinct variation or different data pooling strategies in an integrated analysis will obviously affect the variability of the data. The first type of uncertainty usually can be quantified by a deterministic sensitivity analysis in which different value functions or weights of the criteria are used to see how the overall benefit-risk balance may change because of varied MCDA model setting. To quantify the second type of uncertainty, probabilistic modeling may be used to incorporate the variability of clinical data into the MCDA model.

In this article, we propose two probabilistic approaches (the δ-method approach and the Monte-Carlo approach) to incorporate the variability of clinical data into the MCDA modeling. The merit of the δ-method approach is that it provides a closed-form solution to quantify the variability by imposing an asymptotically normal distribution to the overall benefit-risk score from the MCDA model. Compared with simulation-based methods, the δ-method approach based on a known distributional form of the overall benefit-risk score is much simpler and less computationally intensive. However, the Monte-Carlo approach proposed in this article is one type of simulation-based method. It uses a unified multivariate normal sampling scheme to sample from the parameter space of the criteria in the MCDA model so that the correlation structure of the criteria in the MCDA model could be preserved. In addition, the Monte-Carlo approach could assemble the true distribution of the overall benefit-risk score, which, in turn, would enable the computation of any desired probabilistic/statistical measures to compare the benefit-risk profile of different treatment options. In the Results section, the proposed methods were applied to a case study, and a discussion on the performance of the proposed methods appears in the Discussion and Conclusion section.

Methods

The δ–Method Approach

Without loss of generality, we use the weighted summation form of the MCDA as [13, WP3] follows:

$$s = \sum w_i f_i(\mu_i) \tag{1}$$

where s is the overall benefit-risk score of a certain treatment option. Usually, the higher the score, the better the benefit-risk profile of the treatment. w_i is the weight of the ith criterion, $f_i(\mu_i)$ is the corresponding value function transforming μ_i into a unified scale, and μ_i is the true clinical mean effect (parameter), such as the reduction in blood pressure from baseline to final, the response rate, or the chance of a certain adverse drug reaction for the corresponding treatment option. Usually, the true μ_i is unknown but can be substituted by its estimator, $\hat{\mu}_i$. Thus, an estimator of s can be defined by

$$\begin{aligned} &\hat{s} = \sum w_i f_i(\hat{\mu}_i) \\ &\hat{s} \sim AN(s, \nabla s' \Gamma \nabla s) \end{aligned} \tag{2}$$

According to the central limit theorem and with sufficiently large sample size, using the δ-method [27], $\hat{s}$ in Equation 2 is asymptotically normal, with $E(\hat{s}) = s$ and $\text{var}(\hat{s}) \approx \nabla s' \Gamma \nabla s$, where ∇s is the gradient vector of s with respect to μ_is and Γ is the variance-covariance matrix of μ_is. In practice, s is estimated by $\hat{s}$ and $\text{var}(\hat{s})$ is estimated by $v \approx \nabla \hat{s}' \hat{\Gamma} \nabla \hat{s}$, where $\nabla \hat{s}$ is ∇s evaluated at $\hat{\mu}_i$s, and $\hat{\Gamma}$

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