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Periodic benefit-risk assessment using Bayesian stochastic multi-criteria acceptability analysis

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ABSTRACT

Benefit-risk (BR) assessment is essential to ensure the best decisions are made for a medical product in the clinical development process, regulatory marketing authorization, post-market surveillance, and coverage and reimbursement decisions. One challenge of BR assessment in practice is that the benefit and risk profile may keep evolving while new evidence is accumulating. Regulators and the International Conference on Harmonization (ICH) recommend performing periodic benefit-risk evaluation report (PBRER) through the product's lifecycle. In this paper, we propose a general statistical framework for periodic benefit-risk assessment, in which Bayesian meta-analysis and stochastic multi-criteria acceptability analysis (SMAA) will be combined to synthesize the accumulating evidence. The proposed approach allows us to compare the acceptability of different drugs dynamically and effectively and accounts for the uncertainty of clinical measurements and imprecise or incomplete preference information of decision makers. We apply our approaches to two real examples in a post-hoc way for illustration purpose. The proposed method may easily be modified for other pre and post market settings, and thus be an important complement to the current structured benefit-risk assessment (sBRA) framework to improve the transparent and consistency of the decision-making process.

1. Introduction

Benefit-risk (BR) assessment is essential to ensure the best decisions are made for a medical product in the clinical development process, regulatory marketing authorization, post-market surveillance, and coverage and reimbursement decisions. However, to reach a consensus on the evaluation of benefit and risk is a challenging and complex process as it involves various stakeholders, different data sources, and exhibits dynamic nature as new information continues to emerge. To this end, the structured BR assessment framework has evolved rapidly in the last few years, as evidenced by a large number of regulatory and industry-wide initiatives on structured BR assessment [1–3]. Although it has been widely acknowledged that structured BR assessment is mainly based on a qualitative and descriptive BR framework, quantitative approaches play an important role in order to complement qualitative frameworks by providing objectivity and transparency on the impact of weighting and uncertainty when assessing the BR profile of a medical product [2].

2. Literature review and motivations

A recent systematic review by Mt-Isa et al. [4] identified multi-criteria decision analysis (MCDA) to be among the most promising methods for conducting a quantitative BR assessment, and the method was also highlighted by regulators [1]. The debut of MCDA for the BR assessment of new drugs was provided by Mussen et al. [5]. The principle of the method is to compare drugs using utility scores calculated from multiple criteria of benefits and risks, taking into account their relative importance according to the preferences (a.k.a. weights) of the decision makers. However, in its standard implementation, the impact of uncertainty of criteria and preference on the choice of optimal decision was not considered. Tervonen et al. [6] proposed to use a stochastic multi-criteria acceptability analysis (SMAA) approach for evaluating a drug benefit-risk profile which can account for both variations inherent in criterion measurements and lack of preferences information. Waddingham et al. [7] proposed a Bayesian MCDA model to estimate the distribution of the criterion via synthesizing the evidence observed in previous studies. To mitigate the high degree of uncertainty in the

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results of SMAA, Saint-Hilary et al. [8] proposed a simple way to control the weight space of SMAA in benefit-risk assessment. Each of the above approaches has its own advantage of incorporating different sources of uncertainty in BR assessment. However, how to combine these advantages in a real working procedure of BR assessment in the pharmaceutical industry still needs more researches.

One additional challenge of BRA in practice is that the benefit and risk profile may keep evolving while new evidence is accumulating. For example, it is recommended by regulators and the International Conference on Harmonization (ICH) to perform periodic benefit-risk evaluation report (PBRER) through the product's lifecycle for such consideration [13–16]. In (ICH) E2C (R1) guideline [16], it is stated that meta-analyses or pooled analyses could be performed to summarize all available information from any other clinical trial sources in addition to those clinical trials or no-interventional studies completed or still ongoing during the reporting period, such as randomized clinical trials, and safety information from co-development partners or investigator-initiated trials. However, methods and examples of implementing an integrated benefit-risk analysis are rare in literatures, especially those in a quantitative way. How to integrate all the cumulative clinical trial data sources together in a quantitative way to perform a comprehensive BRA remains an open question. Therefore, a quantitative assessment method that can be applied in practice to satisfy the needs of benefit risk assessment with accumulating information during the drug development is much needed.

In this paper, we propose a general statistical framework that could be used for the quantitative benefit risk assessment in which Bayesian meta-analysis and stochastic multi-criteria acceptability analysis (SMAA) will be combined to synthesize the accumulating evidence from early stages of the clinical development to late stages. Specifically, we first adopt a Bayesian approach to conduct a cumulative meta-analysis (CMA) based on the summary level data to get the posterior distribution of the criteria values from the selected benefit and risk endpoints across multiple studies. Then the SMAA approach is used to perform the BR assessment based on the synthesized benefit and risk evidence from the cumulative meta-analysis. The proposed framework is a dynamic process in which the posterior distribution is updated whenever a new clinical trial or another new data source regarding the medical product becomes available for inclusion. The proposed approach aims to systematically assess the benefit-risk balance across the lifecycle of a medical product. Therefore, the approach is ready to be modified as needed to address all stakeholders' requirements in both pre and post market setting.

The remaining of the paper is organized as follows. We first introduce a two-step approach for periodic BRA based on Bayesian evidence synthesis and the SMAA method in Section 3. The details of the proposed method are then illustrated in Sections 4 and 5. Section 4 describes the Bayesian meta-analysis as the first step and Section 5 describes the SMAA as the second step. Next, we show how to apply the proposed method for periodic BRA using two case studies in Section 6. Concluding remarks and discussions are presented in Section 7.

3. A general framework for periodic BRA

Fig. 1 shows the flows of the proposed framework of the periodic BRA. In a drug development program, we usually have multiple studies conducted at different stages (labeled as study 1, 2, …, K + 1). Some studies provide pivotal information on both efficacy and safety for registration (e.g. study 1 and 2); some studies may only provide the long-term safety data (e.g., study K and K + 1). Other data sources could also be included in the framework. As the first step in the process, the Bayesian meta-analysis approach will be used to synthesize different data sources together in a temporal sequence which will give the posterior distribution of the selected key efficacy and safety endpoints (a.k.a., criteria). It is repeated whenever a new data source is available, and respectively for each endpoint if the endpoints are independent. After we get the summary of each endpoint across studies, those summary data will be put into the so-called stochastic multi-criterion acceptability assessment (SMAA) framework as criteria values for ranking of the different treatments included in the drug development program. One thing worth mentioning here is that endpoints could be correlated. However, such cases may need patient-level data or correlation information, and are beyond the scope of this paper.

4. Bayesian meta-analysis for evidence synthesis

To perform the periodic benefit-risk assessment, the first step is to identify the endpoints to be included in the value tree or effect table of the sBRA as in the usual benefit-risk analysis. Thereafter, we can integrate the information from different studies to produce across-study summaries of the data for those endpoints selected. In this paper, we focus on the scenarios that the summary level data are available for each treatment arm in the comparison. In scenarios where pairwise comparisons between treatment arms are available, and where there is a need for indirect treatment comparison, different techniques such as network meta-analysis may be used.

We propose using Bayesian hierarchical models to synthesize the evidence across all trials for each treatment group respectively, for its flexibility and ease to implement [12]. Without loss generality, we consider the count type data first. For treatment arm i in study k, and the selected endpoint j, the number of patients having an event is denoted by Y_{ijk}, where $i = 1, \ldots, I$; $j = 1, \ldots, J$; and $k = 1, \ldots, K$. The outcomes Y_{ijk} are assumed to follow independent binomial distributions

$$Yijk \sim \mathrm{Bin}(n_{ik}, p_{ijk}) \tag{1}$$

where the total number of patient n_{ik} in arm i and study k is known. For different treatment arm i and endpoint j, the probabilities of the event p_{ijk}'s are assumed to be independent and come from the same prior distribution across studies. This is equivalent to assuming that each study has its own independent population which is a sample of the overall population. In the hierarchical model, we use a link function to transfer the probabilities p_{ijk} onto the *logit* scale as

$$g(p_{ijk}) = logit(p_{ijk}) = log\left(\frac{p_{ijk}}{1 - p_{ijk}}\right) = \theta_{ijk}$$

After transformation, the parameter of log odds ratio is assumed to follow a normal prior distribution as

$$\theta_{ijk} \sim N(\mu_{ij}, \sigma_{ij}^2) \tag{2}$$

Note that u_{ij} and ${\sigma_{ij}}^2$ are parameters across the K studies for treatment i and endpoint j. We use a non-informative or weak hyper-prior distribution $p(\mu_{ij}, {\sigma_{ij}}^2)$ for these parameters, to represents the lack of information about the effect at the (overall) population level before the current data are available. For example, $u_{ij} \sim N(0, 10^4)$, and ${\sigma_{ij}}^2 \sim Gamma$ (0.001,0.001), where $i = 1, \ldots, I$; *and* $j = 1, \ldots, J$.

In this paper, we consider the three most common data types and their corresponding metrics: continuous data (e.g., change from baseline for an efficacy endpoint), binary data (the metric is percentage, e.g., the proportion of subject meeting an efficacy endpoint or having a safety event among the population of interest), and Poisson count data (the metric is exposure adjusted incidence, e.g., the rate of subjects experiencing a safety event in one patient year). The link functions allow us to model different data types with minimal changes of the above model. Table 1 lists the likelihood and link functions to be used in the Bayesian hierarchical model for different data types.

When data are accumulating after the completion of each relevant study, cumulative meta-analysis can be used to update the posterior distribution of the criteria measurement for each endpoint. In the Bayesian framework, cumulative meta-analysis is a natural process for updating across study summaries in a chronical way. Essentially, the information from earlier studies is utilized to form a prior distribution