Incremental Benefit of Treatment: a willingness-to-pay approach

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Abstract

Several health technology assessment (HTA) methods try to perform the quantitative assessment by combining benefits and risks data to derive a statistic for regulatory or clinical decision making. For example, comparisons between *NNT, NNH, Benefit-Risk Ratio, Benefit-Less-Risk Analysis*, and *Global Benefit-Risk*, etc., as described in the PROTECT Work Package [1]. Some methods combining benefits and risks data without taking into account their relative importance from either clinical or users' perspectives, or use relative weighting without sufficient justifications. In this research, we combine benefit and risk data with a parity weight which represents the users' willingness-to-pay for the amount of risk given one unit of benefit received. The quantity estimated from this procedure can be used for regulatory and clinical decision making.

Keywords: willingness-to-pay, benefit-risk, health technology assessment, clinical trial.

1 Introduction

Several health technology assessment methods try to perform the quantitative assessment by combining benefits and risks data to derive a statistic for regulatory or clinical decision making. For example, comparisons between *NNT, NNH, Benefit-Risk Ratio, Benefit-Less-Risk Analysis*, and *Global Benefit-Risk*, etc., as described in the PROTECT Work Package [1]. Some methods combining benefits and risks data without taking into account their relative importance from either clinical or users' perspectives, or use relative weighting without sufficient justifications.

In econometrics and cost-benefit research, the concept of willingness-to-pay is a common metric to evaluate the relative merits of cost and benefit in choice selection. However, this metric was rarely used in the evaluation of benefit-risk trade-off for medical products.

In this research, we combine benefit and risk data with a parity weight which represents the users' willingness-to-pay for the amount of risk given one unit of benefit received. Willingness-to-pay is an aggregated measure from the users' perspectives. It varies according to various perspectives and value the product offers. It is a subjective measure, however, some kind of aggregated measure can be estimated with large sample to provide some useful reference metric.

In the following, we describe how this metric can be used for benefit-risk analysis to compare medical products. We also develop procedures for the statistical inferences so that it can be used for clinical or regulatory decision making purposes.

2 Benefit-Risk Assessment of Treatment Effect

HTA assessment can be for one product only if the product is the first in its class for certain treatment, or it can be for multiple products to compare the relative merits of the products in their perspective treatments. In this section, we will discuss two cases, one for a single product for treatment and the other for multiple (specifically, for two) product for treatments.

§ **The case of one treatment:**

Let ρ_i be the quantity of willingness-to-pay of risk for one unit of efficacy for treatment i, namely,

$$\rho_i = \{\text{units of acceptable risk}\}/\{\text{one unit of efficacy}\}.$$

Denote the quantity of efficacy and risk of treatment i as (E_i, R_i), then one can compare the amount of differential risk a patient received given the amount of efficacy E_i with the amount of risk R_i actually received due to the treatment by considering the following quantity

$$\Delta_i = \rho_i \times E_i - R_i \quad \text{or} \quad \frac{\Delta_i}{\rho_i} = E_i - R_i/\rho_i,$$

which can be considered as the net benefit of the treatment after adjusting for the amount of risk.

§ **The case of two treatments:**

Let $\rho_{ijk}, i \in \{1, 2\}$ be the quantity of willingness-to-pay of jth risk for one unit of the kth efficacy for treatment i, namely,

$$\rho_{ijk} = \frac{\text{units of risk } j \text{ received from treatment } i}{\text{one unit of efficacy } k \text{ received from treatment } i}.$$

Denote the difference of the quantity of j-th efficacy and k-th risk between treatment 1 and 2 as $(E_{1j} - E_{2j}, R_{1k} - R_{2k})$, then one has the incremental net

benefit (INB) of treatment 1 over treatment 2 for the j-th efficacy and k-th risk as

$$\mathrm{INB}(\rho_{jk})_{12} = (E_{1j} - E_{2j}) - (R_{1k}/\rho_{1jk} - R_{2k}/\rho_{2jk}). \tag{1}$$

Since clinical trial usually collects multiple efficacy and safety endpoints, it is a common practice to evaluate the effectiveness of a treatment by considering the endpoints jointly via a multi-criteria decision analysis and weighting the endpoints relative to their clinical relevance and importance. Assuming P efficacy endpoints and Q safety endpoints are under consideration for the treatment evaluation, with weights

$$\sum_{p=1}^{P} w_p + \sum_{q=1}^{Q} w_q = 1,$$

then equation (1) can be extended into

$$\begin{aligned}\Omega &= \sum_{p=1}^{P}\sum_{q=1}^{Q} \mathrm{INB}(\rho_{pq})_{12} \\ &= \sum_{p=1}^{P}\sum_{q=1}^{Q} \Big\{ w_p(E_{1p} - E_{2p}) - w_q(R_{1q} - R_{2q})/\rho_{pq} \Big\}. \end{aligned} \tag{2}$$

If the treatment evaluation is based on the point estimate of equation (2) without considering the variations of the endpoints and the subjectivity of ρ's, then one can conclude that treatment 1 is better than treatment 2 if equation (2) is greater than 0.

However, in order to perform a rigorous statistical inference, one needs to consider the variations and the correlations among the endpoints. Let

$$A = \sum_{p=1}^{P} w_p(E_{1p} - E_{2p})$$

and

$$B = \sum_{q=1}^{Q} w_q(R_{1q} - R_{2q})/\rho_{pq},$$

and assuming that they have joint normality, then

$$\hat{\Omega} \sim N(\Omega, \Sigma_\Omega)$$

where $\Sigma_\Omega = (\sigma_A^2 + \sigma_B^2 + 2\sigma_{AB})$ being the variance of $\hat{\Omega}$.

The $100(1-\alpha)\%$ confidence interval for $\hat{\Omega}$ can be estimated as

$$\big(\hat{\Omega} - z_{1-\alpha} \times \hat{\Sigma}_\Omega^{1/2} \le \Omega \le \hat{\Omega} + z_{1-\alpha} \times \hat{\Sigma}_\Omega^{1/2}\big)$$

and the superiority, inferiority, or indifference between treatment comparison can be concluded depending on whether the interval include or exclude 0.

§**A few points to note:**

One needs to be cautious when using the procedures described here. Often the summary data is shown in tabular format, in that case, the Σ_Ω may not be readily estimable. In addition, the normality assumption may not be plausible due to the nature of data, especially, if some endpoints are discrete. In that case, the confidence interval can be better estimated empirically using, e.g., bootstrap methods. The values for weights and willingness-to-pay may be subjective even if they are obtained from subject experts. To overcome these issues, patient-level data is needed to estimate the covariance, and sensitivity analysis is needed for various combinations of weights and willingness-to-pay so that one can evaluate how sensitive the results are to the assumptions.

3 Example of an oncology clinical study

Data from a recent clinical trial is used below to illustrate the implementation of the procedures described above. This data is from a hematology study of sample size about 700 subjects. Patients were treated with an experimental drug to compare with the control treatment. Various types of data were collected during the study.

The primary efficacy endpoint (for benefit) is treatment response. Patients started with a stable disease status (SD) and, after treatment, the disease status could improve to complete response (CR) or partial response (PR), or deteriorate to progression disease (PD) or not evaluable (NE). For the analysis purpose, we define a new variable: *cpr =1 if CR/PR and 0 otherwise.*

Since the serum level changes from baseline is an important indicator of the treatment effect, therefore, it is selected as the second benefit variable and is defined as: *serumchg = 1 if >50% reduction, 0 otherwise.*

To select the variables for the risk consideration, the gastrointestinal (GI) and infection (INFC) adverse effects are selected since these two are the most commonly occurred among all the serious adverse events under this type of treatment. We define the variables: *gi34 =1 if the grade of GI adverse event is* ≥ 3 *and 0 otherwise.* Likewise, we also define the variable: *infc34 =1 if the grade of infection is* ≥ 3 *and 0 otherwise.*

The covariance matrix of these selected efficacy and safety variables is estimated and shown below for each treatment group:

```
[1] "Covriance matrix of Group 1"
                 cpr    serumchg        gi34     infc34
cpr      0.250692119 0.053357584 0.006261267 0.01116244
serumchg 0.053357584 0.250257533 0.005625483 0.02657417
```

```
gi34     0.006261267 0.005625483 0.117821272 0.02348378
infc34   0.011162439 0.026574169 0.023483775 0.20483518

[1] "Covriance matrix of Group 2"
                 cpr      serumchg          gi34       infc34
cpr      0.161823362  4.256410e-02 2.083842e-03  0.004167684
serumchg 0.042564103  1.120879e-01 7.326007e-05 -0.002710623
gi34     0.002083842  7.326007e-05 8.074888e-02  0.010069190
infc34   0.004167684 -2.710623e-03 1.006919e-02  0.145852666
```

For the relative weights and willingness-to-pay index among all the benefit and risk variables, after consulting with the subject experts, the following numbers are assumed. As mentioned previously, the weights can be subjective and sensitivity analysis to perturb the weights is important to understand how the overall estimate of the benefit-risk merits (INB) can be affected due to various sets of weights. The results are shown below, with INB of treatment 1 relative to treatment 2 being approximately equal to 0.886, and also presented graphically in Figure 1.

```
Weight for each variable: cpr (0.5)
                          serumchg (0.25)
                          gi34 (0.1)
                          infc34 (0.15)

Willingness-to-pay is rho11 (gi34 vs. cpr) = 1.2
                      rho12 (infc34 vs. cpr) = 1.2
                      rho21 (gi34 vs. serumchg) = 0.8
                      rho22 (infc34 vs. serumchg) = 0.8

[1] Original weighted score of treatment 1 = 1.168592
[1] Original weighted score of treatment 2 = 0.2822899
```

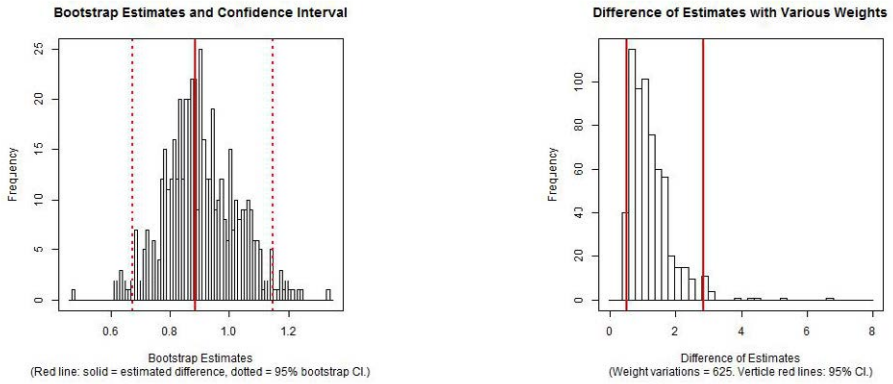

Figure 1: Estimated INB and confidence interval (left) with sensitivity analysis (right)

The left panel of Figure 1 shows the original estimate of the INB between the treatments. The red solid vertical line indicates the estimate, the two dotted lines are the 95% confidence interval of the bootstrap samples. The right panel of Figure 1 shows the distribution of the INB after sensitivity analysis with more than 500 combinations of the various weights. The two red vertical lines are the 95% confidence interval of the values of INB produced by the sensitivity analysis.

4 Summary

Incremental treatment benefit after considering the multi-dimensional information collected (or not collected) in a trial is an important consideration for regulatory approval of drug marketing and pricing. It is also an important consideration for planning the drug development program. Due to the high cost of drug and drug development, careful consideration of these dimension of data will greatly help to target the potential products with high value and reasonable cost-effective ratio. Patient's perspective in treatment benefit used to not been considered as critical, however, it is getting more and more attention in the evaluation of the overall merit of treatments, especially in the setting of personal medicine nowadays. We propose a method using patient's willingness-to-pay to assist the overall assessment of benefit and risk, which not only fits into this line of consideration but also can be useful in decision making for all stakeholders. Since most of the assessment involves certain subjective factors, decision makers need to collaborate with subject experts from various disciplines and take into account of this subjectivity to derive a fair decision.

References

[1] Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium. *Protect: Review of methodologies for benefit and risk assessment of medication.* Version 4 Date: 14 Feb 2012.