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Benefit - Risk Analysis for Oncology Clinical Trials

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ABSTRACT

The conventional analysis of safety and efficacy of clinical trials provide information on risks and benefits in isolation. In the opinion of the authors, this hampers a comprehensive assessment of benefit-risk and leads to underestimate or overestimate the treatment benefit for patients with varying risks.

To some extent the regulatory authorities evaluate the risks and benefits of any new drug therapy during the new drug-approval process. However, quantitative benefit-risk (B-R) assessment is not typically performed, nor is it presented in a consistent and integrated framework when it is used [1].

Integrated analysis of benefit (efficacy) and risk (safety) of cancer drugs is challenging due to complexities in the disease biology and complexities associated with treatment(s) regimens. Nevertheless, we have demonstrated a simple and efficient way to accomplish a benefit-risk analysis by combining efficacy parameters with a score based on a risk index. The methodologies present can be applied on both time to event and binary outcomes that are commonly found in oncology trials.

The proposed benefit-risk analysis provides useful information to all the stakeholders of the tested drug to make informed decisions and hence far more superior to conventional safety and efficacy reporting as well as to some of the existing methods such as Number Needed to Treat (NNT) where there are no details provided to identify different patient subpopulations with varying risks and benefits.

BACKGROUND

Benefit-risk assessment is becoming an integral part of the drug evaluation by the sponsor, the regulatory agencies and reimbursement bodies and other stakeholders. The Food and Drug Administration (FDA) and The European Medicines Agency (EMA) require special management for some products to assure that the treatment benefits outweigh risks in the clinical setting [2].
The FDA is currently developing a structured benefit-risk framework which should be released by December 31, 2012 [4] and EMA has already issued four white papers on benefit-risk [3].

The approaches for assessing benefit-risk can be distinctly classified as quantitative and qualitative methods. The Center for Drug Evaluation and Research (CDER) has found that quantitative analysis risks obscure subjective expert judgment and they prefer a structured qualitative approach where analysis is used to aid rather than replace expert judgment [4]. Most of the frameworks do not integrate the benefits and risks, but assess them separately. This may lead to underestimation or overestimation of the treatment benefit for patients with varying risks. This paper proposes a methodology to integrate the risks when assessing the treatment benefit. The framework can be used as an aid to inform regulatory about the benefit-risk of a medicinal products.

In this paper, benefits are defined as any beneficial effects such as clinical response, Progression Free Survival (PFS), Patient Reported Outcomes (PROs) and Overall Survival (OS) for the target population that are associated with the product. The risks are any detrimental effects that can be attributed to the product or that are otherwise of concern for their undesirable effect on patients' health such as cardiac toxicity, neutropenia and rash [3].

The approach in this paper follows a similar framework as the PrOACT, developed by Hammond, Keeney and Raiffa [5]. The following explain the frame work (**Figure 1**):

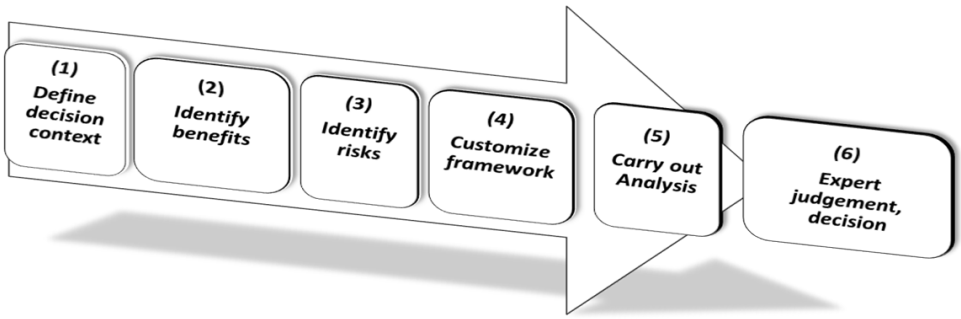

Figure 1 - Framework for Assessment

Step 1: Define decision context (Problem)

It is the initial step of identifying the objectives of the analysis and critical decision criteria such as various tolerance limits and how they would be defined.

Step 2 & 3: Identify benefits and risks (Objectives)

(A) Identification, Indexing and Classification of Risks

Risk of cancer treatment depends on different factors such as patient's demography, medical history, chosen therapy, co-morbidities and co-medications to name but a few. The proposed index based system will rank the risks in order of importance, giving each risk a score. From this created index, we can classify patients as being either exposed to high or low risk using a pre-determined cut-off.

(i) Identifying Risks

A risk of a therapeutic intervention is a function of many different parameters deriving from the biology of disease, stage of disease, characteristics of the patients and also the chemistry of the therapeutic regimen. Hence, different expertise is required in identifying the important risks up front and documenting in the analysis plan. Different risks and their inter-relationships associated with Oncology drugs are shown (**Figure 2a & Figure 2b)**.

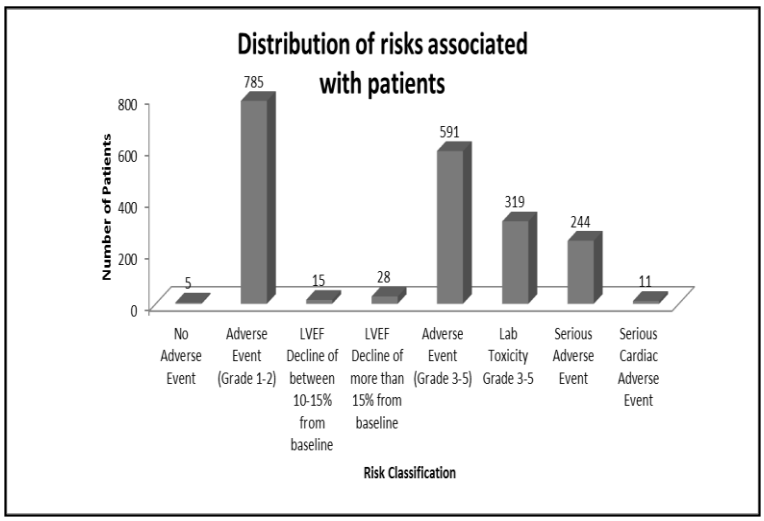

Figure 2a - Bar chart showing the distribution of the number of patients with associated risks.

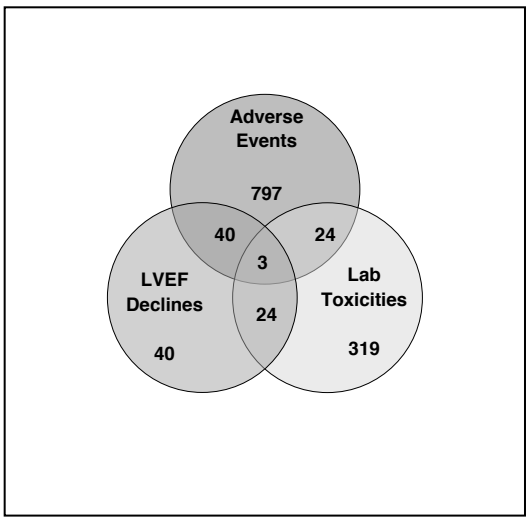

Figure 2b - Venn diagram showing the overall relationship of potential safety risks amongst patients

A broad category of adverse events as shown below would be expanded in to a detailed list with the help of clinical experts before indexing them. It will consider the time to a given event as well as its frequency to compose a comprehensive list or risks.

- Adverse Events (Grade 1-4, serious, related, special interest)
- Cardiac toxicities (measured as Left Ventricular Ejection Fraction (LVEF) and Congestive Heart Failure (CHF))
- Lab Toxicities

(ii) Risk Index

From an exhaustive list, each risk factor is ranked in the order of importance and provides a score. The score is directly proportional to the importance of the risk under a given therapeutic intervention.

Table 1 –Example risk index developed to quantify risks of HER2 positive breast cancer

Safety Risk	Index Score
No Adverse Event	0
Adverse Event (Grade 1-2)	1
Adverse Event (Grade 3-5)	5
Lab Toxicity Grade 3-5	15
Serious Adverse Event (Other than cardiac)	20
LVEF Decline of between 10% - 15% from baseline with an absolute value of less than 50%	20
LVEF Decline of more than 15% from baseline with an absolute value of less than 50%	30
Serious Cardiac Adverse Event	30

(iii) Cumulative Scoring System

Using the risk index each patient will be scored and the cumulative score depending on the number of events experienced by the patient will be calculated. The following table shows a few hypothetical patients experiencing different risks and his/her's cumulative risk score. In this example, each patient is scored only once despite may have had multiple events.

Table 2 – Example of how each individual patient are scored for risks

Patient No.	No AE	AE Grade 1-2	LVEF <50% drop between 10-15%	LVEF <50% drop more than 15%	AE Grade 3-5	Lab Toxicity Grade 3-5	Serious AE	Serious Cardiac AE	Total Score
1		Y	Y				Y		21
2	Y								0
3		Y		Y	Y	Y	Y	Y	101
4		Y			Y		Y		36
5					Y	Y	Y		40

(iv) Risk Classification

The derived risk score can be either used as a continuous variable or as a categorical variable to combine with efficacy for the statistical analysis. The choice depends on the type of statistical analysis designed for efficacy analysis. For example, if the efficacy endpoint is time to event and analysed using Cox regression, the risk can be modelled as a continuous variable. However, its' interpretation may sometimes be clinically challenging.

However, the work presented is transforming the continuous risk score to a binary, dichotomous variable (**Table 3**) based on the 25th percentile of the risk index. Any risk that falls under the 25th percentile is classified as a low risk and vise-versa.

Table 3 –Risk classification of the patients in Table 2.

Patient No.	Total Score	High / Low Risk Classification [*]
1	26	Low
2	0	Low
3	91	High
4	36	Low
5	100	High

*** Based on the 25th Percentile which is equal to 30**

The results of this safety profiling enables analysis to be combined with typical oncology efficacy endpoints depending on the type of analysis being performed. This enables us to have a measure to be able to roughly quantify the safety of the treatment, in combination with the efficacy to determine whether the benefits, outweigh the risks involved with exposure to the treatment.

From the index scale proposed (**Table 1**); these patients can be divided into either a high or low risk category depending on the number and type of risks a patient has been exposed to (**Figure 3**).

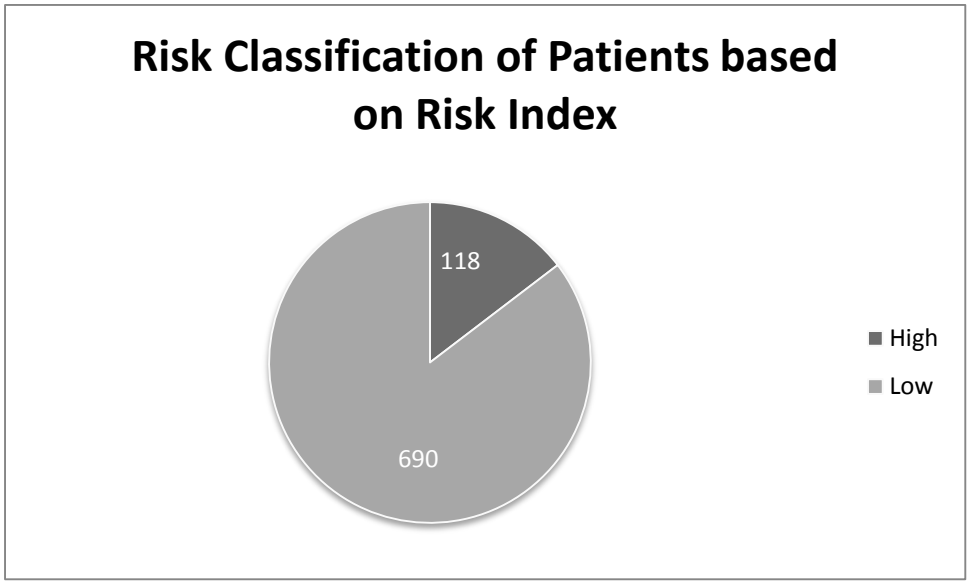

Figure 3 – Pie chart showing the overall classification of patients risk category based on the proposed Index system.

(B) Identification, indexing and classification of benefits

There are numerous efficacy (benefit) endpoints in Oncology trials – broadly categorised into two classes as time to event and binary outcomes such as pathological complete response.

Time to event: The ultimate benefit being time to survival, but there are other numerous other intermediary time to event endpoints too. PFS is widely used to assess medium term treatment benefit and measured as time to progress based on tumor growth. There are a few variants of the PFS definition, such as investigator assessed PFS, Independent Review Facility (IRF) assessed PFS and progression including all-cause death or progression including cancer related death etc. Based on these standard definitions one can also derive other benefit classes (high/low).

An example used in this paper is defined as follows:

High benefit = if patients PFS duration is greater than the median PFS of the control arm.
Low benefit = if patients PFS duration is less than or equal to the median PFS of the control arm.

Binary endpoints: Pathological complete response is a classic example of a binary efficacy measure in oncology applicable to solid tumors. However, it has its variations defined by many different academic and regulatory institutions around the world. A few to mention are: complete response on primary lesion, complete response on primary lesion and no invasive disease, complete response on the primary lesion and no residual disease in lymph nodes and so on.

Similarly, a binary endpoint can be derived using a continuous endpoint by applying a cut-off. In many non-solid tumor cancers like Leukaemia, the treatment benefit will be measured directly using a surrogate on a continuous scale and then converting it to a binary endpoint for the final analysis.

Treatment benefit is an open topic to clinicians, statisticians and regulators – they can be innovative in deriving suitable benefit indexes and classifications to assess the therapeutic value of a given drug. It is important to define clearly how benefit will be assessed in the statistical analysis plan upfront.

Step 4: Customise the framework

Definition of risk and benefit differs with the disease setting and therapeutic intervention in question. Hence, for each analysis the decision frame work need to be customized. It is important that this frame work is developed with the aid of the specialist in statistics, biology, chemistry, and regulatory to ensure final outcome provides value to address the objectives of the analysis.

Table 4 illustrates an example frame work that may help to extract benefit-risk information. Edwards, et al [6] have suggested a similar approach but using three states High, medium and Low instead of the two used in here. From a similar 'consequence tables' we can identify patient categories that have got a net benefit or harm from the treatment. This may be sufficient for simple benefit/risk decisions but other rigorous methods might need to be used for complex analysis.

Table 4 – Customised benefit-risk framework

	Benefit	
Risk	**Low**	**High**
Low	Low risk, Low benefit (No effect)	Low risk, high benefit (Super Responders)
High	High risk, low benefit (should avoid)	High risk, high benefit (Need B-R analysis)

Step 5: Carry out the analysis

Integrated safety and efficacy statistical analysis can be performed in different ways depending on the primary efficacy analysis. If the primary efficacy analysis is based on a regression model the safety or risk can be included as a covariate or can be used to subset the population and model efficacy for different risk classes separately.

All time to event endpoints can be analysed using Cox regression and risk can be modelled as a covariate in the proportional hazards model. A significant p-value implies whether the risk variable can significantly contribute to the model. Further interpretation of the risk in the model follows as any other covariate in the model using regression parameters. Further, model fit statistics such as Akaike Information Criterion (AIC) or log likelihood values can be used to test the model, both with and without risk to evaluate the impact of risk factors on the integrated approach.

The current analysis based on time to event endpoint (IRF-PFS) adopts three statistical approaches to evaluate the benefit-risk of a new antibody therapy against the standard of care.

a) Kaplan-Meier (K-M) approach by the risk classes (**Figure 4a, 4b & 4c**)
b) Cox regression
c) Contingency tables which can be extended for chi-square test or Cochran-Mantal- Haenszel (CMH) test (**Table 5a & 5b**).

(i) Kaplan-Meier (K-M) approach by the risk classes

The Kaplan-Meier plots show the benefit measured as the median PFS between the test arm and control arm. An overall PFS advantage of approximately 15.4 months can be seen (**Figure 4a**). However, for high risk patients, a PFS advantage of over 20 months can be seen (**Figure 4b**), compared to low risk patients showing a PFA advantage of less than 15 months (**Figure 4c**).

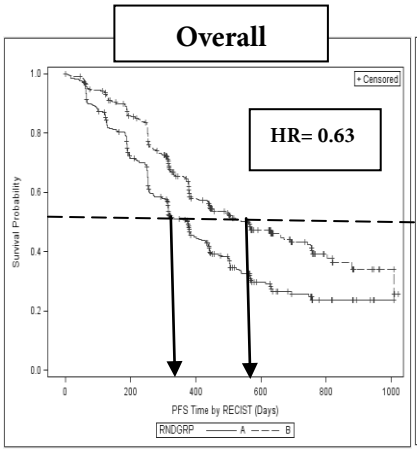

Figure 4a

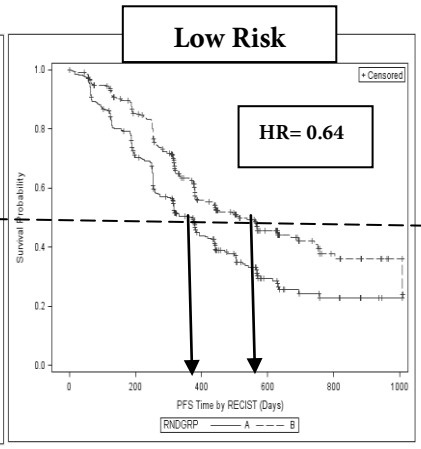

Figure 4b

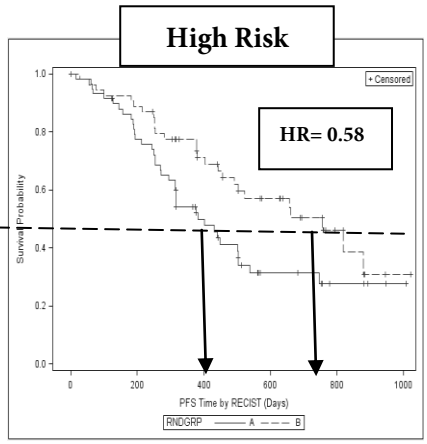

Figure 4c

(ii) Risk Adjusted Time to Event Analysis

The risk adjusted Cox model shows there is a discernable difference between the low and high risk groups. Low risk patients had relatively low benefits while high risk patients had relatively higher benefits in terms of HR.

A PFS advantage for the test arm (HR=0.63) has been demonstrated for the overall study population (**Figure 4a**). The majority of the patients (690/808) showed low risks and the benefit was comparable to the overall population (**Figure 4b**). When the benefit is weighed against the risks, the high risk subgroup showed a substantially greater benefit (HR=0.58, n=118/808) striking a balance between risks and benefits (**Figure 4c**).

(iii) Risk adjusted frequency analysis (contingency table approach)

For this analysis the benefit was derived as described in Step 2 & 3 (B).

High benefit = if patient's PFS duration is greater than the median PFS of the control arm.
Low benefit = if patient's PFS duration is less than or equal to the median PFS of the control arm.
The median PFS for the control is obtained from the K-M analysis (376 days).

Table 5a

Test Arm		Benefit*		
Risk		Low	High	Total
Low	N	183	164	347
	Risk %	52.70%	47.30%	
	Benefit %	91%	81.60%	
High	N	18	37	55
	Risk %	32.70%	67.30%	
	Benefit %	9%	18.40%	
Total		201	201	402

Table 5b

Control Arm		Benefit*		
Risk		Low	High	Total
Low	N	216	127	343
	Risk %	63%	37%	
	Benefit %	84.70%	84.10%	
High	N	39	24	63
	Risk %	61.90%	38.10%	
	Benefit %	15.30%	15.90%	
Total		255	151	406

* The derived benefit index was then combined with the risk index to work out the frequencies for the decision frame work discussed in Step 4.

According to **Table 5a & b**, patients who faced high risks ranged from 14% [(18+37)/402] - 16% [(39+24)/ 406] of the total study population. However, 67% of the patients with high risk in the test arm received high benefits while the 38% of the same in the control arm received only high benefits.

Only 18% of the patients in the test arm, whose PFS is beyond the median PFS of the control arm (High Benefit) had a High Risk while patients with Low Benefit in terms of PFS duration only 9% were exposed to High Risks (**Table 5a**). In contrast, 62% of the patients with high risk in the control arm received lower benefit. However, 84% of the patients who received higher benefit with control treatment were faced with low risks.

The best scenario, low risk and high benefit rate is 41% **[164/402]** for the test arm, while it is 31% **[127/406]** for the control arm. The worst scenario, high risk and low benefit rate is 4.5% **[18/402]** for the test arm and 9.6% **[39/406]** for the control arm.

This shows that risk benefit profile is not the same for patients receiving different trial medications and objective evaluation is possible with the proposed method of B-R analysis.

Step 6: Expert judgment decision

Based on the systematic approach described, the final data will be presented to the decision makers of the sponsor as well as regulatory bodies to make an informed decision on the therapeutic intervention.

Further sensitivity analysis can be performed to fine tune either the risk or benefit indexes and evaluate the robustness of the evidence.

CONCLUSION

Integrated analysis of benefit (efficacy) and risk (safety) of cancer drugs is challenging due to complexities in the disease biology and associated treatment.

The risk and benefit indices depends on the disease setting and the drug tested and need to be pre-specified in the Statistical Analysis Plan.

Clinical and regulatory input is vital to ensure relevant safety and efficacy parameters are included in the risk and benefit indices and they are independent of each other.

The proposed B-R analysis provides useful information in an efficient manner to the stakeholders of the test drug to make more informed decisions compared to information provided by isolated safety and efficacy summaries.

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