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Benefit-Risk Analysis

A Brief Review and Proposed Quantitative Approaches

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Abstract

Given the current status of benefit-risk analysis as a largely qualitative method, two techniques for a quantitative synthesis of a drug's benefit and risk are proposed to allow a more objective approach. The recommended methods, relative-value adjusted number-needed-to-treat (RV-NNT) and its extension, minimum clinical efficacy (MCE) analysis, rely upon efficacy or effectiveness data, adverse event data and utility data from patients, describing their preferences for an outcome given potential risks. These methods, using hypothetical data for rheumatoid arthritis drugs, demonstrate that quantitative distinctions can be made between drugs which would better inform clinicians, drug regulators and patients about a drug's benefit-risk profile. If the number of patients needed to treat is less than the relative-value adjusted number-needed-to-harm in an RV-NNT analysis, patients are willing to undergo treatment with the experimental drug to derive a certain benefit knowing that they may be at risk for any of a series of potential adverse events. Similarly, the results of an MCE analysis allow for determining the worth of a new treatment relative to an older one, given not only the potential risks of adverse events and benefits that may be gained, but also by taking into account the risk of disease without any treatment. Quantitative methods of benefit-risk analysis have a place in the evaluative armamentarium of pharmacovigilance, especially those that incorporate patients' perspectives.

There are few guidelines in the medical literature for the performance of benefit-risk analysis, a fact that stands in stark contrast to expectations of regulatory agencies that pharmaceutical manufacturers generate such analyses on a fairly routine basis. Benefit-risk analysis, despite consuming substantial resources of drug companies, academics and regulators, remains a concept that is paradoxically and primarily undefined. The vast majority of such analyses are, in fact, subjective and simplistic descriptions or reviews of (mostly) clinical trials and (sometimes) epidemiological observational studies of specific drugs, with little synthesis and minor if any quantification. Cost is a factor that is occasionally introduced into benefit-risk analysis ('cost-benefit analysis'), although pharmacoeconomic considerations are explicitly not a factor taken into account by the US FDA or the European Committee on Proprietary Medicinal Products (CPMP). However, in Australia and other countries, local drug authorities are increasingly evaluating drug costs as part of their reviews of a drug's potential effect on the public health. While qualitative listings of a drug's benefits and risks, however defined, may be of use to clinicians, regulators and the public should have available a standardised, quantitative and comparable set of methods and results for

the evaluation of a drug's pre- and postmarketing experience.

The aim of this review is 2-fold: to summarise the current state of benefit-risk analysis and to propose a quantitative approach that synthesises benefit and risk in a way that allows for direct assessments of comparator drugs. For the purpose of the proposed methods, benefit-risk analysis is defined as the quantitative synthesis of drug efficacy (or effectiveness) and adverse event (AE) profile.

1. Regulatory Approaches to Benefit-Risk Analysis

Both the FDA and the CPMP are increasingly requesting benefit-risk analyses of pharmaceutical products. Regrettably, such appeals are not accompanied by suggested methods to be used in these analyses, leading to speculation and presumption and, ultimately, inconsistent and dissimilar investigations which may not address the issues at hand.[1]

1.1 US Food and Drug Administration

In the US, the FDA has established a Drug Safety and Risk Management division, which is charged with evaluating the safety, efficacy and abuse potential of drugs, as well as risk management, risk communication and spontaneous reports stemming from the use of these drugs by the public at large. Little information is available on how such assessments are made, beyond the attempt to reach a consensus through the venue of advisory and other committees. Concerning the use of professional advisory panels, a recent commentary was: "Benefit-risk analysis is more than the subjective opinion of a group of experts and is in its infancy for drug therapy."[2] Subjective assessments are not only difficult to defend, but they are difficult to modify as new information is obtained.[3] Although there is at present insufficient discussion of the point, benefit-risk analysis must be the scientific underpinning of risk management, as risk in and of itself cannot be and, in fact, is not the sole criterion on which regulatory (and clinical) decisions are made; benefit must be accounted for as well.

In a recent publication, the FDA describes its postmarketing risk identification and assessment thus: FDA relies on multiple approaches because no single approach is sufficiently comprehensive to permit full evaluation of all important problems – and then recommends analysis of spontaneous report data and use of large, population-based databases.[4] Methods, *per se*, are not described; nor are any advocated.

1.2 Committee for Proprietary Medicinal Products

The CPMP similarly offers little in the way of methods for benefit-risk studies, other than the assessment of risks (using spontaneous report data and AE data from observational studies, the literature, and sales and product usage data) and benefits and then, "[w]henever possible, both benefits and risks should be considered in absolute terms and in comparison to alternative treatments. The degree of risk that may be considered acceptable is dependent on the seriousness of the disease being treated".[5]

2. Other Approaches to Benefit-Risk Analysis

2.1 Council for International Organizations of Medical Sciences

The Council for International Organizations of Medical Sciences (CIOMS) produced a publication on benefit-risk analysis which introduces a series of subjective weighting schemes with the following: "There are no standard, widely acknowledged definitions of the terms *benefit* and *risk* as applied to medicine and particularly to medicinal products …. It is a frustrating aspect of benefit-risk evaluation that there is no defined and tested algorithm or summary metric that combines benefit and risk data … that might permit straightforward quantitative comparisons of different treatment options …."[6] Although the CIOMS approach is laudable for acknowledging the current state of affairs, few quantitative methods are proposed to allay the situation.

2.2 Medical Literature Review

In addition to the vast majority of the benefit-risk literature, which is qualitative, one can find several published quantitative and semiquantitative approaches to benefit-risk analysis.

2.2.1 Qualitative Benefit-Risk Analysis

In a study of antiepileptic drug therapy, with 'assessing risk to benefit ratio' in the title,[7] the authors acknowledge the difficulties inherent in such an appraisal but nevertheless do not present a 'ratio', a value obtained by dividing one quantity by another,[8] or any other kind of mathematical relationship between variables, and leave the final assessment to the clinician. This common practice of presenting separate lists of benefits and risks (usually adverse effects) and letting the reader do the synthesis cannot be justified as a scientific analysis because it is subjective; there are no standards against which one might make comparisons and no way to expound an argument other than to rely on anecdote. The situation is similar with other drugs used for other conditions: in published studies with the words 'benefit' and 'risk' in the title, there rarely is any quantitative analysis and rarer still is there an attempt to synthesise, (i.e. evaluate simultaneously) benefit variables with risk variables. Thus, in an article on gonorrhoea treatment with the subtitle "Does the benefit outweigh the risk?", no method for weighing benefit or risk is presented.[9] A study on the risk versus benefit of red blood cell administration is likewise lacking a quantitative analysis.[10] Examples of studies or reviews presented as benefit-risk analyses with quantification are legion and affect all fields of medicine, including vaccination,[11] cardiology,[12] rheumatology,[13] gastroenterology,[14] AIDS,[15] women's health[16] and even complementary medicine.[17]

2.2.2 Quantitative Benefit-Risk Analysis

There have been several attempts to quantify benefit-risk analysis. An early attempt by Tallarida and colleagues[18] relied on a severity scale to determine a metric that combined benefit and risk. This excellent early approach requires a survey of physicians (or patients) to generate risk preferences which are divided into seven classes and used in the determination of a quantitative synthesis of benefit and risk. Benefit is defined as probability of response and risk is derived from the survey results.

Chuang-Stein has presented several papers on the simultaneous evaluation of benefit and risk.[19,20] This intriguing approach to benefit-risk analysis is limited by unclear demarcations between benefit and risk in the models presented (e.g. one of the proposed benefit parameters includes AEs).

CIOMS offers a quantitative benefit-risk approach that relies on the "convenient but arbitrary" scoring based on a "principle of threes".[6] This method involves estimating the product of the cure rate, seriousness and duration of the disease (the 'benefit') and dividing this by the average of the products of the individual AE scores (the incidence of the AE $\times$ the seriousness $\times$ the duration). The CIOMS authors acknowledge the limitations inherent in such a method.

A recent publication on benefit-risk analysis[21] offers little beyond Chuang-Stein's approach to benefit-risk and several qualitative techniques.

Another recent book[22] presents few quantitative methods other than a linear model which includes cost, benefit and risks in terms of net worth or a net positive value.

Numerous *ad hoc* quantitative methods have been presented in the literature, many of which are interesting, although none succeed in presenting a convincing method of benefit-risk analysis that takes into account a drug's efficacy, associated AEs, patient preferences and the natural history of the underlying condition. These elements are critical to understanding the balance between a drug's positive effect on disease reduction, prevention or elimination (the benefit) and its negative effect expressed as unwanted or unanticipated adverse outcomes (the risk). All drugs embody both influences; the promise of a successful benefit-risk approach is the objective evaluation of this convergence for any particular medicinal product and its comparison with other drugs.

3. A Proposed Quantitative Approach

3.1 Overview

The quantitative approach proposed here is a rigorous effort to make benefit-risk analysis conform as closely as possible to the current scientific standards used in medical and epidemiological research. Thus, proper study design, minimisation of bias and use of appropriate statistical methods are the cornerstones to any successful method.

Commonly used approaches that do not simultaneously evaluate benefit and risk but are nonetheless useful include the cohort study, nested case-control study, proportional reporting ratio analysis[23] and meta-analysis. These designs can be incorporated into a general assessment of a drug, with the forewarning that they are quantitative methods to determine *risk* only, i.e. a quantitative synthesis of benefit *and* risk is lacking. The advantage to these methods is that they may yield risk estimates based on use of the study drug(s) in real-life situations.

3.2 Relative-Value Adjusted Number-Needed-To-Treat

Although the number-needed-to-treat (NNT) concept is not new,[24] its use in benefit-risk analysis is a contemporary development. NNT is the inverse of the absolute risk reduction due to treatment and is interpreted to mean the number of patients needed to treat to prevent one additional negative outcome, i.e. one additional case of disease. Simple NNT analysis can compare the effect of two or more drugs in this manner; the drug with the lowest NNT is considered more effective, in that fewer patients need treatment for more positive preventive outcomes. It is calculated using (equation 1):

$$NNT = \frac{1}{p_1 - p_2}$$

where p_1 is the proportion of the disease of interest in the control group and p_2 the proportion of disease in the treatment group. In epidemiological terms, p_1 and p_2 are risks associated with treatments; their difference is the absolute risk reduction.

There is a method of adjusting this NNT for a single adverse outcome,[25] although AE-adjusted NNT is useful for situations where there is only one AE of interest and the disease and AE are independent. When the independence assumption is not met, the probability of an AE in the absence and the presence of disease is different, and the model is not supported.

The goal of a quantitative synthesis of benefit and risk requires the number-needed-to-harm (NNH), calculated using (equation 2):

$$NNH = \frac{1}{q_2 - q_1}$$

where q_1 and q_2 are the risks of an AE of interest in the untreated and treated groups, respectively, and it is assumed that $q_1 < q_2$. Treatment is warranted if NNT is low enough that the benefits outweigh the risks.[26] This can be shown mathematically as follows (equation 3):

$$NNT / NNH < 1 \text{ or } NNT < NNH$$

An interpretation of equation 3 is that one needs fewer patients to be treated to prevent one additional occurrence of disease of interest (benefit) than the number of patients to be treated to have one additional AE of interest.[26]

The weakness of this method is that the importance of the AE relative to the benefit is not addressed. To take the relative importance into consideration, patients' preference can be used, and this can be accomplished by adding the relative utility value (RV) into the NNH calculation. RV can be calculated as (equation 4):

$$RV = \frac{1 - \text{utility of AE}}{1 - \text{utility of disease of interest}}$$

Utility is defined as the numeric representation of patients' preferences for specific outcomes. These are subjective assessments based on patient perspectives which are, arguably, a critical component in any sort of risk analysis.[27-29] RV can then be interpreted as the value of avoiding an AE relative to avoiding the disease of interest or target event. NNH adjusted for relative value can then be calculated as (equation 5):

Table I. Results of the relative-value adjusted number-needed-to-trea (RV-NNT) benefit risk analysis comparing three treatment groups, using six adverse events (AEs) of interest, taking into account the relative importance of each AE to improvement

		Drug A minus placebo	MTX minus placebo	Drug A minus MTX
NNT		**4**	**5**	**15**
$NNH_{RV-adjusted}$	E_1 utility = 0.40	42	70	108
	E_1 utility = 0.23	24	40	62
	E_1 utility = 0.10	11	17	27
NNT		**4**	**7**	**9**
$NNH_{RV-adjusted}$	E_2 utility = 0.40	42	70	108
	E_2 utility = 0.23	24	40	62
	E_2 utility = 0.10	11	17	27
NNT		**6**	**19**	**9**
$NNH_{RV-adjusted}$	E_3 utility = 0.40	42	70	108
	E_3 utility = 0.23	24	40	62
	E_3 utility = 0.10	11	17	27

E_1 = ACR20; **E_2** = ACR50; **E_3** = ACR70; ACR is the American College of Rheumatology criteria for improvement, where ACR20 is a 20% improvement in a set of clinical and laboratory measures of inflammatory responses; similarly ACR50 and ACR70 represent a 50% and 70% improvement; **MTX** = methotrexate: **NNH** = number-needed-to-harm; **NNT** = number-needed-to-treat.

$$NNH = \frac{1}{(q_2 - q_1) \times RV}$$

For multiple AEs (k AEs), the adjusted NNH can be calculated as (equation 6):

$$NNH_{RV-adjusted} = \frac{1}{(q_{21} - q_{11}) \times RV_1 + (q_{22} - q_{12}) \times RV_2 + ... + (q_{2k} - q_{1k}) \times RV_k}$$

It is not necessary to assume that the AEs above are independent, as these events, whether they share a common mechanism or not, can occur and each is valued by patients separately, based on frequency and severity. As demonstrated in previous work, treatment is warranted when NNT < NNH, which takes into account all AEs of interest and their relative utility values compared with the utility value of the disease of interest.[26]

Table I shows comparisons between NNT and $NNH_{RV-adjusted}$ calculated using equation 6 and hypothetical data on AE rates culled from clinical trials of a new rheumatoid arthritis drug. The utilities used for the AEs of interest were 0.99, 0.83, 0.70, 0.95, 0.90 and 0.99 for hypertension, pain, infection, abnormal liver enzyme, cardiovascular disease and skin disease, respectively. The conclusion is that Drug A, say a new disease-modifying antirheumatic drug, is better than Drug B, the gold standard methotrexate, as indicated by NNT < $NNH_{RV-adjusted}$. E_1, E_2 and E_3 are results for different American College of Rheumatology (ACR) criteria for improvement. For example, E_1 is ACR20, the number of patients who have experienced a 20% improvement in a set of clinical and laboratory measures of inflammatory responses. Similarly, E_2 represents ACR50, a 50% improvement, and E_3 symbolises ACR70, a 70% improvement.

Focusing on the results of E_1, or ACR20, because 15, the NNT, is less than 108, 62 and 27, the adjusted NNHs, fewer patients are needed to treat to obtain one improvement than need to be treated to obtain adverse outcomes.

The results may be interpreted as follows: rheumatoid arthritis patients, within a range of underlying disease severity, are willing to experience any of a series of potential AEs for a perceived benefit, or improvement, in their rheumatoid arthritis.

The limitations of this method are 2-fold. The first is rooted in the fact that NNT is the reciprocal of the absolute reduction in risk (ARR). Reciprocals have some eccentric properties that have not been fully studied in the case of NNT. Among them is the uninterpretability of the NNT when the ARR is zero.

The second limitation is the availability of utilities for the calculations. There are data for common preferences,[30] but without doing an *ad hoc* study it is a challenge obtaining complex utilities for AEs given an existing condition. Clearly, utilities derived from patients within a hospital setting for a given condition will be different from utilities derived from similar patients in an outpatient setting.

Future efforts will attempt to incorporate time on drug into the model, as the longer one stays on a drug, the more one implicitly is valuing that drug's benefit over potential or actual risk.

3.3 Relative-Value Adjusted Minimum Clinical Efficacy

Minimum clinical efficacy (MCE) analysis is a new method of evaluating the benefits and risks of available treatments. The principles were first introduced by Djulbegovic et al.[31] as a means of choosing high-dose or low-dose chemotherapy for the adjuvant treatment of breast cancer. MCE analysis seeks to improve clinical care by a calculated weighing of the potential (or proven) benefit and the potential (or proven) risk of a particular treatment. It seeks to find the minimal therapeutic benefit at which a treatment is still worth administering. MCE analysis of a new treatment can therefore be interpreted as the minimal clinical efficacy needed for it to be worth considering as an alternative treatment after taking into account not only the efficacy of the standard treatment, but also the AE profiles associated with both the standard and new treatments as well as the risk of disease of interest associated with no treatment. This latter consideration makes this approach unique; i.e. it takes into account the natural characteristics of the disease in the general population, represented by an untreated group.

Consider a situation where there are three therapeutic options for a certain condition: new treatment (T_1), standard treatment (T_2) and no treatment (T_0). Let $P(T_0)$, $P(T_1)$ and $P(T_2)$ represent the risk of disease of interest in T_0, T_1 and T_2, respectively. The efficacy (E) of T_1 relative to T_0 is defined as the relative risk reduction of the disease of interest in T_1 relative to T_0 and can be computed using (equation 7):

$$E(T_1) = \frac{P(T_0) - P(T_1)}{P(T_0)}$$

Similarly, the efficacy of T_2 relative to T_0 can be computed as (equation 8):

$$E(T_2) = \frac{P(T_0) - P(T_2)}{P(T_0)}$$

Let $q(T_1)$ and $q(T_2)$ represent the risk of an AE among people treated with T_1 and T_2, respectively. It has been previously shown that T_1 is warranted over T_2 if NNT < NNH. Consequently, (equation 9):

$$[P(T_2) - P(T_1)] > [q(T_1) - q(T_2)]$$

Based on equations 7–9, it can easily be shown that (equation 10):

$$E(T_1) - E(T_2) > \frac{q(T_1) - q(T_2)}{P(T_0)}$$

Thus, the minimal efficacy of the new treatment T_1 at which this new treatment is worth considering can then be calculated as (equation 11):

$$E(T_1) > E(T_2) + \frac{q(T_1) - q(T_2)}{P(T_0)}$$

Based on this equation, it is possible to generate a series of MCE curves representing the association between $E(T_1)$, $E(T_2)$ and $P(T_0)$, given the availability of the information for $q(T_1) - q(T_2)$. Using these curves, we are able to calculate the approximate minimal efficacy of the new treatment for it to be worth considering, given $E(T_2)$, $q(T_1)$, $q(T_2)$ and $P(T_0)$.

To adjust for multiple AEs and the relative importance of the AEs compared with the disease of interest, MCE curves can be constructed using an expansion to equation 11 (equation 12):

$$E(T_1) \geq E(T_2) + \{[q_1(T_1) - q_1(T_2)] \times RV_1 + [q_2(T_1) - q_2(T_2)] \times RV_2 + ... + [q_k(T_1) - qk(T_2)] \times RV_k \} / P(T_0)$$

where $q_k(T_1)$ and RV_k are the risk of the kth AE and the relative value of the kth AE compared with the disease of interest in T_1, calculated using the formula proposed by Guyatt et al.[26]

An example of MCE analysis uses (hypothetical) empirical efficacies of comparator drugs and placebo as the reference. Efficacy was calculated as the relative increase in the risk of improvement (E_1, E_2 and E_3) associated with Drug A and Drug B using placebo as the reference (table II). Because improvement is the outcome of interest (rather than disease prevention), adjustments were made to the equations by changing the numerator to $[P(T_1) - P(T_0)]$ for Drug A and $[P(T_2) - P(T_0)]$ for Drug B. Table III shows the efficacy of Drug A and Drug B using placebo as the reference for E_1, E_2 and E_3.

MCE curves were constructed using equation 12. Empirical efficacy values for Drug B, $E(T_2)$, used to construct these curves were obtained from table III. The risk of AEs in Drug A and Drug B groups, $q_k(T_1)$ and $q_k(T_2)$, are taken from table IV, and the risk of E_1, E_2 and E_3 improvement among placebo, $P(T_0)$, are from table II. Figure 1 shows the MCE curves using the utility value of improvement among patients of 0.40, adjusted for the multiple AEs listed in table IV and their corresponding RVs (relative importance compared with the disease of interest).

Using E_1 as the outcome of interest, for example, the minimum clinical efficacy of Drug A for it to be worth considering is between 0.40 and 0.60. This can be found as the intersection of the vertical line (of placebo efficacy, 0.26) and the horizontal line (of efficacy of Drug B, 0.73). The value of the vertical line (26.3%, the value for placebo) can be found in table II, the risk of improvement among placebo using E_1 criteria. The value of the horizontal line (0.73) can be found in table III, the efficacy of Drug B using E_1 criteria and using placebo as the reference. This means that for Drug A to be worth considering (instead of Drug B), after taking into account the efficacy of Drug B, the risks of AEs (and their relative importance to the disease of interest) of both Drug A and Drug B, and the risk of improvement using E_1 in the placebo group, its efficacy should be between 0.40 and 0.60. Using the same methods, the MCEs of Drug A for it to be worth considering using E_2 and E_3 criteria and using different utility values of improvement (0.10, 0.23 and 0.40) were calculated and appear in table V. Table V also shows the comparisons between the empirical efficacy of Drug A and the minimum efficacy from the MCE analyses, adjusted for multiple AEs with their relative values, and assuming the utility values of improvement among patients are 0.10 and 0.23. All empirical values in table III are higher than the minimum efficacy, indicating that after taking into account all AEs of interest and their relative values, Drug A is better than Drug B for each improvement criterion used (E_1, E_2 and E_3).

Table II. Percentage (95% CI) improvement according to E_1, E_2 and E_3 criteria

	Drug A	Placebo	Drug B
E_1	52.2 (45.0–60.0)	26.3 (18.0–34.0)	45.6 (38.0–53.0)
E_2	34.3 (27.0–41.0)	7.6 (3.0–12.0)	22.8 (17.0–29.0)
E_3	20.2 (14.0–26.0)	4.2 (1.0–8.0)	9.4 (5.0–14.0)

E_1 = ACR20; **E_2** = ACR50; **E_3** = ACR70; ACR is the American College of Rheumatology criteria for improvement, where ACR20 is a 20% improvement in a set of clinical and laboratory measures of inflammatory responses; similarly ACR50 and ACR70 represent a 50% and 70% improvement.

Table III. Efficacy of Drug A and Drug B using placebo as reference for E_1, E_2 and E_3

	Drug A minus placebo	Drug B minus placebo	Drug A minus Drug B
E_1	0.98	0 (ref)	0.73
E_2	3.51	0 (ref)	2.00
E_3	3.81	0 (ref)	1.24

E_1 = ACR20; **E_2** = ACR50; **E_3** = ACR70; ACR is the American College of Rheumatology criteria for improvement, where ACR20 is a 20% improvement in a set of clinical and laboratory measures of inflammatory responses; similarly ACR50 and ACR70 represent a 50% and 70% improvement.

Table V also shows the comparisons between the empirical efficacy of Drug A and the minimum efficacy from the MCE analyses, adjusted for multiple AEs with their relative values, and assuming the utility values of improvement among patients are 0.10 and 0.23. All empirical values in table III are higher than the minimum efficacy, indicating that after taking into account all AEs of interest and their relative values, Drug A is better than Drug B for each improvement criterion used (E_1, E_2 and E_3).

Given that RV-MCE is a development of RV-NNT, the limitations are basically the same; i.e. the statistical properties have not been adequately studied and data on preferences may be difficult to acquire.

3.4 Markov Models/Decision Analysis

A third approach to benefit-risk analysis is that part of decision analysis known as Markov models. Markov models have long been used in health service decision making, and are used to develop models of prognosis of chronic diseases.[32] These mod-

Table IV. Percentage of adverse events by treatment type

	Drug A	Placebo	Drug B
Hypertension	8.4	4.7	1.6
Pain	0.5	0.8	1.6
Infection	5.8	3.9	6.4
Abnormal liver test	10.5	2.3	7.5
Cardiovascular diseases	11.6	8.6	8.0
Skin diseases	26.8	21.1	22.9

els, which aim to determine the most appropriate therapy, represent random processes occurring over time that attempt to mimic the complex transitions between different health states that patients experience.[33-35]

Markov modelling requires selecting the health states and possible transitions between the states. Common (and simplistic) states are well, sick and dead. Transitions can be from well to sick or sick to dead, or sick to well. Utilities may also be assigned to different states. Next, the cycle length is chosen, which is the time interval reflecting the biological processes being modelled in which patients may make the transition from one state to another. Transition probabilities are needed, and these are determined mostly from rates of events found in published literature. Lastly, estimates of the outcome are determined using matrix algebra, Monte Carlo simulation, or Markov cohort simulation.[36] Results are obtained in the form of quality-adjusted life-years.

The application of Markov models to comparative benefit-risk analysis of different drugs has not been widely adopted, perhaps because of the necessary assumption that the probability of transitions from state to state is independent of prior state movements.[36] However, given that this approach has great flexibility in modelling almost all kinds of longitudinal failure time data, particularly of differ-

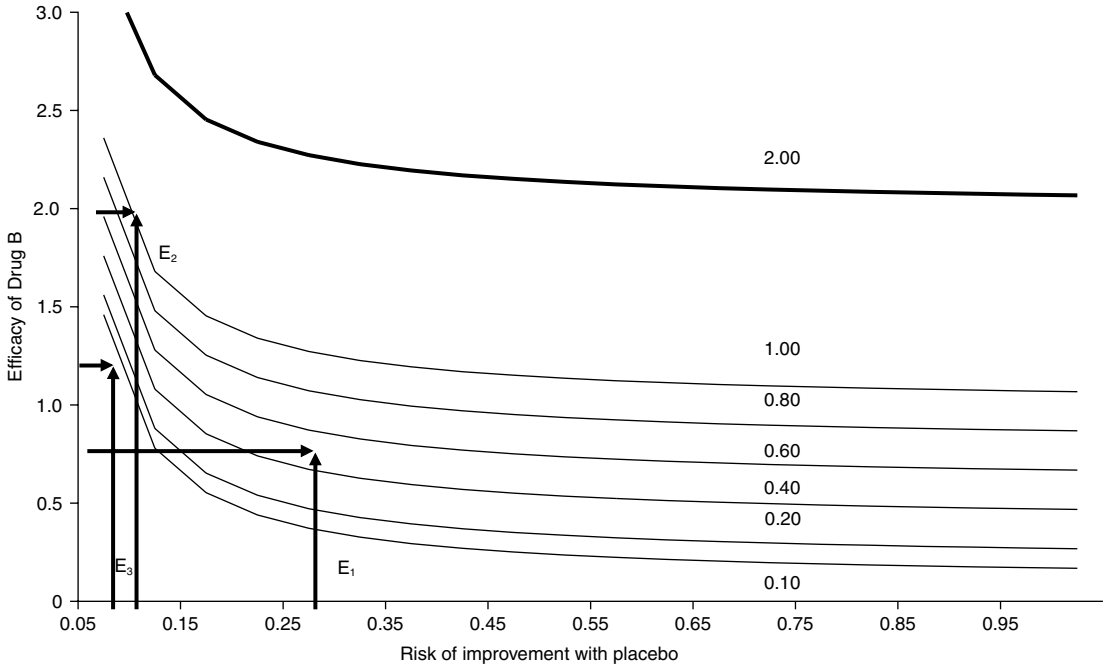

Fig. 1. Minimum clinical efficacy graph of Drug A (adjusted for multiple adverse events and their relative importance). For Drug A, the new drug, to be considered an alternative therapy, its efficacy must exceed the point on the graph where the two lines meet. Thus, for E_1, the minimum clinical efficacy is between 0.40 and 0.60 and empirically the efficacy is 0.98, which is greater. Therefore, Drug A is a safer and more effective alternative. E_1, E_2 and E_3 = ACR20, ACR50 and ACR70 results. **ACR** = American College of Rheumatology criteria for improvement, where ACR20 is a 20% improvement in a set of clinical and laboratory measures of inflammatory responses; similarly ACR50 and ACR70 represent a 50% and 70% improvement.

Table V. Empirical efficacy and the minimum efficacy from the minimum clinical efficacy analyses for Drug A to be worth considering (adjusted for all adverse events of interest and their relative values)

	E_1	E_2	E_3
Empirical efficacy (table III)	0.98	3.51	3.81
Minimum efficacy			
disease utility value = 0.40	0.40–0.60	1.00–2.00	<1.00
disease utility value = 0.23	0.40–0.60	1.00–3.00	0.40–0.60
disease utility value = 0.10	0.40–0.60	0.80–1.00	<0.10

E_1 = ACR20; **E_2** = ACR50; **E_3** = ACR70; ACR is the American College of Rheumatology criteria for improvement, where ACR20 is a 20% improvement in a set of clinical and laboratory measures of inflammatory responses; similarly ACR50 and ACR70 represent a 50% and 70% improvement.

ent events such as occurrence of AEs (risk) and improvement in health states (benefit) which affect directly the risk of death or other outcomes of interest, it is recommended as an additional tool for benefit-risk analysis.

4. Conclusion

This review has attempted to demonstrate that benefit-risk analysis is a necessary part of the risk management of pharmaceutical products, although its technical development has been somewhat neglected. It is hoped that this synopsis represents a new approach, if not a new paradigm, in benefit-risk analysis.

Quantitative synthesis of a drug's promise and potential hazards – and the ability to compare these outcomes among several drugs – can reduce the subjectivity that is a necessary component of current benefit-risk efforts, as well as the accompanying speculation about how drugs are evaluated individually and relatively.

The availability of utilities or patient preferences for these analyses may be limited, and this is the biggest challenge foreseen in adopting the proposed methods. In the absence of obtainable utilities from the literature or other studies, a preliminary assessment might be required to determine these values. Similarly, data on efficacy or effectiveness need to be obtained from clinical trials or postmarketing studies.

These methods are proposed as a strong addendum to current clinical evaluative benefit-risk processes, not necessarily as a replacement. They are methodologically sound and involve relatively easy computations. Most significantly, they add a much needed patient perspective into benefit-risk calculations, while attempting to reduce some of the subjectivity that is currently an integral part of benefit-risk analysis.

By accounting for a variety of critical aspects of a drug's character, patients' perspectives on the kinds and levels of AEs they would be willing to experience, as well as the underlying nature of the condition being treated, RV-NNT and RV-MCE can reduce the variability inherent in benefit-risk evaluation and contribute to successful risk management.

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