A Review On Benefit-Risk Assessment In Drug Development

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Abstract: Major regulatory agencies, like FDA and EMA, have started to request comprehensive benefit-risk analyses of pharmaceutical products prior to approval or labelling expansion. The purpose of this article is to review CIRS's framework and develop a generally applicable and reliable data-driven benefit-risk assessment method, where two or more drugs/doses can be compared and review Benefit-risk tools. We focus to review an approach which is simple, gives comparison of different types of risks and benefits directly, and is implemented in different disease areas during clinical development.

The method involves eight successive steps: 1) establishment of the decision context, 2) identification of benefit and risk criteria, 3) weighting, 4) scoring, 5) evaluation of uncertainty, 6) calculation of weighted scores, 7) visualisation, and 8) discussion and formulation of an overall conclusion.

The method is comprehensive and supported by a qualitative framework with built-in quantitative measures. It describes statistical methods to highlight the clinically significant differences between drugs in clinical trials. The benefit-risk evaluation is based on a eight-step decision-making process given in the book "Benefit-Risk Appraisal of Medicines.
Key words: European Medicines Agency (EMA), Food and Drug Administration (FDA).

INTRODUCTION:

Benefit–risk evaluations of drugs have been conducted since the introduction of modern regulatory systems in the 1960s, following the thalidomide disaster. However, it has only been in the past decade that both industry and regulators have started to focus on the actual methodology for conducting such benefit–risk evaluations. On the regulatory side, the European Medicines Agency (EMA) was one of the first agencies to discuss benefit–risk methodology [10]

METHODOLOGY:

The Benefit Risk Assessment in New and old drugs (BRAIN) method can extract information from clinical trials for Assessment of New and old drugs, which are not captured by statistics. It consists of the following eight steps

Step 1: Decision context –It defines aims and goals related to assessment.

Step 2: Disease profile – Here we will identify the benefits and risks that would characterise the disease. These are measured e.g. Blood Pressure. Once the criteria which is most important is selected in given context of decision, we have to justify these criteria.

Step 3: Weighting –benefits and risks are weighted on same scale to get better comparison.

Weights are justified by selecting weights based on the relative importance of a criteria mentioned in the decision context. Each criterion is given as Low, medium, high importance as weights. They are common in the given assessment for all drugs.

Step 4: Scoring –Performance of a drug is compared with comparator for each criterion by giving a numerical value during assessment. Clinical trial data sets or other information forms basis for giving Scoring. E.g. Preclinical data. Scores are given relative to comparator on a simple scale as inferior (-1), non-inferior (0) and superior (+) 1

Step 5: Evidence evaluation –An objective score can be changed to (-1 to 0,-1 to +1 or 0 to +1) if the evidence is weak. EMA's scientific committee, the CHMP has recommended list of elements for evaluation.

Step 6: Weighted scores –scores weights and are multiplied.

Step 7: Presentation of the results –Tornado diagram helps in visualising the weighted scores.

Multiple trial results are combined to get complete benefit-risk assessment. Each trial based on its importance has assigned its impact factor.

Step 8: Overall conclusion –Finally formulated hypothesis in the step 1 is either accepted or rejected. If any uncertainty found it is described along with its impact on results. Issues that are unexpected are described. Lastly, conclusion and a recommendation are given.

OVERVIEW OF BENEFIT–RISK TOOLS:

There is not any agreed taxonomy for the tools used in Benefit –Risk assessment, but there is one such useful classification i.e. quantitative models, qualitative framework and semi-quantitative framework. Qualitative frameworks generally include visual displays, grids or templates that would give information regarding key benefit and risk attributes and summarises the attributes key aspects. Hierarchic graphic representation of attributes, value tree are some of examples of such framework which are actually developed in Multi-Criteria Decision Analysis (MCDA) [12] and are used in CASS and BRAT. Semi-Quantitative models include graphical tools, tabular tools which are built on basis of qualitative framework and gives information about metrics related to key benefit-risk attributes. Visual tools in the form of benefit-risk summary table and forest plots which include rate or risk difference in the BRAT framework. Typically Quantitative models would calculate score of benefit and risk along with uncertainty and hence requires a method to get all benefits and risks on same scale. An algorithm is included for specific benefit and risk outcomes to combine metrics with measures that have clinical impact, or with weight. Typical methods used in quantitative approach are performance studies and an MCDA model. [12]

Figure 1: Establishing the value of benefits and risks and expert judgement
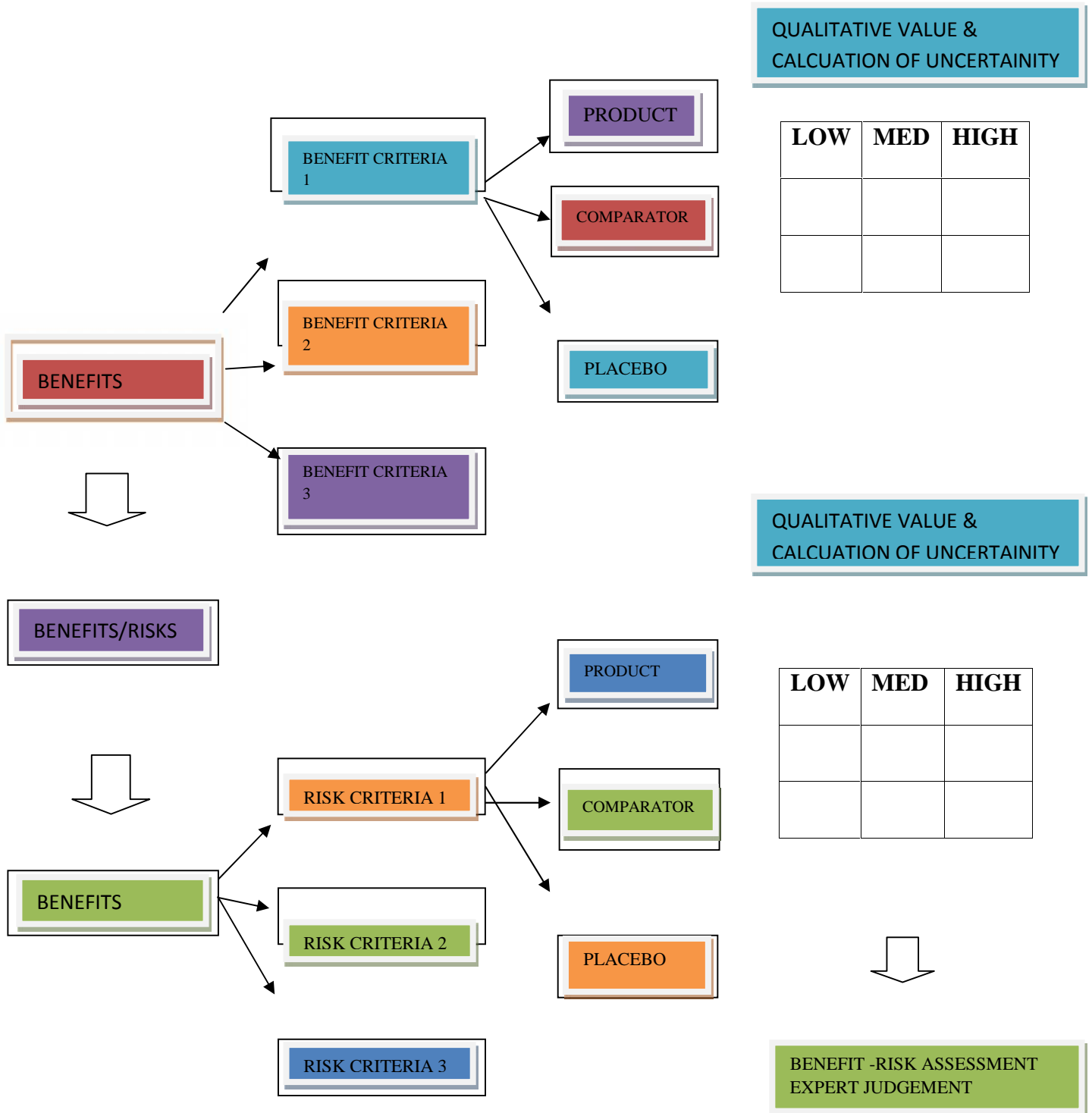
Figure 2: Example VALUE TREE for a Triptan treatment used for acute migraine
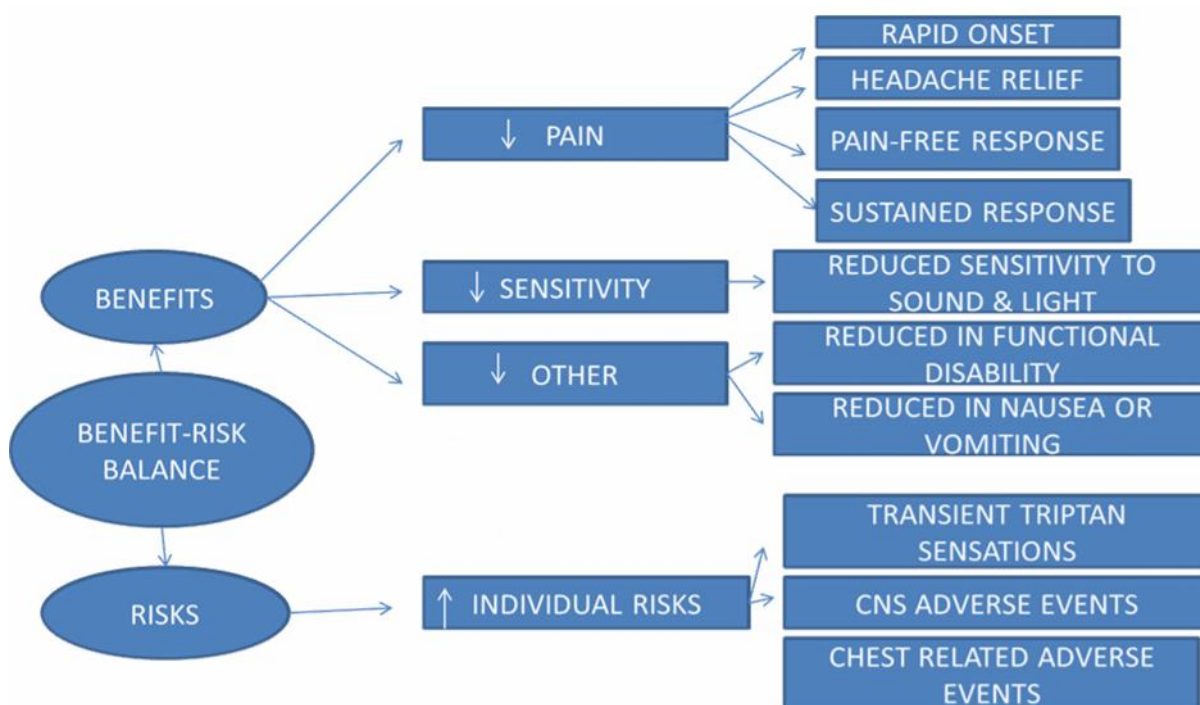
DURING DRUG DEVELOPMENT:

Companies do use certain structured approaches for benefit-risk assessment. Qualitative values give considerable value and are basis for the use of quantitative or semi-quantitative methods during and also beyond regulatory approval phase. Identifying the outcomes is more important and has two components: i) Using value tree for benefit-risk assessment and ii) Precise measures are developed for these outcomes to work in benefit-risk context.

i) **Identifying outcomes**: Generally clinical trials rigorously define efficacy and safety endpoints to be analysed using statistical analysis plan. For understanding efficacy and safety separately these endpoints generally work well, but are not sufficient for benefit-risk assessment. For example in cardiovascular trial for an anticoagulant, death and stroke are primary efficacy outcomes, and primary safety outcomes are haemorrhagic strokes and fatal bleeds are counted twice.
Value tree is the popular approach for counting relevant endpoints in benefit-risk assessment which include only those outcomes which the sponsors/decision makers regard as relevant in assessment. [6, 7, 13]

ii) **Defining measures:** Value tree measures for outcomes are taken from SAP. In many clinical trials efficacy outcomes are defined over time period and intent to treat and safety outcomes are defined over time period and safety population.

Intent-to-treat includes events in random and all patients, safety population includes all patients and events from first dose to a few days or will do follow-up study after last dose.

Important concern is whether measures count events or patients in benefit-risk assessment. Outcomes such as disabling stroke and death count one event per patient, but migraine headaches, bleeding and joint pains occur repeatedly to a patient during a study. In benefit-risk balance, this clinical impact distinction is important as these are different experiences than having many during a year.

A third concern is with composite endpoints which combine several events that provide statistical power for a set of related end points. [14] But complications include

i)   Events that are combined together may have wide range of clinical impact,
ii) Sometimes a composite may include cases where events favour one treatment and other may favour other treatment,
iii) Endpoints are measured with time to first event analysis

A fourth concern is all randomised clinical trials can be measured in benefit-risk assessment.

For example, rare drug adverse reactions are not detected in phase III trials, and on benefit side, some attributes are difficult to quantify related to patient.

Forest plots:

Forest plots are helpful in communicating data on multiple benefits and risks simultaneously.

These displays enable reviewers in their own judgement to compare endpoints related to benefit-risk balance [15]

For complex assessments with many end points of varying clinical impact and different time courses, quantitative models are often considered for benefit-risk assessment. There are other methodologies which have common element that assesses a standardised measure of weight or clinical impact. [2, 3, 12, 16]

Each decision approach has its own advantages and disadvantages. If quantitative methods are well developed with major resources and effort then they would give better benefit-risk decision. Semi-Quantitative or Qualitative methods are found appropriate for benefit-risk assessment and can be used easily by industries.

For better benefit-risk assessment uncertainty has to be developed and discussed. Industries and Regulatory bodies have to put effort for advancing benefit-risk assessment.

Benefit-risk assessment improves interactions between stake holders and assessors:

Tools and methods used in Benefit-Risk assessment helps to make decisions in benefit-risk analysis. These can help to define uncertainties and variability and describes them. [21-23]

They are not used to shift target on benefit-risk analysis to numerical summaries. Uncertainty should be kept in mind and method should be developed and understood with margin of error. In Benefit-risk assessment total score obtained helps in making the final decision even if score obtained is not equal to threshold. Threshold helps to partition the scores into ranges with different actions. These can't make a decision to approve a drug or not, but make suggestions in benefit-risk assessment for making complete decision. [25, 27]

CHMP reviews Drug application in successive steps and issues during review are resolved. Simple method would have an advantage over other methods in benefit-risk assessment, as they are not time consuming. But sometimes simplicity can have disadvantage in assessment of complex multiples of benefits and risks. Like each having different weights and dimensions that are important in a method. Too simple methods may reduce complex issues to simplified quantities which is danger.

Analysis should focus on difference between choice of weights concerned between assessors and stakeholders. These divergences are assessed and reviewed based on their degree and nature. Method used should explicit the consequences of divergences. They also should describe the source of such differences.

All the aspects should be in accordance with CHMP Guidance and should be used for benefit-risk assessment. Templates of benefit-risk section should adequately tested before they are implemented.

CONCLUSION:

It is important that same benefit-risk principles are used both in pre and post approval phases consistently. Quantitative methods can also be used in post approval evaluation of products. Benefit-risk assessment is now a key factor in many of EMEA activities.

Each kind of decision approach has advantages and disadvantages and therefore may not be easily applicable in every decision setting .Quantitative methods that combine metrics with weights may, if well developed, lead to a very high quality benefit–risk decision, but require a major effort and resources, and have less transparency.

Qualitative or semi-quantitative methods seem appropriate for most benefit–risk decisions, and can be more easily used by industry, especially in regulatory settings such as CHMP oral hearings or FDA advisory committee meetings.

Tools like value tree and data tables are essential for better benefit-risk assessment. Stakeholders are made familiar about strengths and weak points of their approach in a educational manner and novel way.

Forest plot is the simplest method used in benefit-risk assessment. Initially one has to start with a approach that involves qualitative framework and developed in to quantitative framework eventually.

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