Benefit-Risk: Qualitative and Quantitative FDA/EU Approach & Frameworks

Benefit-risk assessments are required for informed decision making during early product development, device/diagnostic approval applications, PMS, PSUR and for ad hoc assessments to address new safety concerns.

In the last two decades there has been a shift in the approach to evaluating the benefit–risk (BR) profiles of products from an unstructured, subjective, and inconsistent, to a more structured and objective, process. This paper describes that shift from a historical perspective; the past, the present, and the future, and highlights key initiatives and frameworks that played critical role in changing this field. Starting in the mid-2000s, the BR evaluation field has shifted toward a more structured and quantitative approach.

NNT/NNH

NNT, the 'number needed to treat', is the average number of patients that would have to be treated in order for just one of them to receive the expected favorable effect. NNH, the 'number needed to harm', is the average number of patients that would have to be treated in order for just one person to experience a particular unfavorable effect. Both NNT and NNH are calculated as the inverse of the difference in proportions of the effects between the treatment and control groups.

The denominator is often referred to as the absolute risk reduction. For a given disease, a smaller value of the NNT (i.e., a big improvement in the probability of a favorable effect—which might mean a reduction in the chance of a negative outcome) is better as it indicates a device that is effective for more people, while a larger value of the NNH (a small increase in the chance of an undesirable effect) is preferred because the adverse effect caused by the device is so rare.

EMA view: NNT and NNH might seem practical because of their simplicity but this simplicity is deceiving. Their main problem is that they cannot be combined to determine if benefits outweigh risks because neither statistic takes account of clinical relevance.

Quantitative approaches

Some of the models that are used in BR/Analysis:

- Bayesian belief
- Bayesian statistics
- Decision trees & influence/relevance diagrams
- Evidence-based benefit and risk model
- Incremental net health benefit
- Markov processes
- Multi-criteria analysis
- Principle of threes
- QALYs/DALYs
- TURBO

BRAT

BRAT (Benefit-Risk Action Team) standardizes and supports the decision and communication of a BR assessment between companies and the regulators through a 6-step process: define decision context, identify outcomes, identify data sources, customize framework, assess outcome importance, and display and interpret key BR metrics.

Define decision context	• Define drug, dose, formulation, indication, patient population, comparator(s), time horizon for outcomes, perspective of the decision makers (regulator, sponsor, patient, or physician)
Identify outcomes	• Select all important outcomes and create the initial value tree • Define a preliminary set of outcome measures/endpoints for each • Document rationale for outcomes included/excluded
Identify data sources	• Determine and document all data sources (e.g. clinical trials) • Extract all relevant data for the data source table, including detailed references and any annotations, to help the subsequent interpretations create summary measures
Customise framework	• Modify the va lue tree on the basis of further review of the data and cl inica l expertise • Refine the outcome measures/endpoints. May include tuning of outcomes not considered relevant to a particular benefit-risk assessment or that vary in relevance by stakeholder group
Assess outcome importance	• Apply or assess any ranking or weighting of outcome importance to decision makers or other stakeholders
Display & interpret key benefit-risk metrics	• Summarise source data in tabular and graphical displays to aid review and interpretation • Challenge summary metrics, review source data, and identify and fill any information gaps • Interpret summary information

The framework is flexible to incorporate benefits, risks, and preference weight from different perspectives, and standardized to ensure transparency and consistency. It is also simple and easy to understand, which is very important to improve the chance of successful application, especially in a company with a complicated decision-making structure with numerous conflicting agendas.

PrOACT-URL

PrOACT-URL is a generic decision-making guide with eight steps: Problems, Objectives, Alternatives, Consequences, Trade-offs, Uncertainty, Risk attitudes, and Linked decisions. PrOACT-URL framework covers the important aspects for structuring a decision-making problem. The framework itself is generic and can be applied to any decision-making problem. The summary of its components is shown below:

Problem	• Determine the nature of the problem and its context • Frame the problem
Objective	• Establish objectives that indicate the overall purposes to be achieved • Identify criteria for (a) favourable effects, and (b) unfavourable effects
Alternatives	• Identify the options to be evaluated against the criteria
Consequences	• Describe how the alternatives perform for each of the criteria, i.e., the magnitudes of all effects, and their desirability or severity, and the incidence of all effects
Trade-off	• Assess the balance between favourable and unfavourable effects
Uncertainty	• Report the uncertainty associated with the favourable and unfavourable effects • Consider how the balance between favourable and unfavourable effects is affected by uncertainty
Risk tolerance	• Judge the relative importance of the decision maker's risk attitude for this product. • Report how this affected the balance reported in step 9
Linked decisions	• Consider the consistency of this decision with similar past decisions, and assess whether taking this decision could impact future decisions

PrOACT-URL

Two-fold objectives for the FDA benefit/risk framework: better external communication of the rationale underpinning the Center for Drug Evaluation and Research decisions and internal assurance that the “big picture” for a new medicine is considered throughout complex, detailed reviews. This structured approach best fits the drug-regulatory needs, reflecting the fact that benefit-risk assessment is a qualitative exercise supported by extensive analysis of evidence on benefits and risks. It rigorously communicates in words the basis for decisions while maintaining flexibility to accommodate more complex supporting quantitative analyses that can aid expert judgment.

The FDA developed a structured BR framework with key decision factors as follow: analysis of condition, current treatment options, benefit, risk, and risk management; each factor with two components: (a) evidence and uncertainties; and (b) conclusions and reasons. The FDA did not prescribe any methods in its structured BR framework.

Decision Factor	Evidence and Uncertainties	Conclusion and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk		
Risk Management		
Benefit-Risk Summary Assessmemt		

EMA benefit–risk methodology

The EMA recognized the need to develop a more structured approach to evaluating the BR profiles of products to ensure transparency and consistency across different stakeholders. Based on the early results from the project, the investigators introduced a two-level approach to performing BR evaluation: first, a qualitative approach, mainly consisting of key effects of the benefits and risks and their uncertainty, and second, recommended for more complex situations, a quantitative approach utilizing quantitative methods to incorporate preference weight. One specific quantitative method, the multicriteria decision analysis (MCDA), was specifically mentioned, although it was recognized that the method had significant challenges for successful implementation that needed to be addressed.

Benefit-risk methodology project, work package 4 report: benefit–risk tools and processes, the EMA's suggestions were more specific:

- PrOACT–URL model for qualitative approach which may be sufficient for most cases, or
- MCDA model for quantitative approach, following the eight steps consistent with PrOACT–URL, which are suitable for more complex situations.

IMI: PROTECT

Pharmacoepidemiologic Research on Outcomes of Therapeutics by a European Consortium (PROTECT) was a collaborative European project under the umbrella of the Innovative Medicine Initiative (IMI). IMI–PROTECT contributed significantly to the BR field especially by providing deeper and more careful evaluations of a wide range of BR methods that could be categorized as follows:

MDIC-PCBR

The Medical Device Innovation Consortium (MDIC) is the first-ever public-private partnership created with the sole objective of advancing the regulatory science around the development and assessment of medical devices. The MDIC Patient Centered Benefit-Risk (PCBR) Project grew out of FDA CDRH emphasis on benefit-risk assessment as a central component of the medical device approval process.

Several key terms in the Patient Centered Benefit-Risk (PCBR) Framework can be defined in multiple ways. This is especially true of terms that are used both in a technical manner and in conventional speech, such as risk, preference, and judgment, as well as terms with different meanings in different fields such as risk tolerance.

Benefit, Harm, and Risk Definitions:

The terms "benefit" and "risk" are subject to considerable ambiguity that often leads to confusion in discussions of benefit-risk. "Risk" in particular can refer to the concept of a harmful event, the probability of a harmful event, or the impact of that harmful event on a patient. To lessen this ambiguity, the MDIC PCBR Framework adopts terminology conceptually similar to that in the EMA's Benefit-Risk Methodology Project.

A benefit is a favorable effect or desirable outcome of a diagnostic or therapeutic strategy. A harm is an unfavorable effect or undesirable outcome of a diagnostic or therapeutic strategy. Both benefits and harms are subject to uncertainty. In the Framework, the uncertainty in the occurrence of a benefit or harm will be characterized by probability, with the understanding that this probability may be described in a variety of ways. Risk is defined as the qualitative notion of the probability and/or severity of a particular harm. This definition accommodates how the term "risk" is used in much of the benefit-risk literature and prior FDA CDRH guidance.

PCBR Framework uses the terms "maximum acceptable risk" and "minimum required benefit" to characterize these tradeoffs. Maximum acceptable risk is the greatest increase in probability or magnitude of a harm that a patient would accept for a given benefit. Minimum required benefit is the smallest increase in probability or magnitude of a benefit that a patient would require to offset a given risk. Quantitative assessment of patient preferences can enable computation of these two metrics.

Consistent with prior use in CDRH guidance documents, the term "risk tolerance" is closely intertwined with the notion of maximum acceptable risk, as higher risk tolerance implies a greater maximal acceptable risk for a given benefit. Caution is required with the use of this term, however, in the Decision Analysis literature, "risk tolerance" refers to the impact of uncertainty on decisions and applies to both benefits and harms. To avoid confusion from a potential clash

in terminology, in the MDIC Framework, “risk tolerance” is a notion reflecting the degree to which a patient would accept greater probability or severity of a harm in exchange for a given benefit, while maximum acceptable risk and minimum required benefit are quantitative measures of this notion.

Note that both maximum acceptable risk and minimum required benefit can be applied to cases with no uncertainty, as in the walking example above. However, most therapies have harms and benefits that are probabilistic and require the introduction of an additional notion that reflects how uncertainty impacts patients’ views on maximum acceptable risk and minimum required benefit.

Conclusion

All of these projects and initiatives contributed to a current practice of BR evaluation, not only among industry but also among regulators in their decision-making process, which was more structured, transparent, and consistent. Most of the analyses were qualitative in nature, but quantitative methods were also available and accepted by regulators & notified bodies for a more complex situation where there was no clear advantage of one treatment over the other. When a quantitative approach was necessary, preference weight was needed from different stakeholders, including patients.

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