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Structured Benefit-risk assessment: A review of key publications and initiatives on frameworks and methodologies

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Abstract:	Introduction The conduct of structured benefit-risk assessment (BRA) of pharmaceutical products is a key area of interest for regulatory agencies and the pharmaceutical industry. However, the acceptance of a standardized approach and implementation are slow. Statisticians play major roles in these organizations, and have a great opportunity to be involved and drive the shaping of future BRA. Method We performed a literature search of recent reviews and initiatives assessing BRA methodologies, and grouped them to assist those new to BRA in learning, understanding, and choosing methodologies. We summarized the key points and discussed the impact of this emerging field on various stakeholders, particularly statisticians in the pharmaceutical industry. Results We provide introductory, essential, special interest, and further information and initiatives materials that direct readers to the most relevant materials, which were published between 2000 and 2013. Based on recommendations in these materials we supply a toolkit of advocated BRA methodologies. Discussion Despite initiatives promoting these methodologies, there are still barriers, one of which being the lack of a consensus on the most appropriate methodologies. Further work is needed to convince various stakeholders.

	But this opens up opportunities, for statisticians in the pharmaceutical industry especially, to champion appropriate BRA methodology use throughout the pharmaceutical product lifecycle. Conclusions This article may serve as a starting point for discussions and to reach a mutual consensus for methodology selection in a particular situation. Regulators and pharmaceutical industry should continue to collaborate to develop and take forward BRA methodologies, ensuring proper communication and mutual understanding.

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Structured Benefit-risk assessment: A review of key publications and initiatives on frameworks and methodologies

Short title: (70 chars) Benefit-risk assessment review of key publications and initiatives

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Abstract

Introduction

The conduct of structured benefit-risk assessment (BRA) of pharmaceutical products is a key area of interest for regulatory agencies and the pharmaceutical industry. However, the acceptance of a standardized approach and implementation are slow. Statisticians play major roles in these organizations, and have a great opportunity to be involved and drive the shaping of future BRA.

Method

We performed a literature search of recent reviews and initiatives assessing BRA methodologies, and grouped them to assist those new to BRA in learning, understanding, and choosing methodologies. We summarized the key points and discussed the impact of this emerging field on various stakeholders, particularly statisticians in the pharmaceutical industry.

Results

We provide introductory, essential, special interest, and further information and initiatives materials that direct readers to the most relevant materials, which were published between 2000 and 2013. Based on recommendations in these materials we supply a toolkit of advocated BRA methodologies.

Discussion

Despite initiatives promoting these methodologies, there are still barriers, one of which being the lack of a consensus on the most appropriate methodologies. Further work is needed to convince various stakeholders. But this opens up opportunities, for statisticians in the pharmaceutical industry especially, to champion appropriate BRA methodology use throughout the pharmaceutical product lifecycle.

Conclusions

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Introduction

Pharmaceutical products are prescribed to patients to treat and prevent many diseases. The efficacy of these products needs to be balanced with their safety profile. The importance of considering unfavorable effects within the context of the product's favorable effects is reflected in the position of the health authorities. Periodic Benefit-Risk Evaluation Report (PBRER) for post-marketing pharmacovigilance replaced, in April 2013,[1,2] previous Periodic Safety Update Reports (PSUR). The US Food and Drug Administration (FDA) is now required to perform structured benefit risk assessment as part of the approval process, which is reflected in the reauthorized fifth Prescription Drug User Fee Act (PDUFA V).[3,4] The European Medicines Agency (EMA) suggests the introduction of more quantitative elements, including taking into account direct patient preferences in benefit-risk assessment, and that regulators should shift towards a more explicit decision-making process and should focus more on quantitative descriptions of net health benefits.[5]

Health technology assessors also require costs to be balanced against benefits and risks.[6-8] For pharmaceutical companies, benefit-risk assessment is fundamental to decision-making and to designing development programs, not only to meet the regulatory requirements but also to show added value in view of their benefits and risks throughout the product development process and post-marketing surveillance. Although this process is complex, it is a necessary part of benefit-risk decision making, whether pronounced or not. Structured benefit-risk assessment can make processes transparent, and help with better informed decision-making;[9] and may additionally identify potential gaps in the evidence base. As such, research shows that structured decision approaches can lead to better-informed decisions and can help policy decisions.[10]

Benefit-risk assessment presents challenges and opportunities to statisticians in the pharmaceutical industry.[11] Statisticians, who are experienced in benefit risk assessment, can drive the discussions with clinical colleagues, lead the translation of medical concepts into valid endpoints, analyze both favorable and unfavorable effects, and develop a strategy to assess the robustness of quantitative BRA models. It should be a key strength of statisticians to understand strengths and limitations of clinical trials, observational data, and other non-clinical trial information sources potentially included in a benefit-risk model to transition the compound through the complete life-cycle. Therefore, statisticians need to combine their methodological rigor and strong technical knowledge with influencing skills in order to lead benefit-risk assessments in order to contribute to sound decisions for the treatment of patients.

This article aims to facilitate fast and efficient learning by providing key information to researchers, particularly statisticians, who are new to the area of benefit-risk assessment.

Methods

In the last years, there have been many publications, reviews, and initiatives in this area. Therefore, we carried out a literature search of existing reviews on approaches for balancing

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benefits and risks in decision-making about medicinal products, limiting only to those published between year 2000 and 2013. We also included known work by the regulators, pharmaceutical companies, and other initiatives. Publications were searched for and selected by four independent reviewers. Reviewers revised and discussed each other's work for completeness. We summarized existing reviews and various developments in benefit-risk assessment methodologies from various groups worldwide with the intent to provide an index of resources in this growing body of research.

We grouped the materials into structured resources on benefit-risk assessment to guide statisticians in the learning process of understanding and selecting a useful set of methodologies. We highlighted the methodologies that were discussed in the original publications and the essence of their recommendations, if any. Finally, we discuss the impact the emerging initiatives have on various stakeholders involved in drug decision-making. We focus on the changes, current and potential applications of the formal benefit-risk assessment methodologies for statisticians in the pharmaceutical industry through the different stages of the pharmaceutical product life cycle.

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Table 1 provides technical terminologies used in this article.

Results

This section provides an overview of introductory materials, essential materials, special interest publications for the benefit-risk assessment, and further information and initiatives. The toolkit of available methodologies is then discussed.

Introductory materials to structured benefit-risk assessment

For those who are not familiar with benefit-risk assessment, there are a number of publications that can be used as an introduction to the topic. As introductory materials (Table 2), we recommend the special issue of the Regulatory Rapporteur,[16] and two short reviews on quantitative benefit-risk methods.[17,18]

The special issue of the Regulatory Rapporteur[16] was dedicated to benefit-risk and provided a good summary to date from a regulator's perspective,[19] and an industry's perspective.[20] This special issue acknowledges that although qualitative judgments have been used in benefit-risk decision-making of medical products, quantitative methods may be needed to deal with the challenges posed by the consistency, transparency and predictability of making qualitative decisions. The two short reviews on quantitative benefit-risk methods would be suitable for statisticians (and others) who are new to the field.[17] Guo et al., from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) working group, recommend that new drug therapy evaluations consider the use of multiple benefit-risk approaches across different therapeutic indications and treatment populations.[17] Puhan et al. provide a framework for organizing and selecting quantitative methods for use in a benefit-risk assessment.[18]

Pivotal work on benefit-risk assessment methods

More substantial pivotal work on benefit-risk assessment methods (Table 3) had been carried out in various multidisciplinary initiatives including the European Medicine Agency (EMA) Benefit-risk Methodology Project,[21] the Innovative Medicines Initiative Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (IMI-PROTECT) Benefit-Risk Integration and Representation[22] and the Centre for Innovation in Regulatory Science (CIRS) Unified Methodologies for Benefit-Risk Assessment (UMBRA).[23]

The EMA reviewed the benefit-risk assessment methods in a theoretical and empirical context. They appraised each method's usefulness to the regulators, considering decisions at both pre- and post-approval stages of medical products.[9] Recommended methods went through field testing to assess their feasibility and to gain insights into potential practical barriers,[24] which were later further developed and tested for use in a regulatory setting.[25]

The IMI-PROTECT Work Package 5 (WP5) on Benefit-Risk Integration and Representation performed a review on 47 benefit-risk assessment methodologies and classified them into benefit-risk frameworks, metric indices for BR assessment, estimation techniques and utility

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survey techniques, based on their principle and purpose.[12,26] Mt-Isa et al. recommend 13 methods to be of sufficient variety and should be considered further in real-life benefit-risk assessment.[12,26] Several case studies used publically available data to test the recommended methods in order to assess their practicalities when applied to real-life decision problems of pharmaceutical products with delicate benefit-risk balance.[27-35] The key summary and lessons learned from testing the methods in case studies were distilled into a final set of recommendations in a roadmap of benefit-risk assessment stages.[14] WP5 also conducted a two-part review on the use of visualizations in benefit-risk assessment,[36] and the suitability of visual display for communicating benefit-risk assessment to various stakeholders.[37] The second part of the review also discusses topical issues including the use of non-verbal and numerical representation of benefits and risks, and the use of interactive "dashboards"[13] for presenting benefit-risk information.[37]

CIRS UMBRA initiative coordinates development of benefit-risk assessment methods that can be used internationally during the drug development, regulatory review and post-approval periods.[23,38] Its goal is to establish common elements across the different methodologies (best-in class components) to enable a consensus on a scientifically acceptable framework for making benefit-risk decisions. An eight-step assessment framework, largely developing on the Benefit-Risk Action Team (BRAT) framework,[39,40] was proposed and subjected to prospective evaluations in 2013.[41]

Special interest publications

There are other resources on benefit-risk assessment that we could not review here in sufficient detail that might be of interest to some readers (Table 4), but many of which already overlap with previously mentioned reviews. For instance, the Medicine and Healthcare Products Regulatory Agency (MHRA) in the UK has some resources on benefit-risk assessment: from an academic paper on structured quantitative health outcomes approach,[42] and on some methodological issues in benefit-risk decision-making for individuals and regulators.[43] The US Food and Drug Administration (FDA) considers a more qualitative approach to benefit-risk assessment encompassing the "bigger picture", and was developed specific to the FDA requirements.[44-46] The advancement in this field also includes some changes to regulations concerning medical devices,[47] and also methodological research on economic evaluation and triage for research prioritization in Health Technology Assessments.[48] Other work in HTA include efforts focused on standardizing multi-criteria decision analysis in the economic evaluation framework is being conducted by the EVIDEM Collaboration,[49] and ensuring efficient and sustainable network in Europe that address BRA upfront by EUnetHTA.[50]

Further information and initiatives

Several reviews (Table 5) have also mentioned the Pharmaceutical Research and Manufacturers of America Benefit-Risk Action Team (PhRMA BRAT) and the 4-Agency Consortium of Canada, Australia, Switzerland and Singapore (CASS). Since their introductions, CASS has developed into Consortium on Benefit-Risk Assessment (COBRA); and although case studies found PhRMA BRAT framework to be widely acceptable,[20,40,51]

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PhRMA selected CIRS to further develop the framework under the auspices of the UMBRA initiative [23]. The Dutch Escher project endeavours to stimulate the reform of the regulatory of pharmaceutical products.[52] Escher's Aggregate Data Drug Information System (ADDIS) sub-project demonstrates a software package that could automate a seamless evidence synthesis and benefit-risk assessment.[53] Another IMI funded initiative, the European Programme in Pharmacovigilance and Pharmacoepidemiology (Eu2P), offers courses allied to benefit-risk assessment of medicines, drawing on previous investments and research expertise.[54] The EFSPI BR SIG equivalent, the Quantitative Sciences in Pharmaceutical Industry (QSPI) group, is also working towards the same goal in advocating the scientific and regulatory issues of benefit-risk assessment in the United States.[55]

Toolkit of advocated benefit-risk assessment methodologies

There is no firm consensus on a single methodology that can be used for every decision problem.[17,56] It is therefore, in our view, better to equip benefit-risk assessors (statisticians, regulators, clinicians) with a toolkit of resources that will foster the understanding of methodology choices.

The EMA proposed that an appraisal of a benefit-risk assessment methodology includes the assessment of its logical soundness, comprehensiveness, acceptability of results, practicality and generativeness.[9] These criteria help to ensure that an assessor could appropriately justify the methodology choices. According to the IMI-PROTECT Work Package 5, who cultivated these criteria in their review, a benefit-risk methodology should be transparent, ensure the use of good quality of evidence, address uncertainty and biases, allow meaningful benefit-risk integration, result in interpretable results and eliminate any potential misleading communications.[12]

Table 6 provides an overview of the qualitative methods and Table 7 provides an overview of the quantitative methods, which are referenced in the reviews; where details of the methodologies are also available.[26,57] It was suggested by IMI-PROTECT WP5 to test 13 methodologies in future benefit-risk assessment: PrOACT-URL, BRAT, MCDA, SMAA, NNT/NNH, Impact numbers, QALY, Q-TWiST, INHB, BRR, probabilistic simulations, MTC, and DCE (see Table 6 and Table 7 for abbreviations), and further classifications of methodologies can be found in the PROTECT WP5 report.[12] Other methodologies may also be suitable depending on the situations and must not blindly be dismissed.[12,14,26] The choice of methodologies may depend on different therapeutic area (e.g. depending on use of time-to-event statistics), time of appraisal and regulatory requests. The EMA BR project suggested that MCDA, Bayesian statistics and decision trees are the most comprehensive among the quantitative methodologies.[9] Other useful methodologies include probabilistic simulation, Bayesian belief networks, Markov processes, and QALYs/DALYs.[9]

The combination of evidence data with preference weights in methods such as MCDA and SMAA may lead to high quality and relevant decisions but requires more effort and resources, and much attention should be paid to transparency when using these types of

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methods.[14] Due to the complexity of incorporating weights into decision-making formally, formal estimation of weights should only be considered in complex benefit-risk decision problems. Related to this, there is emerging interest and concern to incorporate preference weights from patients and public in benefit-risk decision-making of pharmaceutical products. In any case, all benefit-risk initiatives agree that a systematic use of a qualitative framework, including supporting other quantitative methodologies, is needed to increase the transparency of a benefit-risk assessment.

Discussion

This review concurs that there is no consensus and not a one-size-fits-all methodology that can be used for every decision problem,[17,56] and there is often the need for multiple methodologies be used in sync.[14] The fast-changing landscape of regulatory benefit-risk assessment, including FDA adoption of PBRER,[1] suggests the need for systematic learning to efficiently identify and fill knowledge gaps in the area. Although the use of quantitative or semi-quantitative assessments to weight benefits against risks is explicitly mentioned,[1,2] formal benefit-risk assessment methodologies are not currently specified. Consequently, those who perform or review benefit-risk assessments for regulatory submissions often find themselves putting more effort than needed to ensure proper conduct and documentations. This article carefully structures the key materials in benefit-risk assessment up to 2013, and is therefore intended to save valuable resources by preventing duplication of efforts and promoting efficient learning.

Opportunities for statisticians in the pharmaceutical industry

There are opportunities, for statisticians in the pharmaceutical industry especially, to champion the BRA methodologies use throughout the pharmaceutical product lifecycle. Assessing the balance between benefits and risks is a complex task driven by the different favorable and unfavorable effects of a drug, the uncertainty about these benefits and risks, and varying preferences of different stakeholders.[21]. This may require pharmaceutical statisticians to continuously adapt to new techniques and methodologies to handle, for example, sources of uncertainties, endpoints that are causally dependent or even double-count the same event, efficacy and safety measures defined over different populations or over different time periods, or to pool data from different sources (mainly clinical and post-marketing data). Because of these needs, benefit-risk special interest groups (BR-SIGs) within the pharmaceutical industry, like ours, are formed. The establishment of BR-SIGs means that pharmaceutical statisticians from various companies would have access to a common platform to exchange knowledge and to advance the topic within the industry. Such collaboration is fundamental, as a first step, to move towards the harmonization of structured BRA.

Benefit-risk assessment is important to the pharmaceutical industry itself throughout the drug development stages. At discovery stage, it is important to identify those compounds for which the estimated potential benefit-risk balance for the preferred mode of action for the

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target population is positive. For example, in phases I and IIA trials, the benefit and risk data can be utilized to assist in "go" or "no-go" decisions. The probability of phase III trial program success can be improved by first assessing the benefit-risk profile estimated based on earlier phases. By indicating, in phase IIB or III, the elements that are missing in the benefit-risk assessment, the design of clinical trials can be set up to incorporate structured BRA methodologies to increase transparency and thence support these decisions seamlessly.

Common understanding of BRA methodologies through systematic knowledge-based sources, like this article, can further facilitate communication among stakeholders.

Implications to other stakeholders

Successful drugs are drugs that demonstrate their value to all stakeholders, including patients, physicians, regulators, Health Technology Assessment bodies (HTAs), and payers.

For patients, the primary decision is whether or not to take a particular treatment for their medical conditions, hence it is important that patients understand the extent of benefits and risks associated with the treatment options. Several methodologies also directly allow patients to be involved at much earlier stages of the benefit-risk assessment, and therefore the final benefit-risk balance would be of more relevance. Structured BRA methodologies tailored to patient communication could help physicians to advise patients better, moving from consultative towards collaborative healthcare decision-making. In reality, the price of treatments may play a major role to patients depending on the healthcare system, and should also be addressed as part of the decision-making.

For payers, the budget impact of benefits and costs is important. This means that a reduction in a laboratory parameter is only important when this also results in reduction of outcomes influencing their budget. As such, benefits and risks should be assessed in terms of costs. As a consequence, payers would be interested in how well the drug works in the population, in real practice versus standard of care. The constraint on costs in BRA presents additional complexity to payers when determining the benefit-risk balance.

HTA bodies compare the incremental benefits and risks versus the costs related to different comparators on the market. The National Institute for Health and Care Excellence in the UK provides guidelines on incorporating health state utility values in economic evaluations, including mapping methods (TSD10),[58,59] alternatives to the well-accepted EQ-5D index (TSD11),[60,61] and their use in decision models (TSD12).[62,63] Moreover, cost-effectiveness models evaluating benefits and risks against monetary costs are already used worldwide. Recent initiatives put these cost-effectiveness models within the context of benefit-risk assessment, with aim to provide more integrated tools.[49,50]

Regulators assess benefit-risk balance of healthcare products and medicines for marketing authorization and as part of continuous safety monitoring.[64] EMA states that, "regulatory assessors will be in a better position to judge the benefit-risk balance when structured

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evaluations are submitted, because a structured evaluation induces a gain in transparency, communicability, auditability and quality."[9,65] Moreover, both EMA and FDA will incorporate a structured benefit-risk assessment into the regulatory review process;[21,66] and this article could contribute towards the bigger picture in terms of contextualizing concurrent initiatives worldwide.

Conclusions

The use of a structured benefit-risk assessment at the different stages of the product lifecycle may offer important added value to ensure better transparency, robustness and a justifiable decision-making process.

We hope that the overview and toolkit of resources provided will not only serve as starting material, but will be used to facilitate further discussion and to reach consensus on which methods to use for a particular situation. For this, the different initiatives in which regulators and the pharmaceutical industry collaborate and better communications and understanding related to benefit-risk assessments are very important.

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Table 1 Glossary of terminologies

Terminology	Description
Benefit	The positive results of a given treatment for an individual or a population. (i.e. efficacy, convenience, or even quality of life).[12]
Dashboard	A dashboard is a visual display of the most important information needed to achieve one or more objectives; consolidated and arranged on a single screen so the information can be monitored at a glance.[13]
Framework	A structured stepwise approach to perform a task.[14]
Qualitative	The system is a purely qualitative framework based on internal experts or management making a "gut decision" on the benefit–risk profile of each product and providing a conclusion. The final decision will be exercised based on Expert Judgment.[15]
Quantitative	The system is a fully quantitative model which includes a benefit–risk balance for a new medicine, and is applied across study data and contributing opinions. The conclusion is based on the cumulative outcome from this single system. The final decision will be exercised based on Expert Judgment.[15]
Risk	The unfavourable negative results (adverse outcomes) of a given treatment for an individual or a population in terms of probability of occurrence having considered the magnitude of severity.[12]

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Table 2 Introductory materials

Publication	Comment
Special issue Regulatory Rapporteur (2012) http://www.topra.org/regulatory-rapporteur-june-2012	Up to date summary from regulator's perspective and industry's perspective
Evaluating benefit-risk: An Agency Perspective	
Evaluating benefit-risk during and beyond drug development: An Industry View	
Guo et al (2010): A Review of Quantitative Risk-Benefit Methodologies for Assessing Drug Safety and Efficacy – Report of the ISPOR Risk-benefit Management Working Group	Recommend the use of multiple benefit-risk approaches across different therapeutic indications and treatment populations
Puhan et al (2012): A framework for organizing and selecting quantitative approaches for benefit-harm assessment	A framework organizing and selecting quantitative methods

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Table 3 Essential materials

Publication	Comment
EMA: Work packages	Methods appraisal, field testing and use in regulatory setting
IMI Protect: Work package 5 and other papers;	47 benefit-risk methods assessed and classified. 13 methods considered further. Case studies and recommendations
CIRS UMBRA: Standardizing the Benefit-Risk Assessment of New Medicines; Building the Benefit-Risk Toolbox Workshop	Target is consensus of scientifically acceptable framework

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Table 4 Special interest publications

Special interest publications
MHRA: • Garisson et al: Assessing A Structured, Quantitative Health Outcomes Approach To Drug Risk-Benefit Analysis • Benefit: Risk Decision-Making for Individuals and Drug Regulators FDA: • A United States Regulator's Perspective on Risk-Benefit Considerations • Benefit-Risk Considerations in CDER: Development of a Qualitative Framework • Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications • Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision Making, Draft PDUFA V Implementation Plan – February 2013 NHS: • Prioritisation of health technology assessment. The PATHS model: methods and case studies EVIDEM: • Provides a framework of multi-criteria health economic evaluation using the multi-criteria decision analysis based on evidence EUnetHTA: • Working with the regulators to ensure benefit and risk questions are addressed at much earlier stage to better incorporate the aspect in health technology assessment

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Table 5 Further information and initiatives

Futher information and initiatives	Comments
PhRMA BRAT: Development of a framework for enhancing the transparency, reproducibility and communication of the benefit-risk balance of pharmaceutical products. Application of the BRAT framework to case studies: observations and insights	Further development framework by UMBRA initiative
CASS - COBRA	Developed a framework "proforma"
Dutch Escher project	Seamless evidence synthesis and benefit risk assessment
European Programme in Pharmacovigilance and Pharmacoepidemiology (Eu2P)	Courses benefit risk
QSPI EFSPI BR SIG	Special interest groups of EFSPI and QSPI related to benefit risk

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Table 6: Qualitative methods referenced in reviews

Qualitative frameworks	EMA	PROTECT	TOPRA
Ashby and Smith Framework (ASF)		x	
Benefit Risk Action Team (BRAT)	x	x*	x
CMR Health Canada, Australia's Therapeutic Goods Administration, SwissMedic, and Singapore Health Science Authority (CMR-CASS)	x	x	x
Value tree	x	x	x
FDA Benefit Risk Framework (FDA BRF)	x	x	x
Problem, Objectives, Alternatives, Consequences, Trade-offs, Uncertainty, Risk, and Linked decisions framework (PrOACT-URL)	x	x*	x
Unified Methodologies for Benefit-Risk Assessment		x	
Southeast Asia Benefit-Risk Evaluation		x	
Consortium on Benefit-Risk Assessment		x	

* Methodologies that were suggested being useful for future benefit-risk assessments

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Table 7: Quantitative methods referenced in reviews

Quantitative methods	EMA	Puhan	Guo	PROTECT	TOPRA
Adverse Event adjusted Number Needed to Treat (AE-NNT)				x	
Bayesian belief networks (BBN)	x*				
Bayesian statistics	x*				
Beckmann model				x	
Benefit-less-risk analysis (BLRA)		x	x	x	
Benefit-Risk Ratio (BRR)				x*	
Boers table		x			
Cross Design Synthesis (CDS)				x	
Conjoint analysis (CA)	x			x	
Contingent valuation	x			x	
Confidence Profile Method (CPM)				x	
Clinical Utility Index (CUI)				x	
Directed Acyclic Graphs (DAG)				x	
Discrete Choice Experiment (DCE)				x*	
Decision tree and influence/relevance diagrams	x*			x	x
Desirability Index (DI)				x	
Discrete event simulation	x				
Evidence based benefit and risk model	x			x	
Gail		x			
Global Benefit Risk (GBR)				x	
Health Adjusted Life Years (HALE)				x	
Impact numbers				x*	
Incremental net health benefit (INHB)	x	x	x	x*	x
Indirect Treatment Comparison (ITC)				x*	
Kaplan Meier estimator	x				
Markov process	x*				
Maximum acceptable risk (MAR)/Stated preference method (SPM)	x	x	x	x	x
Markov Decision Process (MDP)				x	
Minimum clinical efficacy (MCE)		x	x	x	
Mixed Treatment Comparison (MTC)				x*	
Multi-criteria decision analysis (MCDA)	x*	x	x	x*	x
Net Efficacy Adjusted for Risk (NEAR)				x	
Net Clinical Benefit (NCB)		x		x	
Number needed to treat (NNT)/ Number needed to harm (NNH)	x	x	x	x*	
Principle of threes	x			x	

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Probabilistic simulation methods (PSM)	x*	x	x	x*	
Quality/ Disability Adjusted Life Years (QALY/DALY)	x*			x*	x
Quality-adjusted Time without Symptoms and Toxicity (Q-TWIST)		x	x	x*	
Quantitative Framework for Risk and Benefit Assessment (QFRBA)		x	x		
Relative value adjusted number needed to treat (RV-NNT)			x	x	
Risk–benefit contour (RBC)		x	x		
Risk–benefit plane (RBP) / risk–benefit acceptability threshold (RBAT)		x	x		
Sarac's Benefit Risk Assessment (SBRAM)				x	
Stochastic Multi-criteria Acceptability Analysis (SMAA)				x*	
System dynamics	x				
Transparent Uniform Risk Benefit Overview (TURBO)	x	x		x	
Utility- and Time-adjusted Number Needed to Treat (UT-NNT)				x	

* Methodologies that were suggested being useful for future benefit-risk assessments

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