Benefit-risk balance for medicinal products

Report of the CIOMS Working Group XII

Council for International Organizations of Medical Sciences (CIOMS)

Geneva 2025

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Geneva, Switzerland, 2025

Lembit Rägo, MD, PhD
Secretary-General, CIOMS

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ABBREVIATIONS

AE	Adverse Event
AF	Atrial Fibrillation
AI	Artificial Intelligence
AML	Acute Myelocytic Leukaemia
anti-CD19	Antibody to CD19 protein on B cell membranes
AR	Adverse Reaction
ARLG	Antibacterial Resistance Leadership Group
ASA	American Statistical Association
ATMP	Advanced Therapy Medicinal Product
BID	Bis in die [twice per day]
BLA	Biologics Licensure Application
BR	Benefit-Risk
BRA	Benefit-Risk Assessment
BRACE	Benefit Risk Assessment, Communication and Evaluation
BRAD	Benefit-Risk Assessment Document
BRAT	Benefit-Risk Action Team
BRMT	Benefit-Risk Management Team
CAM	Complementary and Alternative Medicine
CAR	Chimeric Antigen Receptor
CBER	Center for Biologics Evaluation and Research (of the US FDA)
CCDS	Company Core Data Sheet
CDC	Centers for Disease Control and Prevention (of the US)
CDER	Center for Drug Evaluation and Research (of the US FDA)
CHMP	Committee for Medicinal Products for Human Use (of the EMA)
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CIRS	Centre for Innovation in Regulatory Science
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019 (the illness caused by severe acute respiratory syndrome coronavirus 2 – SARS-CoV-2)
CMO	Chief Medical Officer
CMR	Centre Medical Research
CRE	Carbapenem-Resistant Enterobacteriaceae

CrI	Credible Interval
CTA	Clinical Trial Application
CTTI	Clinical Trials Transformation Initiative
cUTI	Complicated Urinary Tract Infection
DCDS	Development Core Data Sheet
DCE	Discrete Choice Experiments
DDI	Drug-Drug Interactions
Development RMP	Development Risk Management Plan (RMP)
DLBCL	Diffuse Large B-cell Lymphoma
DMC	Data Monitoring Committee
DOOR	Desirability of Outcome Ranking
DRMP	Developmental Risk Management Plan
DSUR	Development Safety Update Report
EAGLES	Evaluating Adverse Events in a Global Smoking Cessation Study
EBMT	European Society for Blood and Marrow Transplantation
ED	Emergency Department
EFSPI	European Federation of Statisticians in the Pharmaceutical Industry
EGFR	Epidermal Growth Factor Receptor
HER	Electronic Health Records
EMA	European Medicines Agency
EPF	European Patients' Forum
ER	Estrogen Receptor
EU	European Union
EUPATI	European Patients Academy on Therapeutic Innovation
EVDAS	EudraVigilance Data Analysis System
FAERS	Food and Drug Administration Adverse Event Reporting System
FL	Follicular Lymphoma
GE	Gastroenteritis
HCP	Health Care Professional
HEOR	Health Economics and Outcomes Research
HR	Hazard Ratio
HTA	Health Technology Assessment
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

ICH E2C	Guideline pertaining to the submission of Periodic Safety Update Reports (PSURs) to regulators.
ICH E2C (R2)	Guideline pertaining to the submission of Periodic Benefit-Risk Evaluation Report (PBRER) to regulators. E2C(R2) is the second revision of the ICH E2C Guideline.
ICH E2D	Guideline pertaining to the submission of Development Safety Update Report (DSUR) to regulators.
ICH E9(R1)	Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials.
ICH M4E(R2)	Guideline on enhancing the format and structure of benefit-risk information in the ICH – efficacy. M4E(R2) is the revision of M4E Guideline.
iDFS	Invasive Disease-Free Survival
IMI	Innovative Medicines Initiative
IMI PROTECT WP5	Innovative Medicines Initiative Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium Work Package 5
IND	Investigational New Drug
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention-to-Treat
JADER	Japanese Adverse Drug Event Report Database
LST	Large Simple Trials
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MCDA	Multi-Criteria Decision Analysis
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
ML	Machine Learning
NDA	New Drug Application
NH	Null Hypothesis
NIS	National Immunization Schedule
NOAC	Novel Oral Anticoagulant
NPS	Neuropsychiatric Symptoms
NRT	Nicotine Replacement Therapy
NVAF	Nonvalvular Atrial Fibrillation
OAC	Oral Anticoagulant
ORISE	Oak Ridge Institute for Science and Education

OTC	Over-the-Counter
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PCT	Pragmatic Clinical Trial
PD	Pharmacodynamics
PDUFA	Prescription Drug User Fee Act
PhRMA	Pharmaceutical Research and Manufacturers of America
PK	Pharmacokinetics
PKPD	Pharmacokinetics and Pharmacodynamics
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PPS	Patient Preference Studies
PRAC	Pharmacovigilance Risk Assessment Committee (of the EMA)
PREFER	Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle
PRO	Patient-Reported Outcome
PrOACT-URL	Problems, Objectives, Alternatives, Consequences, Trade-offs, Uncertainties, Risk attitudes/risk tolerance, Linked decisions
PROTECT	**P**harmacoepidemiological **R**esearch on **O**utcomes of **T**herapeutics by a **E**uropean **C**onsor**T**ium
PSI BRA SIG	Statisticians in the Pharmaceutical Industry Benefit-Risk Assessment Special Interest Group
QD	Quaque die [one per day]
QoL	Quality of Life
QSPI BRWG	Quantitative Sciences in Pharmaceutical Industry Benefit-Risk Working Group
RCR	Replication-Competent Retrovirus
RCT	Randomised Controlled Trial
REMS	Risk Evaluation and Mitigation Strategy
RMM	Risk Minimisation Measures
RMP	Risk Management Plan
RR	Relative Risk
RT	Rotavirus
RTGE	Rotavirus-Associated Gastroenteritis
RV	Rotavirus Vaccine
RV1	Monovalent Rotavirus Vaccine
RV5	Pentavalent Rotavirus Vaccine
RWD	Real-World Data
RWE	Real-World Evidence

SBRF	Structured Benefit-Risk Framework
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
ScFv	Single Chain Variable Fragment
SIG	Special Interest Group
SMQ	Standardised MedDRA Query
SMT	Safety Management Team
UK	United Kingdom of Great Britain and Northern Ireland
UMBRA	Unified Methodologies for Benefit-Risk Assessment
URT	Uncertainty Reduction Theory
US	United States of America
US FDA	US Food and Drug Administration
UTI	Urinary Tract Infection
VAC4EU	Vaccine Monitoring Collaboration for Europe
WHO	World Health Organization

FOREWORD

A benefit-risk (BR) balance[i] must be established for all medicinal products[ii] prior to marketing. This balance must be reassessed periodically in the post-marketing setting when new information regarding the benefits and risks, or the landscape of their application becomes available. This report provides insights into the current thinking and methods used to evaluate the BR balance of a medicinal product, and supersedes the report of the CIOMS Working Group IV, published in 1998, entitled: *BR Balance for Marketed Drugs: Evaluating Safety Signals*. Many of the concepts in this report apply to medical devices, but they require a different approach to establish their BR balance and so are only briefly discussed in this report.

The report defines and emphasises the need to use a structured framework for every BR assessment (BRA), and additional quantitative analysis to support structured BRA for more complex safety issues. This report presents new, key concepts for consideration when thinking about benefits and risks, including the need to take a lifecycle approach which considers knowledge gaps for products in early development as well as what is known about well-established products with extensive safety data.

This involves assessing a product's BR balance from early development, reassessing when new information becomes available through the regulatory process, ongoing monitoring, and its use in a real-world setting during the period of time when the product is on the market. Another key concept presented in this report is the need to involve patients[iii] in all aspects of the BRA and risk management process. This report describes the importance of selecting an appropriate assessment method, which includes input from patients, who represent the target population and/or who have direct experience with a medicinal product and of the need to follow a structured approach when assessing and reassessing the BR balance of a medicinal product at different points in the product lifecycle.

The guidance contained in this report reflects the consensus opinion of the CIOMS Working Group XII members, which include experts in BRA drawn from academia, industry, and regulatory organisations. It is anticipated that this document will provide important insights on the topic to a variety of different stakeholders including medicinal product developers, regulatory authorities, and key stakeholders including academic and government researchers, health care professionals, and patients and/or consumers, who have experience with the products or are interested in how the balance between the benefits and risks associated with a medicinal product is established and managed.

Like previous CIOMS reports, this one adopts a public health approach aimed at encouraging consistent practices on the part of both regulators and product developers when new information relevant to benefits and risks is identified during the lifecycle of a medicinal product. Examples from case studies are included in the report to illustrate pragmatic approaches to assessing/reassessing BR in a variety of different circumstances. This report also touches briefly on the decision making

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[i] **Benefit-risk balance:** The terms benefit-risk profile and benefit-risk balance are used frequently in this report. The term benefit-risk profile is used to refer to a concise description or summary of the potential risks and benefits associated with a medicinal product, which may or may not have undergone a formal benefit-risk assessment, while the term benefit-risk balance is used to refer to the outcome or result of a formal assessment of the potential risks and benefits of a medicinal product.
Proposed by CIOMS Working Group XII.

[ii] **Medicinal product:** In this report, medicinal products are considered to include prescription and non-prescription pharmaceuticals and biologicals including vaccines.
Proposed by CIOMS Working Group XII.

[iii] **Patient:** A person who has, or had, or is at risk of a health condition whether or not they currently receive therapy to prevent or treat it. Patients are the individuals who directly experience the benefits and harms associated with a medicinal product. Proposed by CIOMS Working Group XII. Combined from: 1) CIOMS Working Group XI, modified from the US National Health Council. Glossary of patient engagement terms. (Webpage accessed 11 September 2024), and 2) modified from US FDA. Patient-Focused Drug Development Glossary (Website accessed 18 July 2024).

needed in taking appropriate actions to manage newly identified risks. However, more detailed information on the topic of risk management is provided in the CIOMS Working Group IX report published in 2014, entitled: *Practical Approaches to Risk Minimisation for Medicinal Products*, and the ICH guideline M4E(R2) published in 2016, entitled*: Revision of M4E Guideline on Enhancing the Format and Structure of Benefit-risk Information in ICH.*

This report consists of four chapters. The first chapter introduces and discusses the BR landscape and provides information on the up-to-date context surrounding BRA of medicinal products and discusses the latest BRA methods and how to determine their fitness for use. The chapter also provides background on various international BR initiatives that have shaped this field over the past two decades and offers guidance on how to use this report.

Chapter 2 presents an overview of the components of a structured BRA framework, the product lifecycle approach, and the need to consider contributions from patients and/or consumers when assessing benefits and risks. The importance of seeking out and including the patients' voice in the overall assessment of BR is emphasised in this chapter. For further insight into how patients can engage in all aspects of medicine development, regulation and safety, the reader is directed to the CIOMS Working Group XI report published in 2022, entitled: *Patient involvement in the development, regulation, and safe use of medicine*.

Chapter 3 covers BRA methodology considerations and includes a discussion on the fundamental principles in assessing BR. Two new points of emphasis are included: (1) a transition from BR evaluation as a post-hoc exercise to proactively incorporating BR considerations into clinical trial design using a structured framework approach, and (2) a pragmatic patient-centric approach to BRA to ensure proper reflection and evaluation of the benefits and risks as experienced by patients and/or consumers. Methods and current thinking on how to attain these goals are described. Key points to consider in addressing uncertainties when assessing BR are presented as are various approaches to visualisation of BRA and the importance of employing a multidisciplinary team that includes the patient and/or consumer perspectives.

Chapter 4 presents key points to consider in special situations where uncertainty about the risks and benefits of the product is high. Guidance is provided on the selection of an appropriate BRA method to address special situations such as emergency use of a medicinal product, repurposing a product and accelerated approvals. Considerations related to legacy products,[iv] special populations and advanced therapies are also presented and discussed in this chapter.

The report concludes with an Appendix that presents several case studies to illustrate key concepts in approaching BRA of special case medicinal products.

To summarise: this report provides practical guidance on the conduct of high quality, balanced and comprehensive evaluation of benefits and risks associated with medicinal products, which incorporates input from key stakeholders, including patients and/or consumers to inform decision making that ensures these products remain safe and effective throughout their lifecycle.

From the CIOMS Working Group XII

May 2025, Geneva, Switzerland

[iv] **Legacy product:** Legacy products refer to medicinal products previously approved prior to current day regulatory requirements. Proposed by CIOMS Working Group XII.

EXECUTIVE SUMMARY

This CIOMS report describes the benefit-risk (BR) landscape, promotes the use of a structured BR framework (SBRF), and provides an overview of BR assessment (BRA) methods to be used across a medicine's lifecycle. Several important new concepts are introduced in this report and discussion on their relationship to the BRA of medicinal products is provided.

New concepts in benefit-risk landscape presented in this report

- Take a lifecycle approach and continuously assess the BR balance of a medicinal product when new information becomes available.
- Increase the role BRA plays in decision making for medicines.
- Adopt specific BR considerations for new and more complex therapies (for example biologicals; monoclonal antibodies; and cell and gene therapies).
- Integrate new sources of data such as real-world data and patient-reported measures.
- Incorporate BR concepts and strategies into clinical trial design.
- Assimilate pragmatic patient-centric BRA methods.
- Include the patient perspective in the assessment of benefits and risks.
- Structured approaches to evaluate the BR balance of medicinal products.
- Develop and continuously update appropriate documentation of the BRA during the product lifecycle.

Components of a Structured Benefit-Risk Framework

Chapter 2 introduces the components of a SBRF, the lifecycle approach of BR, the role of the patient in the SBRF and the additional quantitative analyses that support the SBRF.

The SBRF includes the description of the therapeutic context with analysis of the disease or condition and of the current treatment options. It then includes the description of the product profile with details on the product's benefits and risks including the clinical importance and level of evidence regarding the selected 'key' benefits and 'key' risks, visually presented in a 'value tree', with a description of the associated uncertainties. Next comes the risk management part describing the activities to further characterise or minimise the risks. Finally, the BRA conclusion acknowledges whether the overall BR balance for the product is favourable or unfavourable. We describe how appropriate documentation of all these components is made across the lifecycle of the medicinal product in the BRA document (BRAD).

This chapter describes how a BR framework provides a structured and systematic BRA approach through the lifecycle of the medicinal product with specific goals and deliverables at each stage from pre-clinical through early development stage, to late development stages, and to the post-marketing/on market stage.

The importance of incorporating the patient perspective into the BRA is discussed, and their input into the various components of the SBRF such as description of the medical needs, input into clinical trial design, selection of 'key' benefits and 'key' risks, and development of risk minimisation measures is emphasised in this chapter.

Lastly, additional quantitative BR analysis methods focusing on when they may be needed, their purpose, specific requirements to consider, and the integration of results into the overall evidence are described in the report.

Case studies are presented to illustrate the use of the SBRF.

Benefit-risk assessment methodology

This chapter focuses specifically on methods used in the BRA process. While this includes presentation of statistical and quantitative methods, it also includes pragmatic recommendations around the conduct of BR related activities.

Important considerations about the assessment of the BRA methodologies, the role of study designs and predefined or post-hoc analysis are reviewed. This chapter also introduces innovative methods related to the patient-level BRA and the role of pragmatic or large simple trials. Guidance is provided on how to gain insights from patients and consumers, how to address uncertainties and how to visualise the BRA. Finally, this chapter details which functions are recommended to be part of a multidisciplinary BR management team (BRMT).

Case studies are presented to illustrate the use of some of the methods discussed.

Benefit-risk assessment methods for special situations

Situations where there is an important lack of information on benefits and risks, and uncertainty over the magnitude of the benefits and risks, create a need to consider their balance in a different way. These situations are becoming more and more common and may cover up to half of recently approved drugs or vaccines entering the market. We cover situations impacting the way we need to evaluate the BR balance due to the nature of the medicine itself, the targeted population or the medicinal product's regulatory status. These situations include emergency use and/or repurposing, accelerated/conditional approval, legacy products, special populations such as rare diseases and paediatric, advanced therapy medicinal products, non-prescription products, and combination products.

Summary

This report describes a number of recent new concepts in the BR landscape both in terms of framework and methods. It is intended to provide insight, guidance and best practices on when and how to conduct a BRA of a medicinal product. It gives many examples and recommendations to be implemented throughout the life journey of medicinal products including how to approach special situations where there remains uncertainty over the magnitude of benefits and risks. Only through the continuous and timely reassessment of the BR balance of medicines with input from those who consume the product, can we ensure that patients are assured access to safe and effective treatments.

CHAPTER 1.
BENEFIT-RISK LANDSCAPE

This report presents and explains the use of a Structured Benefit-Risk Framework (SBRF) for regulatory decisions for medicinal products. The report is in response to the many advancements and changes in the field of benefit-risk assessment (BRA) since the publication of CIOMS Working Group IV report in 1998, *Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals*. This report, which reflects the consensus reached by over forty representatives of academia, government regulatory authorities and industry, includes detailed guidance and advice on approaches, processes, and methods for conducting a BRA.

The terms 'risk' and 'harm' are used interchangeably in this report however, for clarification purposes, it should be understood that 'harm' refers to an undesirable adverse outcome incurred as a result of exposure to a hazard, for example liver injury caused by a medicinal product, whereas 'risk' refers to the likelihood or probability of developing such an adverse outcome.

The report has four chapters. The first chapter provides an overview of the benefit-risk (BR) landscape, the factors influencing BRA, and the types of data and analytical approaches that should be used. Chapter 2 presents an overview of approaches to BRA, including examples from case studies to illustrate basic principles of BRA. Chapter 3 covers specific considerations for methods used in the BRA process. Chapter 4 addresses approaches to BRA under select special situations. The report concludes with a series of Appendices, including a glossary and case examples.

1.1. New context

BRA has become an integrated part of any regulatory decision making for approving medicinal products for marketed use. Without a positive BR balance, a product cannot be approved for marketing, nor can it maintain its approval should new information significantly shift the BR balance post-marketing. The previous considerations established by the CIOMS Working Group IV report published in 1998 focused on the post-marketing phase of a medicines' lifecycle, but it is relevant to extend this to cover the pre-marketing phase. In other words, BRA can and should be applied in most types of regulatory decisions both pre- and post-marketing. The context for the BRA may differ when reviewing, for example, a gene therapy for a rare disease, versus reviewing an Over-the-Counter (OTC)-switch for a well-established product for a common disease. Despite this, the structure and aim for transparency in a BRA should be the same.

BRA should be performed in a transparent manner, based on scientifically sound and robust evidence as well as subjective value judgements, and it will have to allow for external scrutiny by relevant stakeholders in order for the result and its implications to be accepted widely.

The contemporary pharmaceutical development systems benefit from the collaborative efforts of multiple parties such as regulators, health care providers, patients, consumers, advocacy groups, health insurers, pharmaceutical companies, and academia; all of which contribute to the understanding of BR relationships, value judgments and uncertainties.

Next to the above-mentioned improvements related to collaboration and the combination of multiple data sources, the modern approach emphasises the transparency of the decision-making process with more focus on the patient role in decision making.

1.2. New products and new data sources

Pharmaceuticals have over the past decades developed from being small molecules and a few, simple biologicals (proteins, peptides, live (attenuated) vaccines) to also including complex biologicals (e.g. mRNA vaccines, monoclonal antibodies) as well as advanced therapies such as gene and cell therapies. With the gradual advance of our understanding of the molecular pathophysiology behind a wide range of conditions, we see a discovery of potential new targets for therapies that is becoming more and more personalised, moving away from the concept of one drug, or for that matter one dose, fits all. The new products bring promise to influence the disease rather than only symptomatic relief, and in some cases, cure. However, this poses challenges when it comes to designs of clinical trials that may have to span over many years to understand the clinical value of such drugs.

Moreover, there has been an increase in the number of pharmaceuticals targeting rare or ultra-rare conditions where the ability to perform Randomised Controlled Trials (RCTs) is becoming increasingly challenging. In such cases, the BRA will have to be based on the responses seen in a few patients who, in addition, may be heterogeneous with regard to most baseline characteristics apart from the fact that they suffer from the same, rare, condition.

This evolution calls for new methods to establish efficacy and safety. In some of these cases, the use of a control group may not be feasible or ethically acceptable, which either leads to the generation of uncontrolled data, allowing patients to cross over or be given rescue therapy or to the use of historical controls or the establishment of natural history cohorts against which to perform the comparison. Another example is pooling the outcome from patients with rare diseases affecting different organs. This has been done to study new drugs in treatment-resistant bacteria or malignancies in different locations that happen to share a common molecular target and may enter the same (basket) trial.

The aforementioned methodological challenges often call for new endpoints, or more frequently for new surrogate endpoints, which need to undergo rigorous validation before being acceptable for regulatory decision making. In addition, there has, rightly so, been an increased focus on patient and/or consumer experience data, for example, Patient-Reported Outcomes (PROs) and patient preference information, as well as quality of life (QoL) measurements to be incorporated in the BRA. Also, in this case, the development should recognise the challenges with these endpoints, which are often methodological.

The above-described scientific developments, which are in many ways welcomed, are inherently linked to the fact that there remain uncertainties at the time of approval. This calls for structured, transparent BR approaches that not only assess the efficacy and safety evidence but also incorporate important uncertainties. The identified important uncertainties should form the base for the post-marketing program and, consequently, the re-evaluation of BR as these programs generate additional knowledge. In addition, this, together with other global trends, has led to an increased interest in the alignment of decision-making considerations between regulatory agencies and payers and Health Technology Assessment (HTA) bodies when a decision is based on data from post-marketing clinical practice, for example Real-World Data (RWD). Although the focus of this report is primarily on the approval of new products, the concept and consideration of BRA should be applied throughout the lifecycle of a product.

Last, it is important that transparency in these BR approaches is of utmost importance as it allows other stakeholders, such as patients and/or consumers, to make informed decisions about their use of medical products.

1.3. New benefit-risk assessment methods

In the last two decades there has been a shift in the approach to evaluating the BR balance of medicinal products from an unstructured, opaque, and inconsistent assessment often performed by a single individual, to a more structured and transparent process including value-judgements from several stakeholders, as part of the decision-making processes. There have been vast efforts from health authorities and academia to standardise, streamline and improve the BRA process. In the wake of these initiatives, the field of BRA has blossomed, with major advances in methodology and implementation. As a result, several SBRFs, a large number of quantitative methods and visualisation tools have been proposed to facilitate the BRA, which, can be very helpful but can also serve to further complicate the BRA picture. It should also be recognised that many of these approaches bear similarities and, most importantly, the methods are of little value if not used properly. In other words, the challenges in implementing a BRA process in any organisation must be recognised.

The descriptive SBRF forms the centrepiece or the foundation of any BRA. It can be used to select, organise, summarise, and communicate data relevant to any BR decision. Various forms of SBRFs are used widely by regulators and other parties. The European Medicines Agency (EMA) template for BRA used in assessments of all new drugs is a good example of this. However, the systematic use of SBRF tends to focus on the Marketing Authorisation (MA) of medicinal products.

Several SBRFs have been proposed.[1,2,3,4] For example, the US Food and Drug Administration (FDA) has adopted a structured qualitative approach that is designed to support the identification and communication of the key considerations in the US FDA's BRA.[5] The EMA eight-step PrOACT-URL provides a framework for addressing the necessary elements in decision problems and has also been repeatedly used as the basis for other methodologies.[2] The Centre for Innovation in Regulatory Science (CIRS) - Benefit-Risk Action Team (BRAT), i.e. the CIRS-BRAT, was developed to standardise and communicate BRA between the pharmaceutical companies and the regulators, and presents BR results of individual criteria as forest plots.[1] The Unified Methodologies for Benefit-Risk Assessment (UMBRA) follows the same principles and contains all the key features of the other frameworks.[4] These approaches are quite similar in their key components, that is defining the context in which the decision is being made, identifying the important relevant information and data regarding benefits and risks, assessing that information with respect to its bearing on the decision, drawing conclusions from the information based on expert judgment, and communicating the decision and its rationale.

A structured framework evaluation may be supported by or include quantitative methods when appropriate. While numerous methods have been proposed, few are used widely or systematically to support decision making. Instead, these methods tend to be used in select cases that are perceived to be challenging or complex for a range of reasons. An EMA methodology report suggested using quantitative approaches such as Multi-Criteria Decision Analysis (MCDA)[6] when there are major benefit or risk issues on which decision makers have divergent views suggesting that quantification could capture the issues of contention that a SBRF alone is unable to. Also, as interventions are given to individuals, it is important to look at benefits and risks at the patient level to help identify subgroups of patients and/or consumers who may experience greater benefits without associated increase in risks. See case study C.

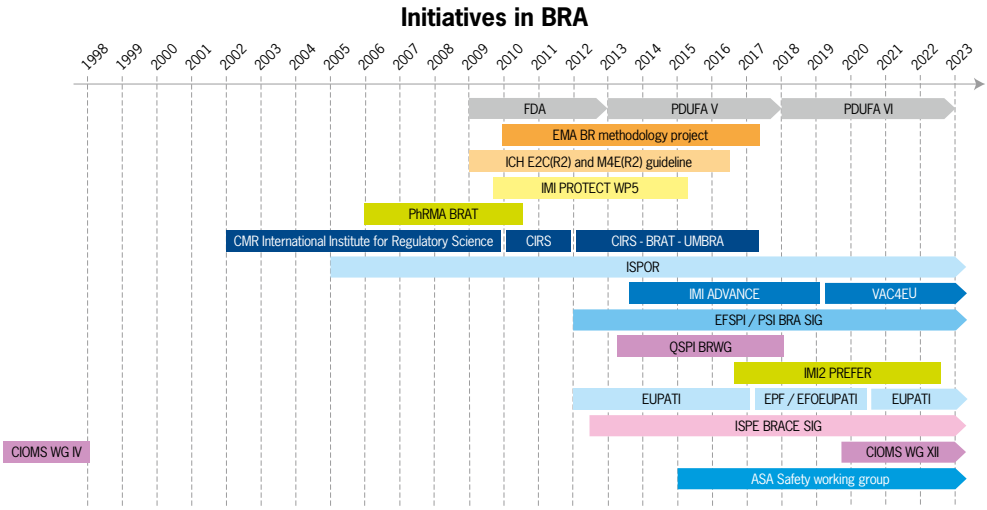
Therefore, a SBRF may be complemented and supported by quantitative BRA methods that include but are not limited to:[7] (i) methods for evaluating benefits and risks at the patient level to provide important insights on the interaction of benefits and risks across patient subsets and over time (ii) methods for quantifying patient preference and satisfaction (iii) methods for synthesising multiple benefit and risk criteria (iv) methods that handle a single benefit and a single risk endpoint and finally (v) methods for characterising uncertainty in BRA.

1.4. International benefit-risk initiatives: the heritage of the CIOMS Working Group IV report

The development of the SBRF and tools, including those described above, has been inspired and driven by several international initiatives focusing on BRA. Figure 1 shows the timeline of several of these initiatives. Please note several initiatives are included for the benefit of historical context but are not discussed in this report; instead hyperlinks are provided for more information.

Figure 1. Timeline of global benefit-risk assessment initiatives

Source: Figure adapted with permission from a BR diagram by the European Federation of Statisticians in the Pharmaceutical Industry (EFSPI)/Statisticians in the Pharmaceutical Industry (PSI) Special Interest Group (SIG) on Benefit-Risk Assessment.[8]



Abbreviations for Figure 1	
ASA	American Statistical Association
BRAT	Benefit-Risk Action Team Framework
CIRS	Centre for Innovation in Regulatory Science
CMR International Institute for Regulatory Science	Centre Medical Research International Institute for Regulatory Science
EFOEUPATI	Ensuring the Future of EUPATI
EFSPI	European Federation of Statisticians in the Pharmaceutical Industry
EPF	European Patients' Forum
EUPATI	European Patients Academy on Therapeutic Innovation
ICH E2C(R2)	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Periodic benefit-risk evaluation report - Scientific guideline
IMI	Innovative Medicines Initiative
IMI2 PREFER	IMI 2 runs from 2014 to 2020 Innovative Medicines Initiative Patient Preferences in benefit risk assessments during the drug life cycle
IMI Advance	Innovative Medicines Initiative Accelerated development of vaccine benefit-risk collaboration in Europe
IMI PROTECT WP5	Innovative Medicines Initiative Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium Work Package 5
IMI VAC4EU	Innovative Medicines Initiative Vaccine monitoring Collaboration for Europe
ISPE	International Society for Pharmacoepidemiology
ISPE BRACE SIG	International Society for Pharmacoepidemiology Benefit Risk Assessment, Communication and Evaluation Special Interest Group

Abbreviations for Figure 1	
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
PhRMA BRAT	Pharmaceutical Research and Manufacturers of America Benefit-Risk Action Team
PSI BRA SIG	Statisticians in the Pharmaceutical Industry Benefit-risk assessment Special interest group
QSPI BRWG	Quantitative Sciences in Pharmaceutical Industry Benefit-Risk Working Group
UMBRA	Unified Methodologies for Benefit-Risk Assessment
US FDA PDUFA V and VI	United States Food and Drug Administration Prescription Drug User Fee Act guidance documents

One of the key initiatives in the development of standardised approaches to BRA has been work by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), which consists of representatives from both regulatory authorities and pharmaceutical industries. The ICH has formulated guidelines covering the format and content of BRA pre-approval (ICH M4E R2)[9] and post-approval (ICH E2C-R2).[10]

In the M4E(R2) guideline, ICH provides guidance focussing on the BRA of the medicinal product in the proposed indication(s) by the sponsor for marketing approval by the regulators. It is recommended in the Clinical Overview to begin with a succinct explanation of the reasoning and judgement used in assessing and weighing the key benefits and key risks. The sponsors should explain how any uncertainties affected the interpretation of the evidence and their impact on the BRA. When describing the BRA, ICH recommends the following additional aspects be considered:

- Therapeutic context and patient and/or consumer perspectives;
- Severity of disease and how expected benefits could influence the acceptability of the risks;
- How the medicinal product addresses a medical need;
- Key aspects of risk management including labelling that are important in reaching a favourable BRA;
- Whether non-responders can be readily identified allowing them to discontinue treatment, and where this might be appropriate;
- Other risk management activities.

There are many approaches available for conducting BRA, and the ICH guideline does not prescribe a specific approach. A descriptive approach that explicitly communicates the interpretation of the data and the BRA will generally be considered adequate. A sponsor may choose to use methods that quantitatively express the underlying judgments and uncertainties in the assessment. Analyses that compare and/or weigh benefits and risks using the submitted evidence may be presented. However, before using any one method, the sponsor should consider its utility, complexity, the extent to which the method is established, the data quality and the ease of interpretation of the results. In this situation, the written summary and explanation of the conclusions should be provided in the main body of the Clinical Overview including any summary tables or figures, while detailed presentations of the methods, assumptions, data, and results can be included in an appendix.

Both the EMA[11] and the US FDA[5] have published reports and guidance[12] on the use of structured frameworks for BRA. The EMA report considers adoption of quantitative tools, while the US FDA Guidance focuses more on '…. a qualitative, subjective judgment that weighs data and information about the drug's benefits and risks, and considers uncertainties within a specific therapeutic and regulatory context'.[12]

Post-marketing covers the concept of Periodic Benefit-Risk Evaluation Reports (PBRERs), which replaced the previous concept of Periodic Safety Update Reports (PSURs). The idea is that safety cannot be seen in isolation, and both benefit as well as risk information continues to evolve during the product lifecycle. It is therefore very important to monitor both benefits and risks on a continual basis and evaluate the BR balance regularly within the PBRER process. Data are submitted by the Marketing Authorisation Holders (MAHs) to the regulatory authorities according to the ICH E2C (R2) guidance. This guidance provides recommendations on the format and content of the PBRER outlining points to consider in its preparation and submission to regulators.

There are a number of areas where the PBRER guidance introduced in 2012 has expanded in scope from the original E2C requirement for a PSUR, which was introduced in 1996. These include:

- Re-focussing from safety to BRA and risk management;
- Clear guidance for the content of an Executive Summary;
- Reference Information including indications, for example from the Company Core Data Sheet (CCDS);
- Section on new, open and closed safety signals;
- Description of identified and potential risks and missing information, making a link to risk management approaches;
- Discussion of benefits as well as an integrated BRA;
- Proposed action(s) to optimise the BR balance, as appropriate.

1.4.1. Innovative Medicines Initiative: IMI-PROTECT

The IMI-PROTECT project, which is about Pharmacoepidemiological Research on the Outcomes of Therapeutics by a European ConsorTium, was initiated by the Innovative Medicines Initiative (IMI) in April 2009. The EMA and GlaxoSmithKline were named as the project co-coordinators and tasked with managing a multi-national consortium of 34 partners. The overall goal of this project was to develop new and innovative methods in pharmacoepidemiology and pharmacovigilance to improve and strengthen the monitoring of the benefits and risks of medicines marketed in the EU. The PROTECT project was initiated in September 2009 and was run over a five-year period.

In line with its mandate, PROTECT undertook to examine the strengths and limitations of the current methods used in pharmacoepidemiology and pharmacovigilance to strengthen the monitoring of the BR balance of medicines marketed in the EU. Furthermore, PROTECT developed and validated a set of new tools and explored new approaches to integrate BRA methods into scientific assessment of medicines with a particular emphasis on visual methods to display BR profiles in order to facilitate subsequent communication of these benefits and risks to patients, regulators, and the general public.

For further information on the five work packages defined in this project and their results please visit https://imi-protect-eu.cc.ic.ac.uk.

1.5. Assessing benefit-risk assessment methodologies

The assessment of BR balance is a complex and multi-dimensional activity, which changes in focus and scope depending on the nature of the intervention, the context, and the target decision maker and involved stakeholders. BRA activities also aim to support decision making by the patient, primarily supported by the interaction with the Health Care Professional (HCP). This highly personalised final step rests on a complex network of assessments and decision-making processes. Key in this interaction is transparency; this is particularly important when it comes to subjective value judgements.

Four major stakeholder groups drive the overall process: patients and their social environment, health care systems (including physicians and payers), sponsors, and health care authorities. As will be discussed in Chapter 4, a range of methods are used by these respective stakeholders, as well as specialised approaches that meet the unique needs of each one.

Overall, two principles permeate all these activities. One is the desire to make the right decision for the target patients in a given country/region, based on a rigorous and comprehensive analysis of the available information, as well accounting for identified or anticipated uncertainties. The second is the ability to clearly communicate the rationale for the decision, especially for the primary target audience.

The primary focus of the current document is on the BRA of individual medicinal products throughout their lifecycle. In doing so, the respective health authorities and product developers must take into consideration all the other factors that influence the process leading all the way to the patient or person that consumes the product.

In this overall context, it is important to acknowledge and remember that specific BRA methodologies may be chosen depending on different treatment modalities or the primary purpose of the assessment. Such is the case for non-prescription medicinal products,[i] medical devices, diagnostic methodologies, medical and surgical interventions as well as alternative and complementary medicine interventions. The complexity of decision making and variability achieves another level when it comes to considerations of local medical standard of care as well as the socio-economic environment including the field of HTAs. The context for the individual patient or consumer is further influenced by their life circumstances, including the cultural context and the access to health care.

1.6. Purpose statement

This report supersedes the CIOMS Working Group IV report and puts forward a lifecycle-based approach to the BRA of medicinal products to support decision making and transparent communication. A core structured, descriptive approach is established that can be supplemented, as needed, by more advanced qualitative and quantitative methods. In particular, this CIOMS Working Group XII report emphasises the use of patient-centred approaches. Assessments should involve multidisciplinary teams and should be informed by the perspectives of key stakeholders.

[i] **Non-prescription medicinal products:** In this report, non-prescription medicinal products refer to over-the-counter products that have typically transitioned from prescription products to non-prescription products. This excludes e.g. vitamins, supplements and the traditional food industry. Proposed by CIOMS Working Group XII.

Chapter 1 – References

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CHAPTER 2.
STRUCTURED BENEFIT-RISK APPROACH/ FRAMEWORK

2.1. Introduction

The call for use of a structured approach to BRAs for the approval of new drugs by regulatory agencies has a somewhat complex and surprisingly short history[1] but significant progress has been made in a relatively short period of time since the CIOMS Working Group IV report was published in 1998. The report noted:

> *'There are no accepted general methods for deriving a "benefit-risk ratio" or another composite metric, or for using such measures to compare relative merits of alternative treatments. As ordinarily used, therefore, the benefit-risk "ratio" compares figuratively, but not often quantitatively, the relative magnitudes of benefits and risks' and, '…in the absence of a readily available and quantitative relationship between benefits and risks, which is commonly the case, evaluation usually comes down to analyses and conclusions that rely on indirect, informal and unavoidably subjective processes.'*[2]

The CIOMS Working Group IV report provided a foundation on the existing state of the science around BR balance, as well as forward looking recommendations. Since then, there have been several international collaborations and initiatives on structured approaches for greater transparency and consistency in BRA.

2.1.1. Definition of Structured Benefit-Risk Framework

A SBRF provides a systematic approach for evaluating BR, developing risk management options and determining BR trade-offs of medicinal products. The SBRF highlights a number of important considerations and a structured process for assessing key benefits and key risks as well as associated uncertainties. The framework provides a systematic yet flexible approach for incorporating study outcomes and preference weights in BRA as well as strategies for communicating the rationales for BR decisions. In addition, the SBRF can be supported by the use of quantitative methodologies for complex problems to help address specific questions related to benefits, risks, BR trade-offs and associated uncertainties.

2.1.2. Purposes of Structured Benefit-Risk Framework

The ultimate purpose of following a structured approach is to support good decision making but it also serves the purpose of communication, training, and documentation both by sponsors/industry and by regulatory authorities. The US FDA currently uses its SBRF in its New Drug Application (NDA) and Biologics License Application (BLA) reviews, and both US Center for Drug Evaluation and Research (CDER) and US Center for Biologics Evaluation and Research (CBER) have incorporated the BR summary table in clinical review templates. Because the framework is explicit about documenting the dimensions being assessed and the evidence considered, it helps to focus the review on the

evidence or uncertainties that have contributed to the final BR conclusions. It also helps to provide valuable feedback to sponsors even in cases where the conclusion of a review does not support product approval allowing the regulator to point to the evidence, or lack of evidence, leading to the regulatory decision. Pharmaceutical companies use BRA to assess and determine the company's BR position and strategy and to inform dose selection, and go/no-go decisions in their drug development programs. Additionally, pharmaceutical companies use BRA as they develop risk minimisation strategies such as product labelling and use in special populations, and the product use in the post-marketing period. A structured framework could also aid the communication among the multidisciplinary team within an organisation or external communication between different stakeholders such as regulatory agencies, pharmaceutical companies, scientific advisory committees, HCPs, academics, patient, consumer and advocacy groups and the public. Finally, the use of a SBRF may enhance consistency of regulatory decision making by regulatory agencies.

A SBRF can be used throughout a product lifecycle providing a structured approach to BR planning and ongoing product optimisation during early product development through to the approval and marketing of a product. See Section 2.3 on Lifecycle approach to benefit-risk assessment.

2.1.3. Examples of structured benefit-risk framework

A few SBRFs are in the public domain; each with its unique perspective and focus. The key attributes of some of the well-known frameworks are summarised in this section.

The BRAT framework

The BRAT (Benefit-Risk Action Team) framework[3] includes a six-step process, as shown below, with goals for both better BR decision making and communication to stakeholders.

1. Defining the decision context involves specifying the therapeutic context, comparator to use of the product, time horizon for exposure, measurement of benefit and risk, and specifying the perspective of stakeholders (sponsor, regulators, prescribers, patients, etc.).
2. Identifying benefit and risk outcomes: building the value tree includes defining – preferably prospectively – the benefit and risk outcomes which will be considered in the assessment.
3. Identifying data sources for the framework refers to the information or data which will be input into the framework.
4. Customising the framework requires taking into account the quality and characteristics of the data which will be used and updating the value tree accordingly.
5. Assessing relative importance of different outcomes recognises that outcomes will have different weights or importance based on their severity or relative benefit to the patient.
6. Displaying and interpreting key benefit-risk metrics involves the creation of a Key Benefit-Risk Summary (KBRS) table to help users to readily grasp the key issues.

The PrOACT–URL framework

The PrOACT–URL (Problems, Objectives, Alternatives, Consequences, Trade-offs, Uncertainties, Risk attitudes/risk tolerance, Linked decisions) framework is a decision-making framework with the following eight steps:[4]

1. Problems – Determine the nature and context of the problem;
2. Objectives – Establish the objectives which are to be achieved;
3. Alternatives – The options to which the intervention will be compared;

4. Consequences – How each alternative compares in terms of outcomes for the criteria being evaluated;
5. Trade-offs – The balance between favourable and unfavourable effects;
6. Uncertainties – The uncertainties associated with the favourable and unfavourable outcomes or how the balance between these outcomes is affected by uncertainty;
7. Risk attitudes/risk tolerance – The relative importance of the decision maker's attitude towards risk;
8. Linked decisions – The consistency of this decision with similar decisions in the past.

The US FDA Benefit-Risk Framework

The US FDA Benefit-Risk Framework has been published as a draft guideline.[5] It is designed to consider the therapeutic context including the condition being treated and treatment alternatives, the evidence on benefits and risks which are either being submitted for a NDA or found in the post-marketing period, the uncertainties of the benefits and risks, and the regulatory options the US FDA has at its disposal to manage risks or reduce uncertainties.

Some of the frameworks such as BRAT and PrOACT–URL describe a set of processes and tools for selecting, organising, weighting outcomes, summarising, and interpreting data that is relevant to the BR decisions. The others such as US FDA Framework mainly focus on the dimensions of considerations in BRA. The commonalities of these frameworks are to determine whether the benefits of a medicinal product outweigh the risks based on the totality of the evidence, which includes therapeutic context, benefit and risk evidence, uncertainty, weight of benefits and risks, and risk management options. In this chapter, we propose a SBRF, which includes key common elements of existing frameworks, how this SBRF can be applied throughout the product lifecycle for BRA and decision making, how patients and/or consumers can play an important role in SBRF and how additional quantitative analysis can support the SBRF and assist the BRA for complex problems.

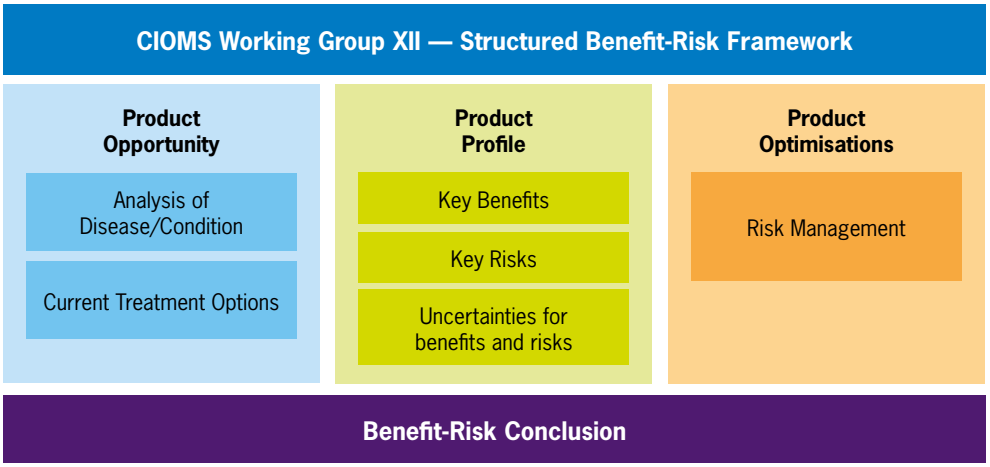
2.2. Components of a Structured Benefit-Risk Framework

Figure 2 depicts the components of a SBRF recommended by the CIOMS Working Group XII. Appropriate documentation of the BRA for each of these components is needed. A Benefit-Risk Assessment Document (BRAD) should be developed as early as possible in a product lifecycle, starting in early drug development and updated continuously post-product licensure. Early in a product's lifecycle, the BRAD may not be complete and there is more uncertainty about both benefits and risks, however, as more data become available along the product's lifecycle, the BRAD becomes more robust. While early development of the BRAD is encouraged, pharmaceutical companies can make their own decision depending on the needs to inform decisions and the new information that becomes available. The BRAD may either inform other critical documents throughout a product's lifecycle (i.e. safety plan, development Risk Management Plan (RMP)[i], or RMP) or be informed by other documents (i.e. Investigator's Brochure (IB), clinical study reports (CSRs) etc.), which are developed during the clinical development process. The end of Phase 2 clinical trial could be a critical point for development or update of the BRAD since it can provide information that may assist in appropriate design of Phase 3 clinical trial to generate BR evidence required for market approval. Each component of the SBRF and corresponding documentation in the BRAD will be reviewed.

[i] The development Risk Management Plan (RMP) is a non-mandatory, internal document used by some pharmaceutical companies during the development of their Risk Management Plan (RMP). The BRAD is often used in lieu of this document.

Figure 2. Components of a Structured Benefit-Risk Framework – perspective of CIOMS Working Group XII

Source: Modified from ICH M4E(R2),[12] EMA PROACT-URL, and other BR frameworks [4, 6]



2.2.1. Product opportunity - therapeutic context

It is essential that any evaluation of the benefits and risks of a medicinal product considers the therapeutic context which consists of the disease or a condition that the drug is intended to treat, the population intended to be treated, and the benefits and risks of currently available therapies, since therapeutic contexts vary a great deal depending on the target of the medicinal product. It is particularly important to consider the target population in cases where a serious risk is associated with the medicinal product and to ensure the benefits outweigh the risks for that population. The tolerance level for potential serious risks might be different depending on the therapeutic context. Greater risk may be acceptable if there are no other available therapies.

Analysis of disease or condition and unmet medical need

The nature and severity of the disease or condition, unmet medical need and the intended population that would be covered by the indication should be the focus of the discussion. Below is some further elaboration.

- **Incidence and prevalence** – The incidence or prevalence of the disease should be discussed. Perspective on frequency of the disease to be treated allows for a determination of the size of the to-be-treated population and thereby the extent of exposure a product may have if approved.
- **Disease duration** – Whether the disease is acute, progressive or chronic should be described. Prolonged (i.e. lifelong) treatment period may impact the risk tolerance for a product. A long-term characterisation of the risk may be needed as part of the product lifecycle, particularly for risks with longer duration to onset (i.e. malignancy).
- **Mortality and severity** – Patients suffering from serious diseases (i.e. those that are life-threatening) may tolerate more risk.[7] An example is the relaunch of thalidomide to treat life-threatening multiple myeloma, while use of the drug during pregnancy is known to cause severe side effects to the foetus including malformation of the limbs.[8] The safety profile of thalidomide may be acceptable in patients with a malignant tumour if a strict pregnancy prevention program is imposed.

- **Quality of life** – Impact on QoL of a patient with a disease or condition to be treated given currently available therapies. Introducing this concept early in the BRAD allows for the narrative to be developed if there is a positive impact on QoL with the medicinal product being evaluated. An example is a discussion in the key benefits section about the improved QoL by use of a medicinal product under evaluation among rheumatoid arthritis patients compared to the QoL pre-treatment or QoL from use of other inadequate treatments.
- **Societal or public health implications** – The outcome of the treatment intervention in terms of social impact should be discussed. For example, the outcome of poor prevention and control of an infectious disease could cause severe medical, economic and societal interruption, e.g. the treatment for the Coronavirus disease 2019 (COVID-19) global pandemic.

Any uncertainties (i.e. natural disease progression not known) in above areas should be identified. If there are important differences in disease outcome or severity in a specific subpopulation, these should be highlighted in the analysis of disease and need to be addressed in the BRA. Including a description of the subpopulation in this early section of the BRAD, helps to build a cohesive narrative in the BRAD.

Current treatment options

The discussion should focus on the aspects of the currently available disease management options for the disease or condition (i.e. those therapies used most frequently and/or recommended in clinical guidelines), their key benefits and key risks, and the intended population (i.e. to-be-indicated population). These management options (curative, resulting in remission, symptom control, or palliative depending on the disease or condition under treatment) include both pharmacologic and non-pharmacologic interventions such as drugs, surgical procedures, diet modifications or physical therapy authorised by regulatory authorities and/or supported by established clinical practice or clinical guidelines. They could be standard care or more advanced treatment. For a particular patient, one or more options could be applied. If there are no available treatments or there are limitations of current treatments to treat the intended population, this should be noted.

An understanding of the disease or condition and uncertainties in the benefits and risks of current therapies and how well the patients' needs are being met by current therapies should also be discussed. Identification of patients' medical needs in terms of efficacy, safety, tolerability, convenience, or preference is important. If possible, the product being evaluated in the BRA should fill an unmet need for the patient population with the disease or condition to be treated. For example, in a disease such as rheumatoid arthritis, there may be an unmet need for more effective products among patients who did not benefit from prior treatment.[9] This should be described in this section, and the product profile may include a key benefit of complete remission or low disease activity in the population who did not achieve their treatment goals with their prior biologic therapies. A patient's perspective of unmet need in the context of the current treatment options may be sought using qualitative or quantitative methods (see Sections 2.4 on Role of the patient in Structured Benefit-Risk Framework and 3.3 on Methodological considerations to gain patient insights).

2.2.2. Product profile

This component of the SBRF can be viewed as the core of the BRA. This is where details about the benefits and risks of the product are considered, which inform the BRA and its conclusions. Uncertainties about the key benefits and key risks are also included here. In early development, the content of this section of the Product Profile of the BRAD may be limited, however, as further data are gathered during clinical development, this section of the BRAD becomes more robust. The evidence of key benefits may be captured through well designed clinical trials and populated in the BRAD as they become available. The same may be done for risks, which may be anticipated

based on a product's class mechanism or included based on regulatory interest but evidence may be lacking early in clinical development.Benefits for a product are the favorable effects the product is intended to provide, such as curing a disease/condition, slowing its evolution or alleviating its symptoms, and the probability of achieving such results. Risks are unfavorable or harmful effects associated with the product. Risks may also include drug interactions, potential for overdose, misuse or abuse, risks identified in the non-clinical data, risks based on pharmacologic class or current knowledge of the product, risks to those other than the patient (e.g. fetus) and device related risks.

A critical step in any BRA is determining which are the key benefits and key risks for the product in a given indication. A useful tool is a value tree (see Figure 3 ahead). It provides the flow and description of the key benefits and key risks in the BRA. A cross-functional BR Management Team (BRMT) (see Section 3.6 on The multidisciplinary Benefit-Risk Management Team) should be formed to discuss the key benefits and key risks, and develop a commonly agreed value tree. Below are key points to consider when determining the key benefits and key risks:

BENEFITS

- A key benefit is one which demonstrates the efficacy required for approval of a product in a specific indication. It may also highlight aspects of efficacy which may be unique for a product, and which can provide support for how the product fulfils an unmet need.[10] In early drug development, the evidence for a key benefit has not been established and therefore cannot be included in the BRAD. Determination of the key benefits at the early stages of development is primarily based on the compound mechanism, properties demonstrated by non-human data, and unmet medical needs identified in the 'Product Opportunity' of the SBRF. The key benefits may be refined when more evidence become available. For marketed medicinal products, the benefits demonstrated as well as the benefits newly identified through post-marketing studies and post-market experience can be updated in the PBRER.
- A key benefit is usually used as the primary endpoints in the clinical trials to establish efficacy or, sometimes, safety of a product for a specific indication.
- A key benefit can also include benefits from among the secondary endpoints, which are considered clinically meaningful and commonly used in clinical practice. These may also be benefits which are included in product labelling since they are relevant to prescribers. An example of this may be health economics outcome research (HEOR) endpoints which may not be primary endpoints of a clinical trial, but which are clinically important and relevant to patients, and therefore may be included in product labelling.
- A key benefit may be a benefit considered relevant to a specific subpopulation (e.g. paediatrics patients).
- A key benefit may be a benefit considered relevant to patients (i.e. PROs characterising QoL, functional improvements, convenience etc.), since these may differ from clinical trial endpoints considered by regulators or prescribers and may need to be captured differently in a BRA.

RISKS

- A key risk is one that is required to contextualise the benefits of a product in a specific indication. [10] When assessing a key risk the team should discuss the severity, frequency of the risk, reversibility, and duration. A key risk should usually include important, identified risks in the list of safety concerns of the product in the Risk Management Plan (RMP) per Good pharmacovigilance practices (GVP) Module V Revision 2,[11] since these are considered associated with the product and might have an impact on the BR. This includes the risks for which there are additional Risk Minimisation Measures (RMMs) or risks requiring minimisation such as Risk Evaluation and Mitigation Strategies (REMS) in the US.

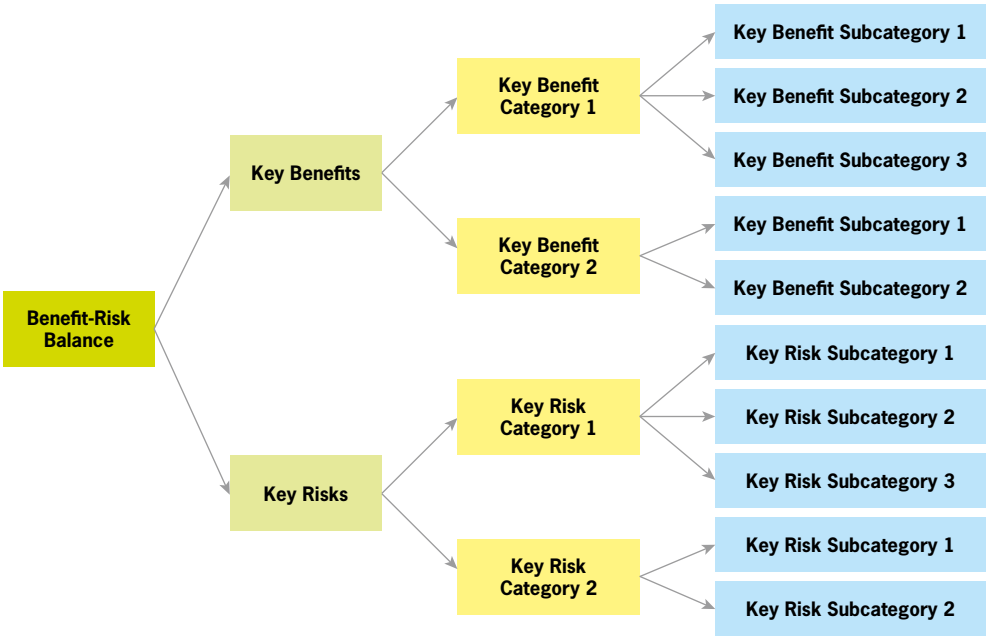
- A key risk may include important potential risks in the list of safety concerns for the product, however not all important potential risks in the list of safety concerns need to be included as a key risk. The BRMT will need to consider each important potential risk and determine whether they need to be included if they impact the BR profile of the product. Important potential risks of regulatory importance (e.g. public health risks) to consider in BRA may be those which, if confirmed, may require risk minimisation beyond product labelling.
- A key risk may also include risks of regulatory importance such as those associated with a class of medicinal products.
- A key risk may also include risks which are not in the RMP, for example, those that impact patient tolerability, QoL and/or patient convenience. These types of risks may not be included in the RMP because they are either difficult to measure or infeasible to mitigate.
- A key risk may also include those risks considered relevant to a specific subpopulation (e.g. elderly patients).

The value tree[12] is crucial to defining what aspects of benefit and risk will be detailed in the BRA. The value tree exercise helps to focus the BRA on specific aspects of efficacy and safety which are deemed relevant. In addition, as will be described later, it also provides the basis for which endpoints may be included in a visual presentation of BR in the BRAD. Due to the overlap in key risks with important risks included in a RMP or BRAD, some key risks are further elaborated on in the Development Safety Update Report (DSUR) or PBRER. Additionally, a BRA for a specific indication will inform the BR evaluation required in a PSUR/PBRER (i.e. Section 18 of the PBRER).

As illustrated by Figure 3, multiple key benefits and key risks are identified and included in a BRA. The general descriptions of these key benefits (e.g. viral clearance, and improvement in function) and key risks (e.g. major cardiovascular events, and gastrointestinal haemorrhage) are described using the branches of 'Key Benefit Category' or 'Key Risk Category'. The end branches 'Key Benefit Subcategory' and 'Key Risk Subcategory' are subcategories of each Key Benefit or Key Risk and may be the defined endpoint to be measured related to each key benefit and key risk. A separate value tree can be developed if the BR profile of a subpopulation is different from the general patient population and a BRA for a specific population is needed for comparison with the general population.

Figure 3. Example of a benefit-risk value tree structure – a visualisation tool used to display key benefits and key risks of a product by indication

Source: Modified from a figure from the Benefit Risk Action Team (BRAT)[3] with permission



Clinical importance and key evidence for the benefits

Each key benefit from the value tree is assessed in the BRA and may include: (1) clinical importance and patient relevance; (2) key evidence supporting the key benefit.

Based on the value tree, further discussion and alignment of the cross-functional BRMT will be needed on the selection of endpoints for the clinical study(ies) to generate evidence for each key benefit. This discussion may take time since many clinical development programs may include multiple endpoints to assess varying aspects of the same benefit. The team would need to align on which endpoint to include in the BRA. Typically, this may be a primary endpoint or key secondary endpoint. To reach a consensus, the BRMT discusses and aligns on the key benefits to include in the BRA. Possible reasons to consider endpoints for key benefits include that:

- They represent an accepted endpoint in determining the clinical efficacy of a product by regulators and/or disease guidelines;
- They are a meaningful endpoint based on a patient's perspective which includes PROs.

In the BRA, a rationale for why each specific key benefit endpoint has been selected is crucial and it may be helpful to include in the BRAD. The rationale may include why the endpoint is important for clinical evaluation of a disease status based on currently accepted clinical practice. It could also include detail on frequency and severity of a specific aspect of the disease under treatment. For example, in a disease such as atopic dermatitis, itching is a primary symptom reported by over 90% of patients with moderate to severe atopic dermatitis.[13,14,15] Further description of the intensity, severity, characterisation of the itching could also form part of the clinical importance section. In addition, if the endpoint, which will be used to demonstrate efficacy of the product, is well established or recognised, this should be mentioned so the reader is made aware of the validity of the endpoint.

Once clinical importance of the key benefit has been described, key evidence is then provided, usually including study data demonstrating the effectiveness of the product. When multiple studies are part of the clinical development program, integrated data are used. Integrated data are typically based on what is prepared for the product submission.[16] If the clinical development program has included comparator groups and/or study arms, characterisation of the key benefit should be in accordance with the Statistical Analysis Plan (SAP) or statistical section of the protocol and may include comparison to the comparator (placebo and/or active comparator) through the relevant timepoint defined by the clinical study endpoints, as appropriate.

The most relevant timepoint as defined in the clinical study (e.g. short-term comparing the product to a comparator) should be discussed, but should also consider commenting on long-term efficacy based on available data, so that duration of treatment effect is elaborated on. Results in key evidence may be based on the overall study population, however, subpopulation analysis may also be considered if a subpopulation's BR profile is different compared to the overall population.

- **Example 1** - Using the example of moderate to severe atopic dermatitis, if a moderate reduction in the worst pruritus numerical rating scale is shown for the overall population; however, if efficacy of the product supports clinical benefit in a younger population considering the epidemiology of the disease condition, inclusion of an analysis for this subpopulation as part of key evidence may be done.
- **Example 2** - Another example may be for a subpopulation which may be more difficult to treat. For instance, if a patient has used multiple therapies such as biologic therapies for an immunologic disease and has not responded to the treatment with the biological drug (inadequate responder to biologics [bio-IR]), it may be helpful to show that the product is non-efficacious in this bio-IR subpopulation.
    - This may be highlighted using data from the clinical development program in the key evidence section.
- **Example 3** - As another example, efficacy or risk of a product for an older subpopulation may be different from the overall study population, and thus a separate discussion on this older population may be warranted.

The key benefits should be included on the BR visual or graphic presentation (see Section 3.5 on Approaches to visualisation of benefit-risk assessment), but tables providing efficacy data should also be considered to be included in the BRAD. Not all efficacy data needs to be part of a table, but primary or key secondary endpoints, which support the key benefits may be included along with supporting statistical values. (See paragraphs on Uncertainties in Section 2.2.2 on Product profile, and Section 3.4 on Methodological considerations for addressing uncertainties in benefit-risk assessment).

Clinical importance and key evidence for the risks

Similar to the key benefits, each key risk in a BRA is determined during the value tree discussion. Discussion and alignment of the BRMT is needed to determine which key risks will be included in the BRA. Possible reasons to include specific risks for discussion with the BRMT include the below.

- The risks determined to be an important identified risk for the product based on sufficient evidence establishing a causal association between the product and the risk. These risks will usually be key risks in a BRA. See the *Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2)* of 28 March 2017.[11]

- Important potential risk (there is not sufficient evidence to establish a causal association between the medicinal product and the risk) for the product with potential outcome of great impact on the BR of the product based on the severity or frequency of the outcome. Since not all important potential risks are considered as key risks in a BRA, these potential risks may require more discussion to gain alignment on whether or not they should be included as a key risk. The cross-functional team may decide to include a potential risk if the risk is known to be of interest to the class of drugs or is known to be of concern to the regulatory authorities. Additionally, if the potential risk may have severe outcomes if not treated appropriately or recognised early enough, the cross-functional team may decide to include it as a key risk, since BR favourability may be impacted if a patient develops this risk.

Clinical importance may be described in the BRAD for each key risk, so the reader is informed on the rationale for why a specific risk was selected for the BRA.

- **Example 1** - a key risk for a product used in the treatment of moderate to severe atopic dermatitis may include serious infections. In the clinical importance section, a description of the frequency of serious infection in atopic dermatitis and how impact of the product on this frequency may further increase this risk could be explained. In addition, the impact of a serious infection on morbidity and mortality could be described to justify why serious infections are a key risk for a product in treatment of atopic dermatitis.
- **Example 2** - for a product used to treat Acute Myeloid Leukaemia (AML). The product may cause tumour lysis syndrome, and this may be determined to be a key risk for the product. In addition, during clinical studies, the frequency of tumour lysis syndrome is observed to be higher than a comparator treatment for AML. It would be appropriate to include tumour lysis syndrome as a key risk since it would factor into the BRA for this product. The product may be more highly efficacious compared to the comparator product however, this higher efficacy would need to be evaluated in context with the higher risk for tumour lysis syndrome. Are there certain subpopulations where efficacy remains high, but the risk for tumour lysis syndrome is similar to the comparator product? This could be detailed in the efficacy section of the BRA and then for the specific key risk of tumour lysis syndrome and summarised in the conclusions.

Supporting the identification of the clinical importance of the key risks above, the key evidence should include clinical study data to characterise the safety of the product for the key risk. During the lifecycle of the product, other sources of safety data may also be used. (See Section 2.3 on Lifecycle approach to benefit-risk assessment). When multiple clinical studies are part of the clinical program, integrated data (i.e. data sets used in the integrated summary of safety SAP) are used. Early discussion with regulatory agency(ies) on what data to include, how to integrate them and what is appropriate for regulatory submission may be helpful.

If the clinical development program has included comparator groups or study arms, characterisation of the key risk should include comparison to the comparator (placebo and/or active comparator) through the relevant timepoint defined by the clinical study endpoints. Ideally, the safety data used should come from the same source as the data used to provide evidence for the key benefits (same studies, comparators, and duration).

Similar to what has been discussed for the key benefits, based on the value tree, further discussion and alignment of the BRMT will be needed for which endpoints from the clinical study(ies) will provide evidence for each key risk. Typically, standardised searches may be applied using MedDRA SMQs[17] and/or similar approaches used to identify cases for evaluation of the key risk as was done for the clinical summary of safety. If post-marketing data are used in the BRA, they would usually be discussed separately from clinical trial data due to the differences in collection, scope, and completeness of the data. In a format of SBRF, a separate section for post-marketing data may be added so that important characterisation of a risk may be included.

In addition, the team should include the most relevant timepoint as defined in the clinical studies (i.e. shorter term comparing the product to a comparator) for the safety assessment but should also consider commenting on long-term safety based on available data. Additional characterisation such as time to onset can be provided especially if risk management relies on timing (early following treatment initiation versus weeks to months after initiation) and when the risk may be most likely to occur.

Other considerations for evidence for the risks should be based on the overall study population, however, subpopulation analysis may also be considered for inclusion if these are considered of interest. For example, using the example of a product for treatment of AML, if tumour lysis syndrome is a key risk, it may be helpful to provide evidence for the risk in an older population since there may be concern for this risk in this more vulnerable population. This will allow the reader to obtain information on the benefit of the product in the older subpopulation with characterisation of the key risk of tumour lysis syndrome permitting some conclusion to be drawn on the benefit and risk of the product in the older population.

The key risks should be included on the BR visual or graphic presentation in the BRAD (see Section 3.5 on Approaches to visualisation of benefit-risk assessment), but also tables with both short and long-term frequencies for the key risks should be included as part of key evidence. Again, data comparing the product to a comparator is much more informative and should be included. Example of a table is shown below in Table 1.

Table 1. Sample table showing short- and long-term frequencies for key risks for product X

Source: CIOMS Working Group XII

	Short-term analysis set				Long-term analysis set		
	Placebo Week 12 N=XX XX PY	Product Dose X Week 12 N=XX XX PY	Product Dose Y Week 12 N=XX XX PY	Active Comparator Week 12 N=XX XX PY	Product Dose X Week 52 N=XX XX PY	Product Dose Y Week 52 N=XX XX PY	Active Comparator Week 52 N=XX XX PY
Serious infections	N(%)	N(%)	N(%)	N (%)	Exposure adjusted rates	Exposure adjusted rates	Exposure adjusted rates
Major Adverse Cardiovascular Event (MACE)	N(%)	N(%)	N(%)	N (%)	Exposure adjusted rates	Exposure adjusted rates	Exposure adjusted rates

Focus of benefit-risk assessment when multiple doses have been evaluated in clinical trials

Clinical development programs may select and assess single or multiple, different doses of a product for approval. Different doses may be required for treatment of a disease with different severity or for a different patient population. If this occurs, then the key evidence section of BRAD should include data from each dose considered for approval. In the scenario where a dose was a part of the clinical development program but is no longer considered for approval, full data on that dose would no longer be needed in the BRAD. The evolving BRAD versions should document the

dose assessment and dose selection decisions during the product's lifecycle. If safety data from an unselected dose provides context about a key risk (i.e. there is a higher frequency and/or severity of a key risk at the higher dose hence it was not selected for further development), the BRMT may consider including this context when characterising the key risk. Also, it may be helpful to provide the dose selection rationale in the appendix of the later BRAD as background information when it is needed, while allowing focus of the BR on the to-be-proposed dose in the targeted population. The dose selection rationale may be included as part of Section 2.5.6 of the Clinical Overview at the time of a product submission.

Visualisation of key evidence in a Benefit-Risk Assessment Document

A BR visual or graphic presentation is crucial to concisely summarise benefit and risk information in one place. (See Section 3.5 on Approaches to visualisation of benefit-risk assessment). A BR forest plot is frequently used, but other types of visualisations may be used if they may better contextualise the data. Examples of other types of useful visualisations include: heatmaps, waterfall plots and tornado plots.

Uncertainties

In this section, we summarise the key uncertainties related to the key benefits and key risks that could impact the BRA. This is not an exhaustive list but highlights the main sources of uncertainty from clinical trial studies, which are typically discussed in the BRAD. (For a more comprehensive list of sources of uncertainty see Section 3.4 on Methodological considerations for addressing uncertainties in benefit-risk assessment). The types of uncertainties to consider when preparing the BRAD are described in Table 2. A more comprehensive list of uncertainties to be considered in BRA is included in Table 17 - examples or sources of uncertainties that could be considered in the SBRF.

The potential impact of uncertainty on BR should be evaluated using appropriate methods (see Section 3.4 on Methodological considerations for addressing uncertainties in benefit-risk assessment) and considered in a final BRA conclusion.

Table 2. Sources of uncertainty from a clinical trial typically discussed in a Benefit-Risk Assessment Document

Source: CIOMS Working Group XII

Sources of uncertainty to consider	Possible considerations
Study design	Choice and clinical relevance of endpoints, including surrogates, which can impact interpretation of study results. Choice of study design (randomised vs unrandomised, and controlled vs uncontrolled), which causes bias to the study results.
Choice of comparator	Relevance of the comparator drug in the treatment landscape when the clinical program has completed and impact on generalisability of the data.
Duration of exposure (e.g. duration of study versus intended use)	For diseases which require long-term treatment, impact of relatively short duration of the clinical program on magnitude and durability of effect.
Studied (enrolled) patient population (as representative of the target population)	Impact of exclusion criteria, which limit generalisability of the clinical program results.

Sources of uncertainty to consider	Possible considerations
Subgroups not studied or studied in limited numbers of patients (consider susceptibility to benefits/risks)	Impact on generalisability of results given possible unique subgroups of patients in the general population which were not evaluated during the clinical program.
Enrichment strategies in a clinical program that could affect the estimate of the product's benefits.	Impact on generalisability to real-world population.
Patient monitoring during the clinical program which may differ from clinical practice.	Impact on detection and timing of detection of an Adverse Event (AE) which may differ from real world.
Completeness of data collection	Data may evolve as studies continue beyond the data collection for a submission.
Statistical methods used to analyse clinical trial data and issues that could affect interpretation of results.	Methods should be scientifically sound with the context of testing hypothesis and available data. Methods not typically used may need to be explained or limitations outlined.
Deviations from guidelines, scientific advice or label instructions	Should be discussed if this impacts applicability of the results.

2.2.3. Product optimisation (risk management)

Whilst much of the details around the safety specification and the pharmacovigilance activities should be described in the RMP for the medicinal product(s), it is valuable to align with the key information in the BRAD, a company-internal document. In particular, when a medicinal product is recognised to be associated with significant risks, it is important to develop an understanding from the outset about how, when and what further information will become available to more fully inform the balance of benefits and risks of the product in real-world use.

Risk management is an important component of the SBRF for a product since the BR balance for a medicinal product may sometimes only be positive if appropriate risk management strategies are in place. Ensuring there are clear measures in place to effectively manage the risks associated with a product may be deemed necessary to supporting a positive BR balance. This also needs to be in the context of emerging safety data obtained throughout the product's lifecycle. The aim of utilising that data is to optimise the safe and effective use of a product throughout its lifecycle. As characterisation of the key risks evolves through the lifecycle of the product, risk management/minimisation strategies may also evolve based on new data that becomes available. For marketed products, additional safety data are obtained from multiple sources including pharmacovigilance studies or post-marketing data. For further information on the lifecycle approach, see Section 2.3 on Lifecycle approach to benefit-risk assessment within this chapter. The rationale for the approach to risk management along with the plans for further data collection are detailed in the development RMP, IB, and/or RMP for the product, however, a high-level description may be appropriate to be included in the BRAD to demonstrate that this has been considered in the context of the product's overall BRA. See Figure 2 on Components of a Structured Benefit-Risk Framework. Recommended references include the GVP RMP Guidance and the CIOMS Working Group IX report which are included in the reference section.

Risk characterisation

Any decision about the balance of benefits and risks of a medicine is based on the information available at that time to inform decision making but it is recognised that there may be uncertainties surrounding the available information or gaps in knowledge. Tolerance for uncertainty along with an appreciation of whether the uncertainty can be addressed, and if so, how rapidly, will need to be factored into the overall BRA. Improving the BR balance through pharmacovigilance activities that are designed to increase the understanding of a medicine's safety profile and reduce the uncertainties in a reasonable timeframe is key to good pharmacovigilance planning.[18,19]

Pharmacovigilance planning should occur early in product development and continue throughout the product lifecycle. For further information on the lifecycle approach, see Section 2.3 on Lifecycle approach to benefit-risk assessment within this chapter. Alongside the identified and potential risks that inform the BR balance, pharmacovigilance planning should also take into account how the knowledge about the safety profile of a medicinal product can evolve over time as new data become available. Consideration should also be given to how the emerging data either addresses the recognised uncertainties or identifies new risks and the implications of this for the balance of benefits and risks.

The approach to pharmacovigilance planning should be clearly described and based on the available non-clinical and clinical data that informs the medicinal product's safety profile. It should also consider the target populations and the broader patient population that may be exposed to the product in routine clinical practice and discuss how this may impact on the product's safety profile and areas that merit further investigation/study. For example, if the medicinal product is subject to renal excretion, then it is important to consider the prevalence and severity of renal disorders in the target population and how this may differ in the broader population that may be exposed in routine clinical practice. If significant off-label use is anticipated and is likely to increase the risk of Adverse Events (AEs) and potentially impact on the balance of benefits and risks, then consideration should be given to the need to monitor the extent of off-label use.

Additional activities may include non-clinical studies, clinical trials or non-interventional studies. Examples of such studies include a post-marketing safety study to characterise hepatic enzyme elevation among patients who have some degree of hepatic impairment. With appropriate monitoring, the BRA in this subpopulation may be favourable, however, there may be uncertainty regarding safety which needs further characterisation. Product labelling may require use with caution in this population with further evaluation from a post-marketing safety study. Data from such a study may further inform BR balance and risk minimisation for use of the product in this subpopulation. Studies in the pharmacovigilance plan may aim to identify and characterise risks, to collect further data where there are areas of missing information or to evaluate the effectiveness of additional risk minimisation activities. They should relate to the safety concerns identified in the safety specification, be feasible and should not include any element of a promotional nature. There should be a clear understanding and description of what information these activities will deliver and how this can result in a more informed consideration of the BR balance (i.e. delivery of decision-relevant data).

When post-marketing safety studies are proposed, it is important to justify why these studies are needed and ideally to consider the feasibility of any proposed studies. A feasibility assessment should ideally be conducted prior to the start of any study in order to support that the study can deliver decision-relevant data with appropriate study objectives and methods. This is particularly important where the BRA suggests that significant restrictions to the use of the medicinal product are likely to be needed to optimise safe and effective use.

Milestones for evaluation of reporting on the different pharmacovigilance activities should take into account the likely exposure of the product and how this will impact the potential identification/characterisation of the AEs/Adverse Reactions (ARs) along with the anticipated timelines for availability of results.

Risk minimisation

The BRAD should also describe RMMs proposed by the MAH, which are public health interventions aimed at minimising the risk of a medicinal product and optimising its safe use throughout its lifecycle. Generally, RMMs focus on lowering the frequency and/or severity of an AR. The CIOMS Working Group IX report[20] distinguished between risk prevention (reducing the frequency of an AR) and risk mitigation (reducing the severity of an AR when it occurs). In line with the proposals of that CIOMS Working Group, here the umbrella term risk minimisation covers both risk prevention and risk mitigation measures.

The ultimate aim of risk minimisation should be improved patient outcomes by providing the medicinal product to the right patient, at the right time and at the correct dose, which should be supported through provision of optimal information and appropriate monitoring.

The concepts of ICH E2E[18] and the CIOMS Working Group VI report[21] have been widely adopted but their interpretation has varied. Within Europe[22,23] and Japan,[24] legislation requires RMPs for all newly authorised products, which include strategies for characterising and managing the medicinal products' risks over time through routine and/or additional RMMs. Other jurisdictions, such as Health Canada,[25] Welfare and the Ministry of Food and Drug Safety in Korea,[26] and Australia[27] accept the submission of RMPs in the EU format and have outlined the particular circumstances under which RMPs should be submitted. In contrast, the US FDA requires formal risk minimisation programmes,[28] known as REMS to be developed and implemented only for those products who's risk(s) cannot be mitigated through routine RMMs such as product labelling alone, i.e. those associated with serious risks.

RMMs support interventions relating to and communication of risks to patients/caregivers and health care providers. The approach to risk minimisation is ordinarily developed to support the balance of benefits and risks at the time of initial authorisation. As new safety information becomes available after regulatory approval, and effectiveness of RMMs is better understood, consideration needs to be given to how the RMMs need to be revised or expanded upon based on new emerging data.

The need for, nature of and approach to risk minimisation should consider the following areas: risk characteristics; effectiveness of the proposed strategy; stakeholder needs; feasibility of the proposed strategy; and also burden to patients or the health care system. This is especially important when additional RMMs are being contemplated. Aspects to consider in relation to these areas are provided in Table 3.

Points to consider for risk minimisation

Determining the need for additional RMMs should also take into account the indication, the target population, the overall BR profile, how the medicinal product will be dispensed (health care setting) or used in routine clinical practice and the burden to the health care system and patients. Introducing RMMs involves interactions between all these stakeholders, therefore, it may be possible that certain measures may apply to one indication, population or health care setting, but not others.

Table 3. Key areas and points to consider in determining a need or approach for risk minimisation measures

Source: CIOMS Working Group XII

	Aspects to consider
Risk characteristics	▶ Risk factors – how reliable are the data and how easily can individuals with the risk factor(s) be identified? ▶ Risk markers/biomarkers – how predictive are they and what is the availability of testing for these in current clinical practice? ▶ Differences in subpopulations (e.g. disease severity, age, genetic, pathophysiological or historical factors) – do the available data support different approaches to risk management and how robust are these data? ▶ Timing – does risk only become apparent after a certain duration of treatment? Where restrictions to duration of treatment are being proposed, it is important to consider the robustness of the data to exclude a risk with shorter duration of treatment and how the restricted duration might impact on the utility of the product (i.e. it may be acceptable for a product that provides rapid symptomatic relief). ▶ Reversibility – do the data suggest that the risk may be mitigated by stopping treatment with the medicinal product or by reducing its dose?
Effectiveness	▶ What data are available to demonstrate the effectiveness of the proposed strategy on mitigating the risk? Possible sources include: — Pre-marketing testing (readability testing, human factors studies on how the measure is handled and used) with stakeholders; — Clinical trials – do these data inform on the impact of restrictions to indication, dose, and duration of treatment? — Published literature; — Post-marketing safety studies designed to evaluate outcomes of key risks targeted by the measure; — Previous experience with similar measures.
Stakeholder needs	▶ Which stakeholders may need additional support? ▶ Type and extent of support required: — Appropriate patient selection; — Training needed to mitigate risk; — Verification of patient monitoring.
Feasibility	▶ Potential impact on prescribers and/or health care delivery system, especially where the measures are likely to be needed long term. ▶ Potential impact on patient access – possibility for treatment interruptions or delays, which may be especially problematic for patients with serious or life-threatening conditions. ▶ Differences in clinical practice across regions – need for flexibility and adaptability (e.g. pre-determining core elements essential for risk minimisation and agree which ones are subject to flexibility). ▶ Unintended effects – HCPs may select an inferior medication to avoid the burden from the formal risk management program. ▶ Sustainability over time – designs based on behavioural change models (e.g. the PRECEDE-PROCEED model[ii]) are likely to be more effective.

[ii] The PRECEDE-PROCEED Model is a comprehensive and widely used framework for guiding the development of population health interventions. It was developed by Larry Green and Marshall Kreuter. Green, L. & Kreuter, M.W. (2005). Health program planning: An educational and ecological approach (4th ed.). New York: McGraw Hill.

Some examples of the additional risk minimisation tools that are available and issues to consider in relation to each of these are provided in Table 4. Additional information regarding the selection of appropriate risk minimisation tools is available through existing guidance[7] and the report of the CIOMS Working Group IX.[3]

Table 4. Examples of additional risk minimisation tools

Source: CIOMS Working Group XII

Category	Important issues to consider
Direct Health Care Professional Communication/Letter	▶ Need for a clear Communication Plan that includes target audience. ▶ Timing and frequency of distribution – one-off distribution may not reach all potential prescribers and/or users.
Educational programmes Health Care Professionals (HCPs) (e.g. HCP guide, Prescriber checklist, Demonstration kit) Patients and/or caregivers (e.g. Patient/caregiver's guide, Risk awareness/ acknowledgement forms, Patient diaries, Patient cards	▶ Need to add value beyond product information – requires clearly defined scope and objective. ▶ Focus should be on specific safety concern; additional information that is not immediately relevant may dilute key messages or be considered promotional. ▶ Who is the intended target audience? ▶ Most suitable format and channels – should support accessibility to different subgroups of target populations (e.g. different age groups). ▶ User testing for readability, accessibility, adequacy and user-friendliness of formats. ▶ Timing and frequency of distribution – one-off distribution may not be sufficient to reach all potential prescribers and/or users. ▶ Avoid unnecessary additional burden – ideally format should be adaptable to help fulfil documentation purposes of health care systems. ▶ Need for materials to be periodically updated and re-issued. ▶ Scope for integration into Continuing Medical Education activities.
Restricted access programmes Examples: ▶ Specific testing to ensure compliance with defined clinical criteria; ▶ Systematic patient follow-up through enrolment in specific data collection system, e.g. patient registry.	▶ Ensure prescribing/dispensing compliance and/or patient monitoring and follow-up. ▶ Potentially highly burdensome – reserved for exceptional situations (e.g. serious risk with significant public health impact) where agreed measures are essential to minimise risk. ▶ Accessibility and availability (e.g. access to certain health care systems or specialists, or availability of clinical testing). ▶ May need to be adapted to local health care settings. ▶ Unintended consequences – may discourage use and result in diversion to less appropriate prescribing options or patient discontinuation.

Ensuring successful implementation of additional RMMs requires contributions from all stakeholders. Therefore, it is key that the development of additional RMMs is driven by clear objectives, defined measures of success with appropriate milestones, and close monitoring of the implementation and their effectiveness.

Effectiveness of risk minimisation measures

Ensuring that the balance of benefits and risk of a medicinal product remains favourable does not end with the introduction of RMMs. As these measures are intended to promote public health by leading to changes in knowledge and behaviour of HCPs and patients/caregivers, it is essential to consider data availability and need of further activities, including studies, to evaluate the effectiveness of the proposed RMMs. Furthermore, increasing numbers of regulatory authorities require MAHs to monitor the effectiveness of these measures[28,29,30] and submit information on effectiveness evaluation of these measures in the context of the RMP or an update to the RMP.

The need for risk management activities should be considered and/or implemented from the earliest stage of product development and where a product is or is likely to be associated with significant risks. Next, it is necessary to consider whether information from the product development programme can be used to support the effectiveness of the proposed risk minimisation and clinical monitoring, where appropriate, as per CIOMS Working Group VI principles for a development RMP and how this can be informative of the approach to risk management and monitoring.[21]

To assess the effectiveness of the risk management and monitoring approach, in accordance with regulatory guidance (EMA,[11] US FDA[31]),[32] any planned activities should examine, whenever possible, the following:

1. Programme implementation – whether the programme has been implemented as planned (e.g. delivery, receipt and uptake of the educational tools/materials, numbers of HCPs or health care setting where staff have undergone any required training);
2. Knowledge – stakeholder (e.g. patient/caregiver, prescriber, pharmacist) understanding the risks and the RMMs that have been introduced to optimise safe use;
3. Behaviour – the extent to which the RMMs are being adhered to in routine clinical practice (e.g. changes in prescribing patterns, patient counselling, conduct of laboratory tests prior to dispensing of the medicinal product);
4. Health outcomes – whether the level of risk control has been achieved (e.g. whether the intervention has resulted in a reduction in the frequency and/or severity of an AR). Occasionally, surrogates of health outcomes may be used, such as an appropriate biomarker for a clinical endpoint or reduction in the number or proportion of patients at greatest risk of having been prescribed a drug.

The selection of the metrics will be determined by the aims and objectives of the RMMs along with feasibility of the measurement. This section of the SBRF should discuss why particular metrics and data sources have been selected and any limitations and resulting uncertainties should be described.

2.2.4. Benefit-risk assessment conclusion – the overall assessment summary

This section is intended to synthesise the evidence in the prior sections of the BRAD to lead to a conclusion. The BRA conclusion should flow from the therapeutic context and address the extent to which the product addresses the unmet need by providing needed benefit, reducing treatment risk, or imposing risks that are acceptable or can be managed acceptably. Here are some points to consider when determining what to include in the BRA conclusion.

- The significance of the disease/condition, the unmet medical need, and the product's place in the treatment armamentarium.
- Description of the key benefits and key risks which were evaluated.

- Any level of uncertainty for key benefit(s) and a causal association between the medicinal product and the key risk(s).
- Explain how any uncertainties impact the assessment.
- If the assessment has revealed patient populations who may benefit greatly while experiencing less risk, this may be included. Alternatively, if the assessment has revealed patient populations who have limited benefit and experience greater risk, this should be discussed with ways to mitigate risk or limit use in this population.
- The reasoning and judgment used in assessing and weighing the key benefits and key risks, within the specific therapeutic context. How the expected key benefits influence the acceptability/trade-off of the key risks. See the Section on Benefit-risk trade-offs below.
- How the benefit(s) and/or risk(s) differentiate the product from other important alternative therapies. As the landscape for alternative therapies evolves, the conclusions of the BRA for a medicinal product should be reassessed, since this impacts how or when the medicinal product may be used.
- Available information on the patient and/or consumer perspective, which highlights why a key benefit of the product should be included.
- How the assessment supports the proposed dose(s) for the intended indication.
- How the key aspects of risk management impact the BRA.
- Any relevant quantitative BRAs supporting the SBRF.
- Acknowledgement of whether the overall BR balance for the product is favourable or unfavourable.

Benefit-risk trade-offs

The conclusion section of the BRAD is the most appropriate place to discuss the BR trade-off, and this forms an apropos conclusion to the discussion of SBRF in the BRAD. The BR trade-offs are an important element of the BRA and will require involvement of the full BRMT. The trade-off between a specific risk versus achieving a certain degree of efficacy is complex and evolves as new emerging efficacy and safety data become available and as the therapeutic landscape changes.

There are multiple factors which impact the BR trade-offs. These include the severity of the disease under treatment (i.e. achievement of efficacy in oncology may be undertaken with a willingness to accept risks not tolerated in other therapeutic areas), regulator position, and importantly, the patient perspective. See Section 2.4 on Role of the patient in Structured Benefit-Risk Framework for a discussion on Patient Preference Studies (PPSs) and how they can inform the BRA. Also, the BR trade-off may differ depending on the patient subpopulation. Additionally, uncertainties for the key benefits and key risks further influence the BR trade-offs.

When the risk for a product is serious but occurs infrequently or rarely, the BR trade-off can be challenging. Some patients may opt for a treatment with a rare but defined risk, if they do not have other treatment options. Alternatively, when a risk is more frequent but easily manageable, if the product provides greater benefit over another comparator, patients may still want to use it. Ultimately, appropriate guidance and information are needed for the stakeholders involved in the treatment decision for a patient. This requires that the information is well communicated, providing the appropriate context for decision making, and is provided in a form which is understood by those in the health care setting and by those being treated. The BR trade-offs are made even in the face of uncertainty, since most medicinal products have uncertainty related to both their benefits and risks. While uncertainty in a benefit may be more easily accepted, uncertainty for a risk is more challenging. This makes identifying relevant uncertainty, which impacts the BR balance an essential part of a SBRF. Even more important, it is critical to have methods which can address uncertainty with frequent reassessment and communication of the BR balance based on emerging data, so BR trade-offs are made by stakeholders with the totality of data for a medicinal product.

Risk minimisation is crucial when a product offers some benefit over alternative therapies but carries some risk. Such a product may only be available on market if it can be safely used with appropriate risk minimisation. Reassessment of the impact of risk minimisation is essential to ensure that the risk is appropriately minimised to provide positive BR balance for the medicinal product.

The decision making involved in BR trade-off requires knowledge of all components of the SBRF (analysis of disease or condition, current treatment options, key benefits and key risks, and product optimisation) and inclusion of all of these elements in a BRA are vital.

In summary, a SBRF includes multiple components described in this chapter, which are important to fully characterise the benefit and risk of a medicinal product for a specific indication. All of these components should be documented in the BRAD and accompanied by tables and graphics, which help to establish and communicate the BR narrative for a medicinal product.

Source and impacted document of a Benefit-Risk Assessment Document

Now that the full concept of SBRF, BRA, and the BRAD have been described, it is further helpful to provide a list of sources of information for various parts of the BRAD. Depending on how early the BRAD is initiated, the BRAD may also inform sections of the RMP, product label, or PSUR/PBRER. The table below outlines types of documents which are usually available during drug development or later and which inform a BRA or are impacted by a BRA. Additionally, Table 5 describes when the information may be available, however, this may be variable depending on the clinical development process. A description of which sections of the BRAD may be informed by these information sources is provided, but it should also be noted that depending on when the BRAD is developed, the BRAD will then inform critical documents (Table 6). There is therefore a lifecycle management process where the BRAD is informed by information sources, and once developed, the BRAD then informs documents developed and revised during the lifecycle of a medicinal product. Within a pharmaceutical company, the BRAD can also be a useful information source for functions such as HEOR, Medical Information, and Marketing.

Table 5. Information sources for the Benefit-Risk Assessment Document

Source: CIOMS Working Group XII

Information sources to inform the Benefit-Risk Assessment Document (BRAD)	Section of Benefit-Risk Assessment Document (BRAD) which may be informed by information sources in column 1
Toxicology reports	▶ Key benefits and Key risks ▶ Product optimisation
Patient journey	▶ Analysis of disease/or condition ▶ Product optimisation
Characterisation of the disease state and unmet need	▶ Analysis of disease/or condition
Disease treatment guidelines	▶ Analysis of disease/or condition ▶ Current treatment options
Target product profile or claims	▶ Current treatment options

Information sources to inform the Benefit-Risk Assessment Document (BRAD)	Section of Benefit-Risk Assessment Document (BRAD) which may be informed by information sources in column 1
Investigational New Drug (IND) for drugs which *are not yet approved* and New Drug Application (NDA)/ Marketing Authorisation Application (MAA)/Biologic License Application (BLA) for *previously approved drugs*	▶ Key benefits and Key risks
Clinical Development Plan/Asset Plan	▶ Key benefits and Key risks
Investigator Brochure (IB)	▶ Key benefits and Key risks ▶ Product optimisation
Patient-Reported Outcomes (PROs)/QoL instruments and domains	▶ Analysis of disease/or condition ▶ Key benefits
Product Safety Plan/Developmental Risk Management Plan (RMP)/Risk Management Plan (RMP)	▶ Key risks ▶ Product optimisation
Regulatory Documents (including Briefing Books)	▶ Analysis of disease/or condition
Development Safety Update Report (DSUR)/Periodic Safety Update Reports (PSUR)/Periodic Benefit-risk Evaluation Report (PBRER)	▶ Key benefits and Key risks ▶ Product optimisation
Clinical Study Reports (CSRs)	▶ Key benefits and Key risks
Epidemiologic study data	▶ Analysis of disease/or condition
Statistical Analysis Plan (SAP) for a product submission	▶ Key benefits and Key risks (key evidence section)
Product Label/Company Core Data Sheet (CCDS)	▶ Current treatment options ▶ Product optimisation
Real-world evidence, if available	▶ Key benefits and Key risks ▶ Product optimisation

Table 6. Documents which may be informed by the Benefit-Risk Assessment Document

Source: CIOMS Working Group XII

Documents which may be informed by the Benefit-Risk Assessment Document (BRAD)
New Drug Application (NDA)/Marketing Authorisation Application (MAA)/Biologic License Application (BLA)
Regulatory documents including Briefing Books
Periodic Safety Update Reports (PSUR)/Periodic Benefit-risk Evaluation Reports (PBRER)

2.3. Lifecycle approach to benefit-risk assessment

A SBRF provides a structured and systematic BRA approach through the lifecycle of the product. While there is considerable overlap in the considerations for the scientific BRA of compounds by regulatory authorities and the companies that develop and market pharmaceuticals and biologicals, there are also additional considerations and timepoints for these assessments by commercial enterprises.

While different companies may have varying terminologies for each step in the process, the medicinal product development program can be considered to include:

- Target discovery;
- Target validation;
- Lead compound identification;
- Lead optimisation;
- Non-clinical development;
- Phase 1 clinical trials;
- Phase 2 clinical trials;
- Phase 3 clinical trials;
- Regulatory submission for Market Authorisation (MA).

Because each step forward in this process requires additional resources and time, often substantially later in the process, companies will make a decision on whether or not to advance a project at each step. Several of these steps take place before any notification or request for approval of the start of clinical trials or submission to a regulatory authority for MA. Depending on the data available at each step, similar evaluations of safety and efficacy, or risk and benefit will be made within the company but maybe with some different considerations.

The decisions for clinical introduction (the start of Phase 1 trials), advancing a compound between phases of trials and especially the decision to advance to full development of a compound (initiation of pivotal clinical trials) are key decision points for sponsors which will not proceed without a favourable internal BRA even before consulting regulatory authorities on their agreement or advice for proceeding.

Regulatory agencies typically review BRA starting from Investigational New Drug (IND) submission through product licensure application and post-market safety surveillance. While clinical trials are ongoing, the sponsor is required by many regulatory authorities to submit a yearly DSUR described by ICH E2D.[33] At several points in that report, the sponsor will provide a summary of BRA and attest that it considers the BR profile as understood at that time to support the continuation of current clinical trials.

Efficacy and safety data from the clinical trials will be reviewed and assessed to decide whether or not the BR balance is favourable enough to support submission to regulatory authorities for MA. This decision on whether or not to submit, while it may be taken after advice from a regulatory authority, is fully within the purview of the product developer.

2.3.1. Pre-clinical

The pre-clinical development stages include both the critical compound selection activities, such as target validation and lead compound identification, and the animal toxicity, pharmacology and other non-clinical studies necessary to allow the first-in-human subjects (including target discovery, target validation, lead compound identification, lead optimisation and non-clinical development described

above). While it may appear that no BRA is performed during these stages, the principles of defining acceptable risks for the targeted indication still draw on the principles of later BRA. A compound which fails in tests of target validation, essentially failing to suggest the potential for benefit, should not advance to clinical development even if it does not show any worrisome toxicity. Indeed, there is evidence that companies have become more selective over time in advancing projects in the pre-clinical stage of development.[34] In addition to generating the toxicology and pharmacology data which allow setting the first-in-human dose and initial projection of safety margins, the toxicology program and core battery of safety pharmacology studies inform the initial understanding of potential important risks which are important inputs to a BRA and inform the targeted safety monitoring and risk minimisation measure for the early clinical trials.

Key deliverables from the pre-clinical stage are the IND or Clinical Trial Application (CTA), or equivalent which are submitted to regulatory authorities to allow the initiation of human studies, and the Investigator Brochure (IB) which informs the study protocols and Informed Consent Form (ICF) documents, which are reviewed by Investigators, Institutional Review Boards and Ethics Committees and ultimately (for the ICF) clinical trial subjects who will decide on participating in the study.

2.3.2. Early development (Phase 1 and Phase 2 clinical trials)

The incorporation of pharmacovigilance activities and BRA is required throughout the entire lifecycle of a product. During Phases 1 and 2 clinical trials, BRA is conducted and updated by pharmaceutical companies based on accumulated benefit and/or risk evidence for a product and is communicated to the regulatory authorities annually in section 18 of the DSUR.

The implementation of a SBRF in early phases of development may be useful to promote consistency and transparency. Thus, in spite of the high attrition rate of compounds in Phases 1 and 2 clinical trials, activities that include risk management planning and safety milestone assessments as early as the start of development should be considered.

Given the limited knowledge available for compounds at early stages, there is a need for guidance to define the scope of such activities. In early development, when the BR profile of a compound is usually insufficiently characterised, the aim of a well-established and effective risk management process is not only limited to the management and monitoring of known or suspected risks (e.g. potential or suspected issues identified in pre-clinical studies, theoretical risks based on the compound's mode of action, target receptors/enzymes/cells, known class effects, etc.) but should also facilitate the timely identification of unknown and unexpected risks. These activities, as in other stages, involve identification, collection, analysis, monitoring and formal documentation of safety issues, as well as the implementation of relevant risk mitigation activities and communication of potential or identified risks. Ultimately, if there is a concern about the BR balance of the product, risk evaluation, signal prioritisation, and management strategies (including communication plans) need to be in place at all clinical phases of product development.

Prior to the start of Phase 1 clinical trial, there is a reasonable amount of data available from pre-clinical studies (toxicity studies, No Observed Adverse Effect Level (NOAEL), target engagement, expected exposure and benefits in humans), which provide a basis for BR and risk management processes. Furthermore, continuous monitoring of other relevant safety data sources, such as literature and online safety regulatory intelligence tools, among others should be performed. A BR-focused proactive planning process should be considered during selection of study design, study population, dosing strength and frequency, inclusion and exclusion criteria, risk mitigation measures, as well as study endpoints and clinical outcome assessments.

Sponsors may discuss with regulatory agencies in a pre-IND meeting about the clinical meaningfulness of a purported benefit or concern from non-clinical safety findings for first-in-human studies. Agencies may provide feedback about the clinical trial protocol and study design including identification, collection, analysing, monitoring, documentation, and mitigation of potential risks in a clinical trial.

In Phase 1 studies, usually conducted in healthy volunteers (unless the product's safety profile requires initial trials in patients), the activities include active monitoring of safety and tolerability in single-rising dose and later in multiple rising dose studies (e.g. safety review prior to dose escalation), dose-limiting toxicity and product-specific toxicity based on pre-clinical findings and/or potential class effect, in addition to routine safety monitoring. Other types of Phase 1 studies include the evaluation of Pharmacokinetics and Pharmacodynamics (PKPD), Drug-Drug Interactions (DDI), electrocardiogram (ECG) QT effects, or focus on special patient populations, such as hepatic impairment patients. If the safety profile is not favourable for a Phase 1 trial to be conducted in healthy volunteers, to whom there is no potential benefit, the trial can be conducted directly in the targeted patient population.

At Phase 2 clinical trial, the dose selection needs to take into account the totality of all available data described above. In Phase 2 studies, usually patients in the target indication are included and data on the clinical benefits are collected proving (or not) the clinical principle of the molecule and providing dose ranging-information related to the efficacy endpoints in addition to safety data. Towards the end of Phase 2, the appropriateness of efficacy and safety endpoints and inclusion/exclusion criteria should be evaluated and if needed, adapted, to provide more accurate data for efficacy and safety and to maximise efficacy while decreasing risks in upcoming trials.

The end of Phase 2 clinical trial is likely to be a critical point for BR planning based on available information about the treatment effect and the safety of a drug, which can influence Phase 3 trial design and ensure that data supporting BRA is appropriately collected. At this point, it may be helpful to communicate with the relevant regulatory agencies about the available information, BR planning and Phase 3 trials design to obtain their useful perspectives. For example, the discussion between sponsor and regulatory agencies could include the best design of a Phase 3 clinical trial aiming to characterise benefits and risks where the population is limited or vulnerable, such as for rare or serious diseases or paediatric populations, or the need for collecting and using patient preference information to inform BRA. Patient experience data collected early in the development program can help identify unmet patient needs and define the target patient population. Patient experience data including patient preference, can also inform the assessment of the clinical relevance of the study endpoints, that is, to help identify endpoints that measure or predict clinical outcomes of importance to patients.

In summary, the implementation of formal BR-based processes and generation of documentation (such as BRAD) for such activities as early as possible during drug development will support the appropriate communication and definition of the scope of BRA and risk management activities, optimise interactions with patients, regulatory bodies (e.g. scientific advisories, pre-IND meetings) and ethics committees, and finally improve patients' experience.

Furthermore, the characterisation and continuous evaluation of the BR profile of a compound is reflected and communicated through documents targeting different stakeholders (internal, regulatory bodies, investigators and subjects/patients). Examples of such documents are periodic reports (e.g. DSURs), development RMPs, development core safety information, and relevant sections of IBs (reference safety information) and patient ICFs.

2.3.3. Late development (Phase 3 clinical trials and regulatory submission preparation)

During late development and in preparation for the submission of a MA application, using a structured approach to the BRA will assist companies in preparing an internal BRAD in alignment with the regulatory authorities' recommendations and support the validation of scientific conclusions. The company's core position on the product's BR profile should be reflected in the BRAD summarising a comprehensive BRA integrating all available evidence.

During late development, the BRAD is used as a standard document which is developed at this stage or earlier and updated by pharmaceutical companies through the lifecycle of the drug. The development of such document is essential at this stage in preparation for communication with the regulators.

During the Phase 3 clinical trials, the BRAs are conducted by pharmaceutical companies upon receipt of new benefit and/or risk evidence for a product and are communicated to the regulatory authorities annually in section 18 of the DSUR. At the end of the Phase 3 clinical trials, efficacy and safety data from the registrational trials will be reviewed to determine the key benefits, key risks, and uncertainties of the medicinal product. At this stage, uncertainties are likely still present mainly due to lack of long-term effects data, insufficient sample size to detect events of low probability and lack of external generalisability of the trial results. The BR outcomes included in the structured benefit assessment will likely include the primary and secondary endpoints from pivotal clinical studies, with consideration of product risks and risk mitigations. The BRA will support the determination whether additional risk minimisation is needed. Based on available data, the BRMT will then further describe in the BRAD the types of RMMs that will best manage the product's key risks.

Patient experience data should also be incorporated into the BRA during drug development when available in order to provide the patient perspective to the relevant attributes and outcomes. Patient preference information in the BRAD can include assessment regarding disease impact and unmet needs, potential benefits, risks and burden of risk mitigation. See also Section 2.4 on Role of the patient in Structured Benefit-Risk Framework and Section 3.3 on Methodological considerations to gain patient insights.

The BRAD will also inform and guide the preparation of the company's core product label often referred to as the CCDS, which communicates the key risks of the product to health care providers and patients, and guides the development of the product's risk management system. The BRAD will also support the preparation of the RMP. The RMP document will describe the risk management system information concerning the product.

While the BRA process facilitates the selection and interpretation of data, it should also be utilised to support regulatory agencies' interactions, such as end of Phase 2 clinical trial meetings, early BR discussion, rapporteur meetings and advisory meetings. Sharing the BR learnings at these milestones will add to the full transparency and allow the implementation of the feedback in real time.

The BRA will support decision making and will integrate the evidence for the submission of a MA application to the regulatory authorities. The BRAD should be utilised as a key source when preparing the market authorisation application. Companies should present the BRA including key benefits and key risks, and uncertainties within the marketing application.

The data can also be summarised and presented within the submission in a graphical or a tabular format such as value tree and effects table, other representation may also be applicable like a forest plot. See also Section 3.5 on Approaches to visualisation of benefit-risk assessment.

The currently available SBRF are aligned with ICH M4E(R2) recommendations as well as the US FDA and EMA's recommendations for BRA. Therefore, the BRAD content can support key submission documents such as Section 2.5.6 of the Clinical Overview as well as clinical efficacy and safety summaries.

The BRAD should present additional RMMs that should be introduced during launch time when applicable.

Regulatory agencies review Marketing Authorisation Applications (MAAs), NDAs and BLAs submitted by sponsors. Considering the therapeutic context, the totality of evidence on the key benefits and key risks, regulatory agencies make decisions on whether the benefits of the product outweigh its risks for market approval. The sources of evidence include clinical data, non-clinical data, patient experience data, product quality information, spontaneous reports of AEs, and, if available, region-specific information. The BR considerations include, but are not limited to, relative importance and time course of the benefits and risks in the overall indicated population, as well as individual patient perspectives, the ability to identify the patient group for whom the benefits clearly outweigh the risks, and whether the benefits and risks can be adequately communicated in product labelling to support informed individual BRAs by patients and providers. The regulatory agencies evaluate the strength and quality of the evidence available and take remaining uncertainties into account in dimensions of the SBRF (therapeutic context, benefits, risks and BR trade-off). Therapeutic context plays an important role in the assessment of the acceptability of uncertainty. For a drug intended to treat a serious disease with unmet needs, a regulatory agency may accept greater uncertainties about benefit or risk at the time of approval. Regulatory agencies also consider the options to reduce uncertainties and manage risks, for example, through the requirement for additional clinical studies conducted pre-market or post-market to further characterise safety, effectiveness, or dose response; additional product quality information; post-market observational studies or enhanced pharmacovigilance; labelling content (e.g. limitations of use); or REMS. Patient Preference Information (PPI) may be best suited to inform regulatory decision making when: 1) significant risks of treatment or uncertainty about risks exist relative to the expected benefits; 2) patients' views about the most important benefits and risks vary considerably within a population; and/or 3) when patients' views as to the most important benefits are expected to differ from those of HCPs.[35] The regulatory agency may seek advice from external advisory committees either on a routine basis or for complex BRAs.

2.3.4. Post-marketing/On-market

When a drug is approved for marketing, a conclusion has been reached that, when used in accordance with approved product information, its known benefits outweigh its known risks. As new information about the product emerges during the marketing experience, BR should be re-evaluated to determine whether benefits continue to outweigh risks, and to consider whether steps need to be taken to improve the BR balance through risk minimisation activities, e.g. labelling changes, communications with prescribers other HCPs and consumers, or other steps. Therefore, it is necessary to continue analysis of relevant safety, efficacy and effectiveness information throughout the lifecycle of a medicinal product – promptly, as important new findings occur – and periodically – to allow an overall assessment of the accumulating data. Real-World Evidence (RWE) is very important for evaluation of benefits and risks post-marketing.

Any safety information from solicited sources (e.g. post-marketing safety studies) that could change the BR balance for the product should be communicated as soon as possible to the regulatory authorities. Furthermore, signals related to adverse effects may arise in the form of an information request or inquiry on safety issues from World Health Organization (WHO) Uppsala Monitoring Centre and regulatory authorities that analyse the spontaneous reporting system for ARs such as the US Food and Drug Administration Adverse Event Reporting System (FAERS), the EudraVigilance data analysis system (EVDAS) and the Japanese Adverse Drug Event Report Database (JADER). Key deliverables are RMP (EU, Japan), REMS (US) and PBRER.

The RMPs include information such as a drug's safety profile, pharmacovigilance plans, risk minimisation activities, and REMS, which are continually modified and updated throughout the lifecycle of a product as new information becomes available. When a safety concern arises post-marketing, a MAH needs to submit an updated RMP to regulatory authorities. Regulatory authorities should conduct a BRA guided by a SBRF and discuss the need for additional risk minimisation activities and/or the pharmacovigilance plan in order to improve the BR balance for the medicinal product. When developing a RMP strategy, using the ICH Q9 framework is recommended, which suggests the systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating, and reviewing risks.[36] At risk assessments, it is important to identify, analyse and evaluate the hazards and effects, considering the likelihoods of occurrence, severity of harm and detectability. At the risk control, it is important to determine whether to add minimisation activities and/or pharmacovigilance plans considering that additional actions can mitigate or avoid the identified risk.

The MAHs periodically need to submit PBRERs to regulatory authorities in order to present a comprehensive, concise, and critical analysis of new or emerging information on the risks of the medicinal product, and on its benefits in approved indications. The requirements of regulatory authorities are described in national or regional legislation and guidance, and usually depend on such factors as approval dates, the length of time the product has been on the market, and the extent of knowledge of the BR profile of the product. A MAH should provide a conclusion in section 18 (integrated BR analysis for approved indications) of the PSUR about the implications of the new information about safety, efficacy and effectiveness that arose during the reporting interval, in terms of the overall BRA. If necessary, the MAHs assess the need for changes of the product information, such as labels and the CCDS, and propose changes as appropriate to regulatory authorities. In addition, a MAH may discuss with regulatory authorities the necessity of additional risk minimisation activities. In parallel, regulatory agencies continuously evaluate a drug's benefits and risks and uncertainties in the post-market setting in light of new information about a drug's risks and benefits that become available post-approval. Post-market evidence can come from a diverse set of sources, such as post-marketing studies, AEs reports, medication error reports and product quality reports. The information can be reported by sponsors, shared between regulatory agencies or collected from medical literature, routine pharmacovigilance, and in some cases, information from drugs of the same class. Uncertainty about serious safety concerns identified in the pre-market review may decrease over time as the body of evidence builds (including from post-marketing clinical trials, studies and surveillance). On the other hand, a new safety signal may emerge in the post-marketing setting, especially for rare AEs that were not observed in pre-approval clinical trials. In some cases, such as vaccines to prevent infectious diseases, clinical endpoints cannot be directly measured in the clinical trials and a product is approved based on the surrogate endpoints. In such situations, post-market BRA becomes critical when RWD on the effectiveness of the drugs become available. Regulatory agencies may conduct BRA, guided by a SBRF, when new information emerges that warrants a re-examination of the BR balance of the marketed drug under the current requirements for approval. Examples of regulatory decisions that may be informed by such assessments include addition of new indications, modification of the current indication(s) of a medicinal product; and rarely, marketing withdrawal of an approved product.

2.4. Role of the patient in the Structured Benefit-Risk Framework

This section highlights the importance of incorporating the patient[iii] perspective into the BRA, and the different patient input into components of the SBRF such as description of the medical needs, input into clinical trial design, and selection of 'key' benefits and 'key' risks. For more information related to patient insights collection, including the spectrum of information regarding patient input types, the practical considerations for implementation and methods, see Section 3.3 on Methodological considerations to gain patient insights.

2.4.1. Importance of incorporating patient perspective

Patients are the ultimate end users of medicines and/or other health care treatments and consequently not only do they experience the benefits but they are also exposed to the potential harms. It is, therefore, vital and increasingly expected that their views, along with those of their caregivers, where appropriate, are collected. On top of incorporating perspectives of physicians and other health care providers, this helps to inform the value of new treatments, the approach to product development including the relevance of clinical outcomes, decisions around the balance of benefits and risks along with the approach and risk proportionality of RMMs. To best support success of a product, involving patients should be incorporated into the process as early as possible and ensure that patients and their needs are at the heart of medicine development and involved throughout the product lifecycle. The CIOMS Working Group XI has recently published a report that includes pragmatic points to consider for patient involvement and recommendations regarding patient involvement throughout the product lifecycle.[37]

In addition, involving patients at the various stages of the product lifecycle and factoring this information in the BRA can help to:

- Improve the quality of the evidence and decision making;
- Increase transparency;
- Support trust and mutual respect between stakeholders;
- Aid effective communication.

Regulatory authorities have increasingly published frameworks, strategies and guidance that focus on patient involvement in the work of regulatory agencies and/or drug development.[38,39,40,41]

Industry and regulatory authorities should ideally have in place a strategy or framework that supports the effective involvement of patients in decision making. If none exists, it is still imperative that existing guidance and approaches are used, whenever possible. In situations where the benefits and risks of a medicinal product are finely balanced or it is recognised that a product is associated with significant risks, it is imperative to gain a better understanding of the patient perspective and to feed that into the BRAs. This may support maximising the use of patient data to aid decision making.[42]

[iii] When we refer to 'patients', we are also including other groups impacted by a medicinal product such as consumers, advocacy groups and care givers.

A number of initiatives and projects are in place to examine the concept of patient engagement and develop guidance that can be used to inform the approach to involving patients in BRAs throughout the product lifecycle. These include the following:

- Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle (PREFER) project – an IMI project to produce recommendations to guide industry, regulatory authorities and HTAs/ reimbursement bodies on how and when to include patient preference information;[43,44]
- IMI-PARADIGM – cross industry partnership that aims to promote greater patient engagement in the development of innovative therapies;[45]
- European Patients Academy on Therapeutic Innovation (EUPATI) – a public private partnership that provides education and training to increase the capacity and capability of patients and patient representatives to contribute to medicines research and development;[46,47,48]
- Clinical Trials Transformation Initiative (CTTI) – focusing on ensuring patients are included as equal partners in the drug development process;[49]
- US FDA's Patient Focused Drug Development Program – aims to support a systematic approach to ensuring patients' experiences, perspectives, needs and priorities are captured and incorporated into medicines development and evaluation;[50]
- EMA – in addition to the Benefit-Risk Methodology Project, the EMA supported the evaluation of methodologies for the inclusion of the patient voice in the decision-making process;[51]
- MHRA – has developed a patient involvement strategy to better engage and involve the public and patients at every step of the regulatory journey; most recent patients have been integrally involved in regulatory decision making with regards to its newly introduced innovative licensing and access pathway;[40]
- PMDA – has developed a patient-centricity working group looking at topics related to patient engagement into drug and medical device regulations in order to enhance the incorporation of the patient's voice in activities of PMDA.[52]

2.4.2. Patient input to inform components of Structured Benefit-Risk Framework

The product opportunity (the unmet need)

Patient involvement/engagement is essential at the very early stages of a medicine's development as it will ensure that the research priorities align with patient needs. In particular, it is important to have an understanding from the patients' perspectives of the disease burden and the treatment burden. This type of input helps to better understand the value, as perceived by patients, of the evidence provided during the BR decision-making process.

Important areas where patient input can be sought and patients can be involved and inform decisions with regards to the product are around:

- Experience of living with the target disease/medical condition, including the challenges patients face in their everyday lives and their goals;
- The aspects of the disease/medical condition that have the greatest impact on patients and their QoL;
- How care is currently administered and what and how current treatments, including medicines are used, as well as how patients make informed decisions about medicinal products under a non-prescription setting;
- Views on the unmet treatment needs in terms of both therapy and QoL;

- Treatment outcomes that are of most value to patients with the target disease/medical condition; ensuring that the development of the product is focussed on areas of patients' care that require improvement as defined by the patients themselves;
- Informing the design and characteristics of the target medicinal product profile (e.g. route of administration, ease of use of product) to best meet patients' needs and preferences and to support significant benefits and risks compared with alternatives;
- Patient insights on treatment burden: preferred treatment attributes and levels, as well as trade-offs among attributes, risks, treatment uncertainties, and levels of tolerance/acceptability;
- Understanding whether the potential benefit of the proposed treatment/product is commensurate with the commitment and resources expected from all stakeholders including patients and HCPs.

Clinical trial design - target population and clinical endpoints

Factoring patient input into the design of clinical trials will better reflect patient requirements for treatment outcomes to ensure that clinical studies measure changes in outcomes that are meaningful to patients,[53] which may positively impact the recruitment to, and retention of patients participating in the trials.[54] It should also help to ensure that medicines entering the market are better able to address the health needs of patients and the clinical information that is collected to inform the evaluation of benefits and risks is aligned with the priorities of patients.

Increasingly, regulatory authorities are requiring patient involvement in clinical trial design. The EU Clinical Trials Regulation (Regulation (EU) No 536/2014) requires that within the trial protocol there is a description of how and where patients were involved in the design of the clinical trial. Similar requirements exist in other jurisdictions including the UK[55] US[56] and Japan.[52]

Involving patients at the trial design stage and during protocol development may also help to identify acceptable comparators (e.g. placebo vs best standard of care, or active comparators), select relevant clinical endpoints (e.g. treatment free, progression-free or overall survival) and identify the relevant target population.[57] It can also help to identify the appropriate exclusion and inclusion criteria to ensure that those who have the greatest need or are most likely to benefit from the treatment are not precluded from participating in the clinical trials. Furthermore, patient input also helps identify relevant patient-centred outcomes relating to QoL or other PROs. It provides for a better understanding of the patients' perception of the product's efficacy, safety, tolerability and convenience.

Patient involvement and preferences can also help in calculating acceptable levels of uncertainty (significance and power).[58,59,60] Their involvement can help with the development of information and questions that are easily understood by patients but also cognisant of their needs, which can aid the correct interpretation and communication of study results.[61]

With some clinical trial designs (doubly randomised preference trials), the effect of preferences on clinical outcomes can be analysed.[62,63] Involvement of patients may also help define subgroups with different BR trade-offs.[64,65,66]

Using patient preference for the identification and selection of a product's key benefits and key risks - the benefit-risk trade-off

Many regulatory agencies already actively involve patients in their decision making both at strategic level but also with regards to BRA for individual products. The latter can be through patient representatives/advocates who are full members of formal committees and fully involved in the decision making of that committee. It may also involve attendance of representatives from patient groups and charities at the advisory committee discussions or seeking their views through formal or informal consultation.

Incorporating patient preference information and involving patients in BRAs can promote a better understanding and common appreciation of:

1. The most important benefits and risks of the medicine from a patient's perspective, including to inform the relative importance of clinical outcomes and safety concerns;
2. The relative importance to patients of different attributes of benefit and risk, including impact on QoL;
3. Patient perspective of risk, which of the medicine's identified risks are patients willing or unwilling to accept;
4. How patients trade-off key benefits against key risks (e.g. in terms of frequency and severity) for a given medicine and how that informs minimum clinically important benefit and effect size;
5. The heterogeneity or distribution of patient preferences regarding benefits and risks of various medicinal products (including to inform patient subgroup considerations as part of BRAs).

It is important to acknowledge that individual patient preferences may vary and that a patient may not assign the same values to various risks and benefits as his/her HCP, a family member, regulator, or another individual with the same disease/medical condition. Some patients, such as those with a life-threatening disease, may be willing to accept higher risks to potentially achieve a small benefit or to live longer, whereas others, particularly those with a minor illness, may be more risk averse, requiring more benefit to be willing to accept certain risks. Regardless of the severity of disease, an individual's personal values, disease stage, family circumstances, age and other demographic characteristics may also influence his/her BR preferences. Utilising a scientifically rigorously designed patient preference study best supports capturing and incorporating information that is representative of the patient population and allows a better understanding of how preferences differ across patients and how the BR trade-offs made by patients align with their medical condition and/or personal values.[67,68,69]

Engaging with patients to understand their views and incorporating those views into decision making is of particular value when:

1. The benefits and risks are finely balanced, that is; when both the benefits and risks are high, when benefits are almost equal to or are equal to the risks, and when both benefits and risks are low;[70]
2. There is considerable variability within the patient population about the most important benefits and acceptable risks, or the views of patients differ markedly from those of HCPs;
3. There is considerable uncertainty or variability in the available evidence if there is only limited or conflicting information available in the case of 1 or 2 above.[71]

2.5. Additional quantitative analysis

Additional quantitative analysis for BR conceptually refers to any advanced quantitative analysis[72] beyond the basic descriptive analyses typically conducted to determine the efficacy and safety of products, such as statistical analysis of clinical trial data. To name a few, the additional quantitative analysis could be modelling and Monte Carlo Simulation to estimate the benefits and risks of a vaccine in a real-world situation with different disease incidences, population immunity, evolving virus and combination of other risk control strategies; MCDA to integrate multiple benefit and risk endpoints of a drug and weights of those endpoints in BRA including patient preference, uncertainty analysis to evaluate the impact of uncertainty in effect size and weight of benefit and risk endpoints on the BR.[73,74] These additional analyses may analyse the data that have already been collected using a more advanced approach, but often time additional data from other sources are needed. For an

example, patient preference data are required for MCDA to incorporate patient's views about the BR trade-off. These quantitative analyses are an optional component of a BRA within the structured framework; it may not be needed for most cases but may be required for some.

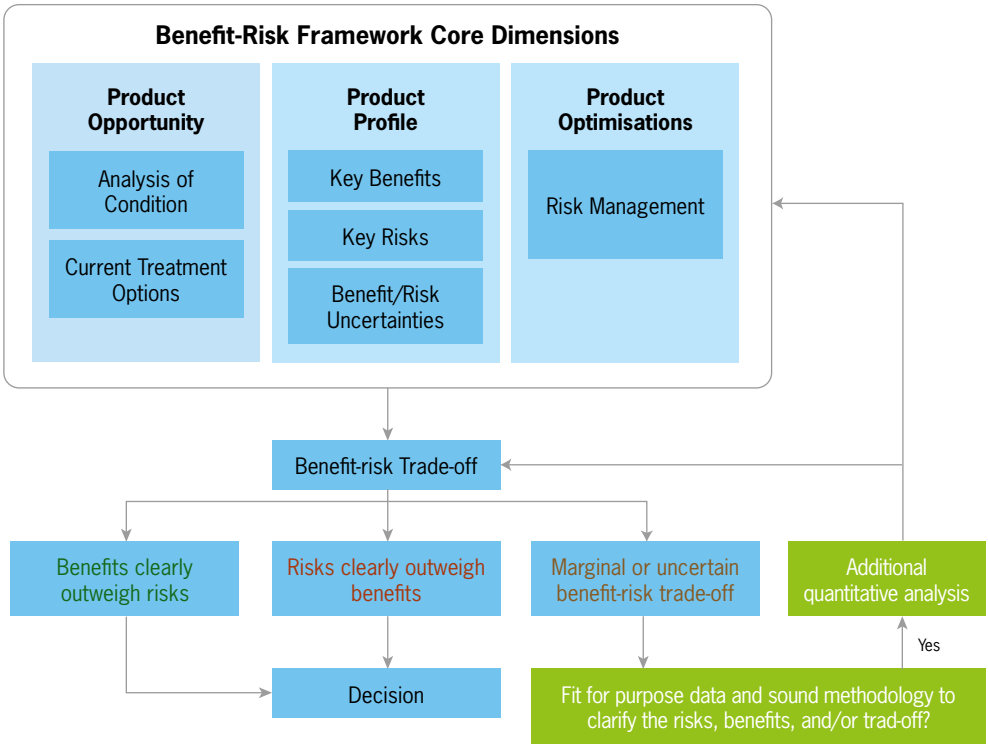
2.5.1. Purposes of additional quantitative analysis

All BRAs follow a SBRF and begin by analysing the core dimensions' evidence and uncertainties, with the core dimensions including analysis of the condition, current treatment options, benefit, and risk and risk management. A decision is then made based on the BR trade-off as described in the figure below. If benefits clearly outweigh the risks or the risks clearly outweigh the benefits, the decision is straightforward, and additional quantitative analysis may not be needed.

However, in some cases the BR trade-off is either marginal or involves high uncertainties, leading to difficult decisions. In such cases, understanding the values of stakeholders with regard to the BR trade-off becomes increasingly important, and additional quantitative analysis may have added value in reducing the uncertainties and understanding the impact of remaining uncertainties in benefits, risks, or BR trade-offs.

Figure 4. Decision tree for additional quantitative analysis in benefit-risk assessment for medicinal products

Source: CIOMS Working Group XII



Additional quantitative analyses can be used for different purposes. For examples, they can be used to facilitate discussion, inform decisions, or communicate benefits and risks.

Some BR problems are exceedingly complex, and people may have different mental models that lead to different conclusions based on different assumptions or different perceptions. Quantitative analysis may be a useful tool helping the team to sort out the key benefits and key risks, evidence related to the key benefits and key risks, uncertainties of the evidence and impact on the BR profile, and to help identify different assumptions among the team and test the impact of those assumptions on the BR trade-off. This will help facilitate discussion among the team by focusing on key issues.

Following the SBRF, we may identify knowledge gaps (or uncertainties) associated with one or more of the core BR dimensions, which are essential for a decision. The results of additional analysis may inform decision making:

- MCDA to incorporate patient preference for a trade-off between the clinical benefits and severe adverse effects of the treatment;
- BRA for a subpopulation which has a different BR profile from the general patient population.

The additional quantitative analysis can be designed to address critical questions related to the BR decision. Examples of such questions could be the following.

- What are the expected benefits of the drug post-market?
- What are the expected risks in the real population?
- How could the knowledge gaps impact the BR balance or whether the benefits outweigh the risks for specific patients?

Quantitative analysis may also be helpful in communicating the BR of a drug/treatment. Examples include publication in peer-reviewed journals, presentation in professional conferences and workshops. This could support communication of the drug BR profile to patients. When appropriate, sponsors may include quantitative BRA in their regulatory submission as part of the overall evidence. In such cases early communication between the sponsor and regulatory agency may be helpful. The regulatory agency could provide useful input at an earlier stage about usefulness of the study, and the appropriate study design including data collection and analysis plan. Regulatory agencies may use information from quantitative BR analyses to help communicate the rationale for the regulatory decision to the sponsors and public. Examples are US FDA presentations of BRA in US FDA advisory committee meetings, and inclusion of BRA in review memos. This enhances the transparency of regulatory decisions and helps to promote public confidence in public health decisions.

2.5.2. Methodologies and tools

Different types of additional quantitative analyses can be used, and the most frequent ones and their main purposes are described in more detail in Chapter 3 (see Chapter 3 on Benefit-risk assessment methodology considerations). The appropriate methods for additional quantitative analyses are determined on a case-by-case basis in terms of whether the methodology is scientifically sound to address the specific challenges and questions as well as whether the quality of the available data is fit for the purpose. The appropriate methods used have to be applied with a predefined analysis plan[75,76] and be based on high-quality data.[76] For example, integration of benefits and risks requires valid measures of endpoints for all the relevant product attributes; and extrapolation and simulation require reliable scientific evidence to validate model assumptions. Moreover, when needed, multiple methodologies can be used in synchronisation. The below *IMI-PROTECT five-stage roadmap and recommendations for benefit-risk assessments* of medicines draws from practical experience from real-world case studies.

Figure 5. MI-PROTECT five-stage roadmap and recommendations for benefit-risk assessments

Source[75]

1. Planning: Use of a descriptive framework such as BRAT or PrOACT-URL to structure each benefit-risk assessment is recommended. A set of benefits and risks should be chosen that covers the full range of treatment effects and represented visually using a tree diagram to indicate the hierarchy. A table template ('effects table' or 'source table') should be prepared, to represent the data that are required to be collected.
2. Evidence Gathering and Data Preparation: Assessors should review all available evidence and select data that are sufficient to and appropriate for the decision problem. The table template must be completed highlighting where data are available or missing for example by colour-coding missing data. The tree diagram and table produced initially may need to be revised in the light of available data.
3. Analysis: The analysis should be appropriate to the complexity of the task. Simple descriptive methods may suffice for everyday benefit-risk assessments, while quantitative decision models can provide additional clarity for more complex problems. When a quantitative benefit-risk assessment approach is used, stakeholders' value preferences and the benefit-risk magnitudes (by criteria and overall) should be represented by suitable bar graphs (particularly useful is the 'difference display'), dot plots or line graphs to promote accurate point reading, local and global comparisons, and judging trade-offs among alternatives. Care should be taken to avoid double counting events or effects in any analysis.
4. Exploration: All benefit-risk assessments should include a sensitivity analysis of some kind. Where benefits and risks are finely balanced, quantitative decision models facilitate the execution and communication of sensitivity analyses by clearly setting out the respective impacts of effects uncertainty and preference uncertainty on the results. The visual representations which should be used at this stage are distribution plots, line graphs, forest plots or tornado plots to provide comprehensive overview of the benefit-risk analysis allowing better-informed decisions.
5. Conclusion and dissemination: Adopting a formal structure for a benefit-risk assessment is an effective way to improve the overall transparency and communicability of the process and facilitate robust decision making.

Analyses conducted at different stages of the product lifecycle depends on the objectives of the product development program and the challenges at the different stages from early drug development to management of uncertainty at the time of regulatory approval. It also depends on the availability of data at each stage. The specific challenges at each important stage of development are described in the section related to lifecycle management (see Section 2.3 on Lifecycle approach to benefit-risk assessment). For example, evaluation of patients' preferences using measurement methods in early drug development may help identify the patient's needs and the benefit endpoints that are important to the patients; while MCDA may be especially helpful during late drug development stage when there is a difficult trade-off decision for a product with clear clinical benefit but severe adverse effects based on available evidence.

Additional quantitative analyses require high transparency on the method(s) used including model inputs, assumptions and limitations. Model inputs and assumptions and sources of data need to be presented as well as the rationale for selection. Limitations of the methods chosen need to be presented and discussed.

As for the main BRA, a cross-functional BRMT is involved in the decision of when and which additional quantitative analyses are appropriate.

2.5.3. Integration of additional quantitative analysis in the overall evidence

The results of any additional quantitative analysis performed to address specific outstanding questions that are critical for decision making are to be merged with all other evidence. In the end, the decision taken is a judgement call and should be made based on the totality of evidence including additional results from quantitative analysis within the context of the SBRF.

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CHAPTER 3.
BENEFIT-RISK ASSESSMENT METHODOLOGY CONSIDERATIONS

This chapter will focus specifically on methods used in the BRA process. It builds from the concepts outlined in Chapter 2, while providing more specific insights into some of the key methodological considerations. While this includes presentation of statistical methods, pragmatic recommendations around the conduct of BR-related activities have also been provided. For example, specific recommendations around the membership of certain teams are provided. At the same time, the complexity and scope of the methods used in the field of BRA are highlighted. The chapter provides an overview of the field as well as specific insights to drive the continued evolution of the science of BRA and management.

First, a brief review of the complex interface between the BRA for medicinal products and the broad array of other therapeutic interventions, including health care access, all of which are critical steps in the ultimate goal of BR evaluation at the point of interface between the patient and their HCP. Following this, the evolution and future of BR as it relates to study design, including statistical considerations is presented. Building on concepts from the CIOMS Working Group XI report and Chapter 2, methodological considerations relative to eliciting patient insights are presented. The chapter concludes with a review of methods to address aspects of uncertainty, followed by an outline on visualisation methods, and finally specific recommendations about structuring an effective multidisciplinary team, all in the service of BRA across the product lifecycle.

3.1. Applying benefit-risk assessment methodologies across the many dimensions of patient care: different scopes and purposes

Chapter 1 highlighted the respective context of BRAs from the approval of an individual medicinal product to the last step being the interaction between the patient and their HCP. These incorporate three key dimensions: the patient, the HCP and the integrated health care system. Chapter 2 outlines the BR considerations for an individual medicinal product.

All of these efforts converge ultimately on informing the patient. Chapters 1 and 2 focus on medicinal products and the evolution of the BRA with a focus on interactions between regulatory authorities and industry. In clinical practice, there are many intermediate steps that ultimately lead to patients making a choice. The options that are presented to the patient by the HCP are increasingly modulated by health care system-linked financial considerations. These considerations range from the system in the USA, where patients still control much of their health expenses to countries such as Canada and most European countries, where regional or national health agencies, based on country-level health economics considerations, determine accessibility to treatments. Compounding these realities, patients frequently have the opportunity to choose between treatment modalities, for example between a medicinal product, a medical device (and sometimes a drug-device combination product) or a surgical procedure. At present, the frameworks to assess the BR profile for these different treatment modalities differ frequently, such as the approach to a medicinal product (as outlined in Chapter 2) compared to a surgical procedure, especially relative to elements such as robustness of data, level of uncertainty and characterisation of risks. This also applies to the assessment of the value of the distinct therapeutic intervention in the integrated health care system.

This chapter will briefly describe how the frameworks to assess BR vary between different treatment modalities and in the context of the integrated health care system. This is an important consideration to understand the extent and complexity of interactions at play in the decision-making journey that leads to the patient.

Medical devices are rapidly evolving in number, scope and complexity. This is being driven by technological advances including 3D printing and Artificial Intelligence (AI). Regulatory authorities have long played a key role in the oversight of medical devices and it is important to understand their interface with medicinal products.

The US FDA defines a medical device as (elements that pertain to therapeutic nature have been bolded): 'an instrument, **apparatus, implement, machine,** contrivance, **implant**, in vitro reagent, or other similar or related article, including a component part of accessory which is:

- Recognised in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them;
- **Intended for use** in the diagnosis of disease or other conditions, or **in the cure, mitigation, treatment, or prevention of disease, in man** or other animals; or
- **Intended to affect the structure or any function of the body of man** or other animals; and
- **Which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolised for the achievement of any of its primary intended purposes.**[1]

This definition is amongst the most comprehensive but also aligns well with that of most other regulatory authorities.

At a high level, a fundamental difference between medical devices and medicinal products is that the latter are discovered while devices are designed. As a result, device risk can, to an extent, be mitigated by changes in design. There is generally much less that can be done to change the risk associated with the active ingredient of a medicinal product.

The risks and complexity associated with medical devices has been demonstrated in several instances. We provide a few examples here.

One complex example relates to metal-on-metal hip implants, which triggered intensive monitoring, studies, and responses from multiple health authorities.[2] A key component of this complex topic relates to the potential release of particulate metal materials (e.g. cobalt, chromium) causing local tissue reaction or systemic effects. These devices continue to be in clinical use in most countries but are subject to on-going clinical monitoring.[3,4,5,6]

Another example relates to one subset of breast implants, and the potential link to anaplastic large cell lymphoma.[7,8] A third example is provided by the use vaginal mesh products in the management of pelvic organ prolapse.[9] These three examples – a small sample of those in the field of medical devices – highlight the complexity of the BRA for medical devices and differences from medicinal products. In most countries, the oversight, reporting and tracking systems differ from those of medicinal products (e.g. role of Notified Body in Europe). In many instances, the experience and skill of the surgeon can modulate the risks from the device. This can vary greatly between countries, and between medical centres within a given country. Medical professional societies (surgical specialties especially) tend to play a more active role in providing clinical recommendations around the use of the device.

When it comes to devices, the assessment of BR follows a different framework in most instances from that for medicinal products. Many of the elements of this framework are derived from engineering and manufacturing processes. The medical device risk management process is a holistic, systematic lifecycle. Governed globally by the ISO 14971 standard, this connected loop of activities is presented in Table 7.

Table 7. ISO 14971 Standard Risk Management Process

Source:[10]

Risk Management Planning	Overall Residual Risk Acceptability
Risk Analysis	Risk Management Review
Risk Evaluation	Production & Post-production Information
Risk controls	

As was stated earlier the oversight of medical devices in most countries follows a process parallel but distinct to that for medicinal products. There are however significant differences in the approach. By contrast to medicinal products, most countries classify medical devices in different categories, based on the risk they may present, and this in turn determines the level of rigor applied to the BRA, as opposed to the same standard being applied for all prescribed medicinal products. For example, the US FDA categorises devices as Class I, II, or III medical device, with Class III posing the highest level of risk, usually the ones that provide a therapeutic benefit that may be competing with medicinal products or complementary. Most regulatory approvals are provided by a distinct division of the US FDA. In Europe, the process may involve different stakeholders including EMA, national regulatory authorities and Notified Bodies. As with drug risk management, medical device and drug-device combination product risk management is an enterprise-wide process. Stakeholder involvement extends from the sponsor/company, to the end-users outside of the business, to the internal-facing functions of the product supply manager, manufacturing manager, quality reviewer, regulatory head, commercial manager, and safety reviewer who contribute to the medical device product risk management team. Together these differing perspectives and experiences yield a total risk management lifecycle which includes: design, development and manufacture.

The device risk management aims to identify hazards; estimate and evaluate risks; and develop, introduce and monitor the effectiveness of risk control measures within the product's intended, normal use. As a device is designed, developed and manufactured, the Risk Management File (RMF) is created and thus the BRA begins to take shape. The RMF houses all pertinent information related to the risk management activities and records of evidence as outlined in the following device BRA explanation.

Essentially, a device BRA consists of a risk analysis and a risk evaluation, or as industry refers to it, the evaluation of overall risk acceptability. Much like a medicinal drug product, the BRA for a medical device looks at the results of the risk analysis, risk evaluation and risk control activities to ensure that the medicinal benefits of the device, when used as intended and under normal conditions, outweigh the residual risks and that the residual risks are acceptable. On the surface, the device BRA may appear similar to a RMP for a medicinal product. They actually differ as the device BRA is engineered into the device by design with an assumption that the device would work in everyone for whom it is indicated. In an analogous manner, both the device BRA and the medicinal product RMP continue to evolve throughout the lifecycle post-marketing, while using different methodologies.

Device BRA = risk analysis + risk evaluation + risk controls

Risk analysis:
The process of listing out each potential hazard or hazardous situation, which could be a source of harm. The intended use and end user (the patient) are the foundation for this exercise.

Risk evaluation:
The process by which the product developer of the device evaluates the identified harms to determine if the risk warrants a risk reduction. Through this process the risk acceptability is determined with all risks reduced as far as possible.

Risk controls: Measures are used to reduce risks to acceptable levels. Risk controls are employed to address the items identified during risk evaluation requiring risk reduction to acceptable levels. As a best practice, all risks should be reduced as far as possible. For devices, this is usually linked to the engineering of the device, or associated elements of a procedure (e.g. operating room checklist).

In cases where the overall risk is deemed acceptable and the BRA is favourable, the product can then be released for commercial production. Of course, like medicinal products, device risk management is a holistic process that is continuous through the device lifecycle. That said, the device developer must regularly review all incoming field data, complaints and other data and material feeding into the risk management process to ensure the product's BR balance remains favourable under normal, intended use.

There are several instances where it is critical to understand the assessment of BR for devices in conjunction with the BRA of medicinal products. For one, devices may offer alternative treatment modalities that must be considered in the therapeutic armamentarium for the disease of concern and compared to the efficacy and safety of a medicinal product (e.g. Left Ventricular Assist Devices – LVAD - for heart failure). This assessment can be very complex. In addition, there are a number of instances where one or more devices (e.g. filter, syringe) are part of the end user interface with medicinal products such as delivery devices. Another paradigm combines a device and a medicinal product (e.g. medicated intra-uterine device, drug-eluting intravascular stents); this is frequently referred to as a drug-device combination product and is becoming an increasing area of interest and scrutiny for regulatory agencies.

For a wide range of medical conditions, medical interventions that do not include using a medicinal product are widely and increasingly used as treatment options. These must be considered in the overall BRA of a medicinal product, especially relative to available treatment options. For the purpose of the following paragraphs, we will label this type of medical intervention 'therapeutic procedure'. Surgical procedures are clearly encompassed in this category. However, a broad range of non-surgical interventions are also relevant under this label of therapeutic procedure. As examples, we list radiation therapy, shock wave lithotripsy, uterine artery embolisation for the treatment of leiomyomas, physiotherapy and a very broad range of dietary modification. A major challenge in considering these different therapeutic modalities, i.e. medicinal product compared to therapeutic procedure, is the frequently differing framework that is used to assess the BR balance of therapeutic procedures. We are focusing specifically on those instances where a medicinal product and a therapeutic procedure are considered therapeutic alternatives; we are not addressing the complimentary use of therapeutic procedure and medicinal product, even though some of the concepts may apply to both situations (see below).

Usually, therapeutic procedures are not subject to any formal approval by a national health authority. In most instances, acceptability and spread of use becomes driven by local medical standard of care, which itself is the subject of a wide range of influences. They may, or may not be supported

by local payer and reimbursement agencies, but this is highly variable. Some therapeutic procedures have been subject to detailed and rigorous studies. An example is comparative studies of coronary artery bypass graft (CABG) surgeries compared to transcutaneous stenting procedures.[11,12] In this particular instance, a surgical procedure was compared to an interventional procedure using a drug-device combination product (we will not address the added complexity of a drug-device combination product as it is beyond the scope of the current document). In addition to these studies, other parallel evaluations have highlighted that the BR of the procedures themselves may be influenced by local factors, such as the level of quality-of-care protocols and the experience and annual volume of cases for the specific therapeutic procedure for the person performing the procedure (e.g. a surgeon) and the medical centre where the therapeutic procedure is performed.[13,14]

Another example is the assessment of different surgical approaches for the management of prostate cancer. This provides an example of how evaluations and assessments of surgical procedures progress over time. Traditional operative procedures for prostate cancer have been gradually replaced by minimally invasive or robotic-assisted surgery approaches. Early assessments found that there was little overall additional benefit from the minimally invasive or robotic-assisted surgery in the management of these patients.[15] Despite such early assessments, the novel methods continued to gain in popularity amongst urologic surgeons.[16] More recent re-assessments have demonstrated incremental benefits and a more favourable BR profile for the newer techniques, including robotic-assisted surgery, provided additional variables are included in the evaluation, such as the surgical volume at given treatment centres.[17,18,19] This type of progressive improvement in the benefit profile over time, linked to increased expertise by the physicians performing the procedure, is very different from the context of medicinal products. The evolution of this type of surgical approach must be considered in updating the BRA for relevant medicinal products.

The interface between a pharmaceutical therapy and a therapeutic procedure presents a high level of complexity when there is a clear recognition that the physician performing the therapeutic procedure and the patient-level characteristics (e.g. the overall state of health and the quality of the tissue in surgery) themselves influence the overall outcome generally much more than with a medicinal product. A clear example of this is the BRA of anti-thrombotic agents used in the context of surgical cardiac revascularisation.[20,21] In this context, the data show that an overall assessment can be reached, but the level of uncertainty around the robustness of that decision is modulated significantly by the operative skills of the surgeon, the underlying characteristics of the patient undergoing surgery, and treatment duration.

Therapeutic procedures may be important considerations among the therapeutic alternatives to a medicinal product. The process to assess the BR of these procedures generally relies on a range of different frameworks, with varying levels of rigour and duration of follow-up. Ultimately, this generally leads to greater uncertainty in comparing efficacy and safety of such procedures compared to a medicinal product. The impact of local medical practice in the overall efficacy and risks of such procedures is also much greater than for medicinal products. These are all important considerations to evaluate while conducting a comprehensive BRA for a medicinal product relative to therapeutic alternatives.

OTC medicinal products are frequently already approved medicinal products that late in their lifecycle receive approval for access OTC. Special considerations around these are discussed in Chapter 4.

Lifestyle modifications, including diet and exercise regimens, are the subject of increasing scientific scrutiny with rigorous evaluations conducted in many instances. This is generally driven by the medical community with little direct involvement from National Health authorities. Practically, it is not uncommon to find labels for medication that advise following specific dietary or exercise recommendations; this is the case for the management of hypercholesterolemia, type 2 diabetes mellitus or the treatment of obesity. These are important medical interventions that are fully dependent on patient adoption

and persistence. Nonetheless, they may impact the BRA of medicinal products but they are seldom encompassed in our current frameworks beyond some basic requirements in some clinical studies for patients to adhere to certain instructions, e.g. dietary modification.

Within each community, the so-called standard of care evolves and this has direct impact on how patients are provided medical care. The oversight and regulation of medical practice varies greatly from country to country, and even between regions (usually based on an administrative construct such as district, state or province) within each country.

Guidelines from national and international professional medical societies provide further input to medical professionals around the treatment of specific medical conditions. A range of organisations also provide systematic BRAs for medicinal products as well as medical interventions. Some of the more prominent ones include the Cochrane collaboration (cochrane.org) and the US Preventive Services Task Force (uspreventiveservicestaskforce.org). These groups use their own specific frameworks and approaches to conduct their evaluation and derive a BRA on a topic, which at times may differ from similar assessments conducted by regulatory authorities or professional societies. While supporting the knowledge base for clinicians, conflicting opinions from these various sources increase the challenges for the practicing clinician.

In most instances, medical practitioners are given a broad range of autonomy in their practices. As highlighted in Chapters 1 and 4, this becomes a very important interface between national regulatory authorities and the medical community. A major part of the challenge lies in the fact that the standard of care is generally defined in a broad manner, with highly variable systematic or framework-driven analysis. Specifically, the standard of care may range from a reference to the medical practice standards upheld by a local community of physicians all the way to medical guidelines generated by international medical speciality societies. Nonetheless, the standard of care that most influences the HCP providing the medical care to a given patient is ultimately what most frequently informs the decision by the patient. We view this area as a great opportunity for future improvements, including an increasing use of personalised evidence-based, decision-making support tools, potentially augmented by AI.

Patients and HCPs live in communities where the social and economic environments ultimately play a determinant role in the access and quality-of-care provided. This is widely acknowledged in terms of health care disparities seen across the world. They are seen across international borders, potentially related to access to health care, as demonstrated in a study of a technologically complex procedure such as a lung transplant that found significant differences in survival between US and EU patients.[22] They are consistently confirmed through global studies on the burden of illness such as cancer and Chronic Obstructive Pulmonary Disease (COPD).[23,24]

As highlighted in Chapter 1, we are witnessing the advent of increasingly complex medicinal products. These scientific advances, while overall positive, have put further pressure on the economic aspect of health care delivery. This is frequently compounded by the aging of the population with increasing need for medical therapy. Considering this, there has been a significant focus on evaluating the cost effectiveness of treatments within communities. These efforts encompass most countries and regions of the world but are implemented in a range of ways. In a broad manner, the field is referred to as HEOR. A key methodology in this field is referred to as HTA.

As described in the CIOMS Working Group XI report, HTA is a multidisciplinary process to determine the relative value of an intervention developed to prevent, diagnose or treat medical conditions; promote health; provide rehabilitation; or organise health care delivery. The intervention can be a test, device, medicine, vaccine, procedure, program or system.[25]

The conduct of HTA requires to select which benefits and risks to include while carrying out evidence-based assessments. By contrast, the benefits and risks are not limited to the medical

aspect of the event, but also encompass the related costs, cost-savings or additional expenditure, as well as societal considerations, such as time away from work, quality and duration of life. In this context, new technologies are usually costlier than older ones and may contribute to rising health expenditures, but these increases may be counter-balanced with lower, long-term costs and improved societal conditions. In this context, the HTA process is meant to ensure that new technology is not added until it is proven to be cost-effective from a system or societal level. Meanwhile, with time, older technologies may become less effective, as newer technologies are introduced, rather than becoming ineffective.

The methodologies used to conduct HTAs are varied, but they overlap in many instances with that for BRA of medicinal products.[26] Two important differences, and indeed challenging areas, are that HTA usually include consideration of a comparator medical management plan (considered as the established standard of care in the community, including medications but not exclusively) as well as consideration of a cost component. HTAs also frequently draw on data from real-world evidence (RWE), which presents its own specific set of challenges, especially when comparing a new medicinal product where all the evidence comes from pivotal clinical studies and the comparator data set derived from RWE. Guidelines are being developed to address such challenges, leveraging the opportunities of AI.[27] The need to generate economically relevant conclusions generally drive the use of quantitative methodologies, usually with the inclusion of weighting factors. The cost consideration has led to widely accepted constructs such as the Quality Adjusted Life Year (QALY), which aims to consider morbidity and mortality in a single index, or the incremental cost-effectiveness ratio.[28, 29]

How HTAs are conducted, coordinated and their conclusions implemented varies highly from country to country. In many countries, government-sponsored groups have the ultimate authority in the area, which ultimately recommends for or against reimbursement and effectively access to a medicinal product. These include the National Institute for Health and Care Excellence (NICE) in the UK, the *Institut Für Qualität Und Wirtschaftlichkeit Im Gesundheitswesen* (IQWIG) in Germany, the Canadian Agency for Drugs and Technologies in Health (CADTH) and the Centers for Medicare and Medicaid Services (CMS) in the United-States. The pivotal role these agencies play in the access of medicinal products for patients continues to be an area of scientific interest as well as broad political debate.[30,31]

For this complex topic, the USA provides a clear example of challenges linked to HTA assessments. The majority of patients access care through private health care insurance systems; many others access care through government-sponsored programs (Medicare or Medicaid), while a significant number are still left to pay directly (i.e. out-of-pocket) for their health care. In this context, access to reimbursed medications becomes a major driver of the quality-of-care provided to patients. While CMS plays a key role in such reimbursement determinations for patients on government-sponsored programs, many private insurers draw on other bodies or their own internal analyses to make such determinations. One group that has generated large output and exerted a great influence in the HTA area in the US is the Institute for Clinical and Economic Review.[32,33,34] Authors have highlighted discrepancies between the HTAs conducted by Institute for Clinical and Economic Review (ICER) and other HTA researchers and the opportunities for further evolution.[35,36] Ultimately, the recommendations from such groups determine whether or not an individual patient in the US has reimbursed access to a medicinal product, regardless of the approval status of such a drug and the BRA for that particular patient by the treating HCP.

The interface between regulatory approval and HTA recommendations continues to be an area of great interest and controversy. At present, regulatory approval and HTA recommendations continue to be considered as separate processes with overlapping considerations and methodologies, but with different ultimate focuses and scopes. These sometimes occur in parallel and at other times sequentially. These pathways are likely to evolve further over time, given the overall economic context of health care delivery.

Additional patient-level characteristics impacting the benefit-risk assessment

As stated in Chapter 1, the BRA leading to the approval of a medicinal product relies predominantly on data generated from highly controlled clinical studies. These involve a relatively narrow population of highly selected patients. Although this is a major concern regarding the use of clinical trial results in the applicability of these results to the general population, considerable efforts to expand the access and diversity of patients in clinical trials is ongoing. (See US FDA guidance *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs*).[37] Until these efforts yield major differences in the generalisability of clinical studies, patients will continue to contend with a range of social, cultural, psychological and economic circumstances in which they live and operate that differ from those that applied to the study populations for a given medicinal product.

Commonly, a caregiver (e.g. spouse, parents or adult children of elderly individuals) is a critical contributor to the patient's health care, including the use of a medicinal product. These individual circumstances which may vary greatly from country to country, between regions, between races, and between individuals of differing socio-economic standings, are all important considerations for National health authorities as they look to assess the BR profile of a medication. They are equally important considerations by the HCP for the individual patient according to their psychosocial dimensions. These important elements have generally not been included in the BRA, although the increasing focus on considering patient input (see later) may help incorporate these dimensions in the BRA.

The final decision about using a medicinal product rests with the patient, supported by their HCP and according to patient's preferences, circumstances, beliefs and values. This is the final pragmatic synthesis of all the information generated. While this seems obvious, it is not always given the fullest attention in discussions around BRA. We wish to highlight a few concepts that capture the challenges in this interface as well as the potential opportunities.

One important component is the time given to making such a decision. It is a reality of modern health care that in most instances the face-to-face time between the patient and their HCP is very limited, frequently less than 10 minutes per visit. In this context, the challenges of conveying an appropriate BRA upon initiation of a medicinal product becomes obvious. Alternative ways must evolve to better inform this dialogue.

This naturally leads us to the discussion around information for the patient. While there were initially high hopes that the internet and online sources would provide expanded and potentially tailored information to patients, the reality is now that such information sources are an undistinguishable maze of reliable and unreliable, even dangerous, information.[38] We can only hope that this situation will improve over time. This would involve better access by patients of reliable sources of information such as that generated by National Health authorities, physician groups and other patient-focused stakeholders. The infodemic linked to the COVID-19 pandemic give us pause that such a positive reality can ever exit, but we should still strive for it.[39,40]

On the very positive side, there has been an increasing focus and involvement of patients in the development of new drugs. This was highlighted in Chapter 2 and will be further developed later in this chapter. Such efforts allow to highlight what is truly relevant to patients in considering a medicinal product and how to generate fully relevant information for patients in making such a decision. The evolution of AI can further complement these efforts by providing patient-level advice on their best therapeutic approach, in a wide range of medical conditions.[41,42,43,44,45]

Fundamentally, the key element in the sharing of information between the patient and their HCP is the ability of the HCP to communicate effectively, which is a frequent point of failure. [46,47,48] This is also an area of great interest which has been the focus of the CIOMS Working Group XI, as a great example, and where continued efforts are likely to yield significant improvement overtime.[49]

3.2. Study designs and statistical approaches to generate data that inform the benefit-risk assessment

Most medicinal products are developed with the goal to be approved and used in many countries, frequently worldwide. In this context, methods to assess the BR balance of a medicinal product must be flexible enough to meet the expectations of most national health authorities. We will focus first on the a priori design of pivotal studies and the predefined SAP. We will then address more recent approaches to study design in support of conducting a BRA, classic study design and statistical approach to inform the BRA, leading to registration.

The majority of new drug development has been following a classic methodology that has evolved since the 1970's. This evolution has been driven by the advances in medical science, biostatistics and the guidance provided by health and regulatory authorities. In general, it involves an orderly progression from pre-clinical assessments, through Phase 1, Phase 2 and Phase 3 human trials. The total number of human subjects evaluated (i.e. sample size) is linked to the medical condition under study, as well as the minimum duration of treatment and follow-up. The results of the study can be a clear clinical endpoint (e.g. death, disease-free-progression) or a surrogate end-point (e.g. serum lipids, hemoglobin A1C).

Another important aspect of trial design is the control or comparator group, either in the form of a placebo or an already-established therapy that is considered the standard of care. If randomisation is possible, the choice is usually focused on the relevant comparator, given available therapeutic options (e.g. standard of care). However, how should one handle benefits from one data source and risks from another source, since you cannot assess the interaction of benefits and risks? Increasingly, alternatives for the comparator group are becoming accepted (e.g. ICH E8 and E10 guidances). These can include treatment switching, open label studies, historic controls, case-matched controlled, and some of the more novel trial designs (e.g. platform trials). Regulatory authorities are a key stakeholder in this complex process, and there can be significant variability in their specific requirements, for example the choice of the comparator group or overall sample size.

While there is quite a degree of flexibility in the elements being assessed during Phase 1 and Phase 2 clinical trials (e.g. focus on PK/PD parameters, optimal efficacy dose, focus on specific identified or potential risks), the approach to the assessment of Phase 3 clinical trials is generally similar. The primary objective targets efficacy (i.e. benefit), and the primary statistical analyses are powered to demonstrate the desired level of efficacy based on RCTs. This efficacy assessment can be in the form of superiority to the comparator arm, or in the form of non-inferiority. In most instances, the assessment of efficacy is based on an Intention-to-Treat (ITT) statistical analysis, with a clearly pre-defined statistical threshold, which also takes into account potential statistical penalties for interim analyses.

By contrast, the safety assessment is conducted using a different approach. Seldom is a study powered to demonstrate a target level of safety. Rather, all safety events are captured as part of the study procedure and these are then analysed, generally based on the entire population enrolled (i.e. safety data set) in the study. There is also greater variation in the analysis and interpretation of the safety data. In many instances, a numeric imbalance alone raises safety considerations, independent of a statistical threshold (e.g. an AE list purely based on numeric excess in the treatment arm). At the same time, there can be more flexibility in gaining an in-depth understanding of a safety event, especially in the attempt to identify a subset population at risk for the AE, which may then drive the implementation of risk management measures.

While this overall approach has fuelled drug development and the related BRA process, several limitations of such an overall approach have been noted, as outlined in the next sections. The universe of methodologies to sustain the traditional approach may continue to grow; the overall approach may persist in the near future in guiding the cascade of drug development. However, transformational progress rests more likely on novel approaches, as detailed below, with a greater focus on integrated patient-focused approaches to assess the BRA.

3.2.1. Patient-level benefit-risk assessment – example of a novel paradigm through drug development and lifecycle management

As just stated above, RCTs have been and continue to be the gold standard for evaluating the benefits and risks of interventions, ultimately yielding the data to be used as inputs to generate the BRA. Despite the preferred status of RCTs, this approach often fails to provide the practical evidence to inform medical decision making in clinical practice.[50] BRA based on RCTs may often fail to achieve the ultimate goal of clinical relevance because they overlook the most important questions for treating patients in clinical practice. Meeting the needs of the patient should be the primary driver for the design, monitoring, analysis, and reporting of clinical trials and product development.

The conventional approaches to BRA have synthesised information obtained from separate marginal analysis of the benefit outcome(s) and the risk (also referred to as harms or hazards) outcome(s), as outlined in the section above. Such a construct does not address the most important questions for clinical practice as they are not patient-centric. It fails in multiple ways. It does not adequately incorporate associations between the positive and negative outcomes. It does not account for the cumulative nature of outcomes in individual patients. It suffers from competing risk complexities during the interpretation of component outcomes. Finally, since efficacy and safety analyses are often conducted on different populations (e.g. efficacy from ITT population, safety from safety data set of all enrolled patients), generalisability to patient populations is unclear.

These challenges can be addressed by placing increased emphasis on BRA and by focusing on questions of a pragmatic origin to match their clinical importance. This can be accomplished by:

(1) Transforming BRA from a post-hoc exercise to one that is thoughtfully integrated into clinical trial design, conduct, and analyses; and

(2) Adding patient-centric BR analyses.

Issues to consider for improving benefit-risk analyses

Several areas offer significant opportunities for improving the BRA. These are shown in Table 8 and discussed on the next page.

Table 8. Issues to consider in improving the conduct of clinical trials to inform the benefit-risk assessment

Source: CIOMS Working Group XII

1. Generalisability
2. Importance of Intention-to-Treat and the strategy of application
3. Absolute vs relative risks
4. Pre-specification and evolution away from the tradition of BRA as a post-hoc exercise
5. Pragmatism and patient-centric evaluations
6. Approaches to assess competing risks
7. Consideration of cumulative effects on patients

1 - Generalisability: to whom do analyses apply?

The topic of generalisability usually comes up around the questions of how representative patients and the controlled conditions of clinical trials can be applied to the real-world situation. As highlighted above, if efficacy is evaluated in one group (e.g. ITT population) and safety in another (e.g. entire population), then BRA, which combines those two has no clear generalisability. Restrictive entry criteria further limits generalisability.

2- The importance of Intention-to-Treat and the strategy of application: beyond statistical properties

Here, we are focusing on a different but related notion. Analysis populations are carefully defined during the design and analysis of clinical trials. As stated above, an ITT population is typically used to analyse efficacy endpoints in late-phase trials. A distinct safety population is used for safety endpoints. BRA may combine these marginal analyses together. To whom does this BR analysis apply? The target population and estimand are not well-defined (see Section 3.2.2 on Estimands in benefit-risk assessment).

Different analysis populations address different questions. Which questions are most important for BR analyses and informing medical practice? We illustrate the point with the following example.

Suppose a randomised trial is conducted to compare two interventions A vs B. Suppose a trial participant is assigned to A, subsequently discontinues A, and begins treatment C. This participant then experiences a Serious Adverse Event (SAE), adjudicated as related to C and not A. This leads to the belief that safety is not an issue for A as the event was considered related to C. Now suppose 10 additional patients that were randomised to treatment A, subsequently discontinue A, begin treatment C, and experience the same SAE. Adjudication again is linked to C but not A. There are no such events in arm B despite the facts that a comparable number of subjects also discontinued B and began treatment with C. C may indeed be the biological culprit but these events are downstream consequences of being assigned to A, as they are not observed in B. The events that occur in people initiating A, are endured by those patients, regardless of adjudicated attribution. Could a Data Monitoring Committee (DMC) conscientiously allow continued randomisation to A? When considering the interests of patients and the value of interventions to treat patients, adjudication is not the relevant question, the impact of the strategy of application is. The most relevant question for someone initiating a treatment is where they end up, and how that ultimate path to the outcome compares with that which may occur had they initiated an alternative therapeutic strategy. ITT addresses the most relevant question for clinical practice regardless of whether outcomes are labelled as efficacy, safety, or BR.[51,52]

3 - Absolute vs relative risk

Suppose an intervention increases the risk of death from 1 in 10 to 2 in 10. This is a Relative Risk (RR) = 2 and very important. Now suppose an intervention increases the risk of death from 1 in 100,000 to 2 in 100,000. This is also a RR = 2 but nearly irrelevant. Is the RR the most informative measure when summarising the impact of the intervention?

Consider the THALES clinical trial,[53] a randomised, double-blinded, placebo-controlled trial (N=11,016; 1:1 randomisation) comparing Ticagrelor and aspirin (Ticagrelor) vs aspirin and Ticagrelor-placebo (placebo) in acute ischemic stroke or TIA. The primary outcome was the time to stroke or death at 30 days resulting in a Hazard Ratio (HR) = 0.83, 95% CI = (0.71, 0.96), p=0.015. The primary safety outcome was the time to severe bleeding by 30 days resulting in a HR = 3.99 95% CI = (1.74, 9.14), p=0.001. Is there too much bleeding relative to the benefits being observed?

Further examination of the primary outcome revealed that there were 303 events (5.5%) in the Ticagrelor arm and 362 (6.6%) in the placebo arm. Ticagrelor had 59 fewer efficacy events in the trial. For the safety outcome, there were 28 events (0.5%) in the Ticagrelor arm and 7 (0.1%) in the placebo arm. There were 21 additional safety events observed in the Ticagrelor arm. If the events are comparable, then there was a total savings from Ticagrelor of 38 events.

Suppose instead that for the primary safety outcome of severe bleeding, the results were 10 events for Ticagrelor and one event for placebo. This represents a HR = 10. This sounds worse than the earlier HR = 4. However, the cost is only 9 events resulting in a total savings of 50 events i.e. a better overall result for Ticagrelor. Comparing HRs from multiple outcomes can be misleading due to the different baseline risks. Absolute risks summaries are more appropriate when synthesising the result of multiple endpoints.

4 - Evolve away from the tradition of benefit-risk as a post-hoc exercise

A fundamental principle in the design of clinical trials involves setting out in advance the endpoints that will be assessed in the trial[54,55] as failure to pre-specify endpoints can introduce bias and create opportunities for manipulation. Trial protocols further describe how these endpoints will be analysed. Such practices help to ensure that trial researchers and sponsors diligently consider the appropriateness of endpoints and associated analyses, and provide transparency and context for error control.

BRA is the ultimate evaluation of the clinical utility of an intervention. Despite this, it is typically treated as a post-hoc exercise. Rarely are BRA endpoints and methodologies pre-specified and documented in a trial protocol or statistical analyses plan.

5 - Pragmatism and the need for patient-centric approaches

Typical current approaches to BRA are not pragmatic. They fail to incorporate associations between outcomes and recognise the cumulative nature of outcomes in individual patients, and suffer from competing risk complexities during the interpretation of component outcomes. Treatment effect heterogeneity is typically evaluated based on a single efficacy or safety endpoint, and rarely evaluated based on BRA. These limitations highlight the need for more pragmatic patient-centric approaches.

6 - The challenge of interpreting individual outcomes: competing risks

Suppose the duration of hospitalisation is measured. A shorter duration is interpreted as better. However, the faster the patient dies (a competing risk), the shorter the duration of hospitalisation. The interpretation of the duration of hospitalisation needs the context of survival status. Summary statistics of duration of hospitalisation are not interpretable unless survival status is known. However, once the survival status is established, then the duration of hospitalisation has context for meaningful interpretation.

7 - Cumulative effects on patients

It is important to recognise that patients experience the cumulative and multidimensional effects of an intervention. The Antibacterial Resistance Leadership Group (ARLG) conducted a study on Staphylococcus aureus bacteremia.[56] Twenty representative patient profiles summarising the major events and outcomes (benefits, harms, and QoL), were constructed based on experiences observed in prior trials. The profiles were sent to 43 expert clinicians. The clinicians were asked to rank the patient profiles by the desirability of the overall patient experience. Factors driving clinician rankings were evaluated. Findings revealed that the cumulative nature of events were a major driver of clinician ranking e.g. patients that had clinical failure and SAEs were ranked as having a worse experience than patients that had clinical failure without SAEs. This is intuitive though often goes unrecognised when analyses consist of separate marginal analyses of each outcome.

Changing the paradigm and the clinical trial arithmetic: from using patients to analyse outcomes to using outcomes to analyse patients

In the context outlined above, it has to be acknowledged that up to now, the approach to BRA has been to use the patients to analyse the outcomes. Typically, in trials, the first endpoint is analysed; results in treatment A are aggregated, results in treatment B are aggregated, and then treatments are compared. This process is repeated for all of the other endpoints. The resulting BR analysis is usually conducted by combining the separate marginal analyses together in some way. Unfortunately, this approach does not compose data in a manner consistent with the way the outcomes are experienced by patients.

This can be illustrated clearly with the following example. Suppose a person is diagnosed with a serious disease. Treatment is being selected among three treatment options: A, B, and C. A trial comparing these alternatives was conducted (see Table 9 below). There are two major outcomes, considered equally important: (i) treatment success, a binary efficacy variable, and (ii) a binary safety event. There were 100 patients in each arm. There was a 50% treatment success rate in A, 50% in B, and 50% in C. The safety event rate was 30% in A, 50% in B, and 50% in C. Which treatment do you choose? They all have the same success rate, and A has the lowest safety rate. B and C are indistinguishable. Clearly, A should be chosen. These analyses are the typical approach to BR analyses, which can be described as 'using the patient to analyse the outcomes'. Patients are randomised, followed over time, and used to analyse the outcomes.

Table 9. Outcomes tables for each treatment

Source: CIOMS Working Group XII

Traditional approach 'analyse the patient for the outcomes'

Outcome	Treatment A	Treatment B	Treatment C
Efficacy – Yes	50	50	50
Efficacy – No	50	50	50
Safety event – Yes	30	50	50
Safety event – No	70	50	50
	'Best Choice'		

Now, let's apply a different paradigm: 'using the outcomes to analyse the patients'. There are four possible 'patient outcomes'. For any patient in the study, one may experience of four outcomes: treatment success with or without the safety event, or they may not experience treatment success with or without the safety event. Treatment success and safety outcomes can be cross-classified to examine the distribution of the patient outcomes by treatment arm.

A more granular analysis (Table 10) of the data reveals the following, focusing on Cell M – efficacy (or success) without the safety event. For treatment A, there was no correlation between the success and the safety event, resulting in 35/100 patients that experienced the treatment success and avoided the safety problem. In treatment B, the outcomes were positively correlated resulting in zero patients with success without the safety event. In treatment C, the outcomes were negatively correlated resulting in 50 patients that experienced success and avoided the safety event. This is striking since the typical analyses was unable to distinguish between treatments B and C though they are importantly different. Since treatment success and the safety event have similar importance, nobody assigned to treatment B had a net benefit. In contrast, treatment C may actually be the best treatment if the right subgroup of patients for its application can be identified.

Table 10. A more granular analysis of the data

Source: CIOMS Working Group XII

Outcome Category (Cell)	Treatment A	Treatment B	Treatment C
Success with Safety Event (L)	15	50	0
Success without Safety Event (M)	35	0	50
Conclusion	Original 'Best choice'	No net benefit	Potential 'Best choice' in preselected population

It becomes obvious, from the above example, that typical analyses combining marginal effects are blind to this type of difference. Critical thought is needed regarding how to aggregate data to describe treatment effects on patients and better inform medical decision making. The purpose of measuring the outcomes in the trial is to inform patient status particularly in late phase trials where there is a focus on describing and making inferences regarding the disease burden and impact on patients.

A global outcome representing an overall assessment (BR endpoint) for the patient is needed. Component outcomes may be used to holistically evaluate the patient status and experience. Aggregations over treatments A and B can then be made, and the treatments can be compared. This evaluation therefore clearly reflects how treatments compare with respect to their effect on patients.[57]

Integration of benefit-risk assessment into design, conduct, analysis, and reporting

The culture of post-hoc BRA can be transformed to a culture of diligent forethought and resulting integration into clinical trial design, conduct, analyses, and reporting. This new approach will provide an opportunity to better understand and describe the benefits and risks of interventions on patients and enhance transparency. Advancements to clinical trial protocols and adjustments to standard processes are needed to accomplish this goal. Recommendations for integrating BR into clinical trial processes are provided in Table 11.

Table 11. Recommendations for integrating benefit-risk into clinical trial processes

Source: CIOMS Working Group XII

Clinical trial design	Pre-specify BR endpoints, representing a global patient outcome, in the trial protocol in parallel with efficacy and safety endpoints, for transparency. Examples where this proactive strategy is being implemented include the Bacteriophage Therapy in Cystic Fibrosis Subjects Colonized with Pseudomonas aeruginosa (PHAGE)[58] and the Dalbavancin as an Option for Treatment of S. aureus bacteremia (DOTS)[59], the Comparison of Uncomplicated Candidemia Therapy Duration in Children (COUNT),[60] and the ARV-1801(ACG-701) for the Treatment of Cystic Fibrosis Pulmonary Exacerbations (REPRIEVE)[61] clinical trials. These endpoints can provide important information unable to be gleaned via siloed marginal analyses of efficacy and safety. See Chapter 3 Annex for examples (Example i, Example ii, Example iii).
	Construct a structured data collection schedule to provide comprehensive assessment of the nature, severity, and timing of benefits and harms.
	Describe analysis methodologies for BR endpoints in the statistical sections of protocols and SAPs.
	Pre-specify procedures to identify subgroups of patients with a positive BR profile based on BR endpoints in trial protocols and SAPs. Provide subgroup analyses based on BR endpoints.
	Consider designing late-stage clinical trials to evaluate clinical utility based on BR endpoints. For example, consider conducting one Phase 3 trial with a primary focus on such pragmatic questions.
Clinical trial conduct	Monitor BR using BR endpoints during trial conduct. The definition of a DMC: 'a group of individuals who review accumulating trial data by treatment group in order to monitor patient safety and efficacy, ensure the validity and integrity of the trial, and make a benefit-risk assessment'.[62] Concepts and methodologies for data monitoring based on BR have been described and implemented.[63]
	Emphasise the importance of continued follow-up on all randomised participants regardless of treatment status, i.e. the ITT principle. Censoring patient follow-up can hide important BR signals.

Statistical analyses	Present analyses of BR endpoints as a standard section in clinical study reports (CSRs) along with efficacy and safety endpoints.
	Conduct BRA under ITT. BRA is most pragmatic under ITT and further retains the benefits provided by randomisation.
	Use absolute risk when reporting results for trial endpoints to provide for greater interpretation. Synthesising the results of multiple endpoints that reported on a RR scale is challenging due to different baseline risks.
	Identify subgroups and estimate effects within subgroups based on BR.
Reporting	Report the analyses of BR endpoints when publishing trial results in the medical literature and when reporting trial results in clinical trial registries.

Patient-centric analyses

Later in this chapter, we will cover methods to elicit patient insights, input into the clinical trial and BRA, including PPS. However, the current methodological approach to BR should incorporate a clear focus on patient centricity. We therefore present this component of the methodology in this section.

Patient-centric endpoints can more closely reflect the status and experience of patients and address many of the challenges associated with traditional BR analysis approaches. The concept is based on synthesising the traditional outcomes (benefit, harms, and possibly QoL) to globally analyse the patient status or experience, rather than using patient data for separate evaluation of each outcome.

The Desirability of Outcome Ranking

The Desirability of Outcome Ranking (DOOR)[64] methodology uses outcomes to analyse patients, resulting in an ordinal global outcome based on desirability. The experiences of all trial participants are categorised according to the DOOR. The top and bottom categories are often obvious, e.g. the most desirable category is often a form of efficacy without toxicities and complications. The least desirable category is death. There are layers in between. The number and definitions of the categories of the ordinal DOOR outcome is tailored to the clinical disease. Strategies for developing a DOOR outcome have been described.[65] Recent publications have developed and applied DOOR outcomes for complicated intra-abdominal infections (cIAI) based on an FDA ORISE fellowship[i], and complicated Urinary Tract Infections (cUTI) based on a working group consisting of academic investigators, regulators and industry partners.[66,67]

Researchers have proposed use of the DOOR that integrates patient preferences of outcome importance concluding that it can be used in pivotal trials or comparative effectiveness trials for a patient-centred evaluation of a therapeutic intervention.

[i] US FDA Oak Ridge Institute for Science and Education (ORISE) an educational and training program designed to provide college students, recent graduates, and university faculty opportunities to connect with the unique resources of the FDA.

A simple example of a three-level DOOR for a life-threatening disease is in Table 12.

Table 12. A simple example of a Desirability of Outcome Ranking incorporating survival status and serious adverse events

Source: CIOMS Working Group XII

Desirability of outcome rank	Patient-centric outcome
1 (most desirable)	Survives without a Serious Adverse Event (SAE)
2	Survives with a Serious Adverse Event (SAE)
3 (least desirable)	Death

The DOOR distributions are compared between therapeutic strategies during analyses. If a new treatment offered global improvement in patient outcome relative to control, then there will be a shift in the distribution of patients to more desirable categories in comparison to the control. Further gradations could be defined to e.g. recognise the differences between SAEs with transient/resolved vs permanent/unresolved sequelae.

Though one may be tempted to analyse the DOOR outcome using a proportional odds model, the assumption of proportional odds infrequently holds and the interpretation of model results is suboptimal. Two methods for the analysis of the DOOR, a rank-based approach based on pairwise patient comparisons and using *partial credit* have been proposed. The recommended SAP for the DOOR and a freely available online application https://methods.bsc.gwu.edu/) implementing the recommended analyses are developed.

Rank-based analyses based on pairwise comparisons

Treatments can be compared based on the concept of pairwise patient outcome comparisons. All possible pairwise comparisons of the outcomes from patients in one treatment arm to the outcomes from patients in the other treatment arm are conducted. For example, if one treatment arm has N1 patients and the other treatment arm has N2 patients then there are N1 times N2, denoted N1*N2 possible pairwise patient outcome comparisons. When comparing a specific patient's results from one treatment group to a patient from the other treatment group, a more desirable (MD), less desirable (LD), or equally desirable (ED) result will be observed.

Once the DOOR outcome is constructed for each trial participant, then the *DOOR probability* (i.e. the probability of a more desirable result [adjusted for equal desirability]) in one treatment relative to another treatment, and the proportion in favour of treatment,[68] can be estimated using the pairwise comparison results. During the pairwise comparison process, let the number of pairwise comparisons with a more desirable result be denoted as #MD, the number of pairwise comparisons with a less desirable result be denoted as #LD, and the number of pairwise comparisons with equal desirability result be denoted as #ED. Then the DOOR probability and the proportion in favour of treatment may be estimated by:

$$\text{DOOR probability} = (\#MD + 0.5[\#ED])/(N1*N2)$$

$$\text{Proportion in favour of treatment (net benefit)} = (\#MD - \#LD)/(N1*N2)$$

The DOOR probability and the proportion in favour of treatment are absolute risk measures, consistent with recommendations for benefit-risk evaluation. Approaches for incorporating for example, stratification variables into calculations are available[69] as are methods that account for censoring.[70]

Using the rank-based approach, for example the DOOR probability is estimated along with an associated Confidence Interval (CI). No difference in DOOR distributions implies that the probability is 50%. Hypothesis testing can be conducted to test a Null Hypothesis (NH), e.g. the probability is greater than e.g. 50%. Trials can be sized using standard rank-based methods or via simulation. Though different from measures traditionally used in clinical trials (e.g. the difference in means, difference in proportions, or a HR), this metric may have an intuitive appeal with clinicians as they envision having to select a treatment by comparing treatment alternatives, i.e. what is the probability that this patient will have a probability of a more desirable overall outcome based on their BR profile, on one treatment relative to another?

One concern with the rank-based methods based on pairwise comparisons is that a decrement in a very important component could be offset by a large advantage in a component outcome of lesser importance despite appropriate prioritisation. In the case of the simple three-level DOOR outcome above, the step between 'survives without SAE' and 'survives with SAE' may be viewed as smaller than the step between 'survives with SAE' and 'death'. Researchers may wish to directly account for such perspectives during analyses.

Partial credit analyses

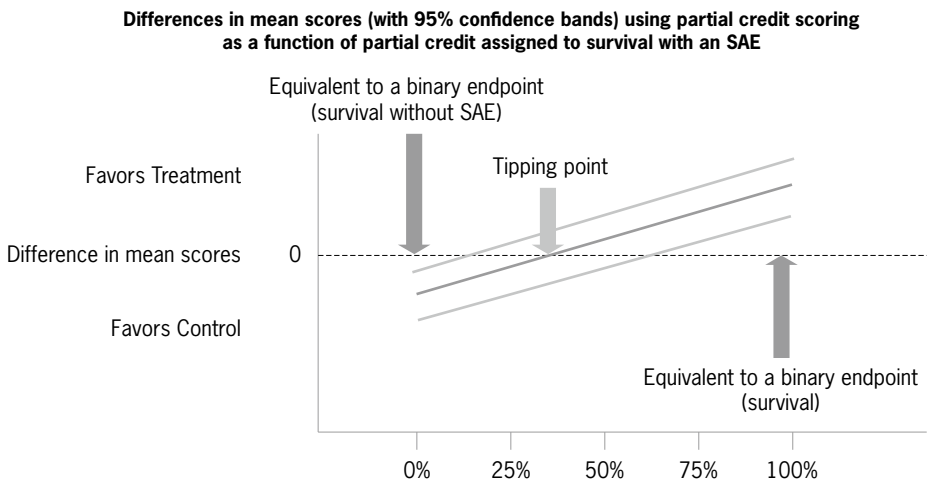
Partial credit analyses[57] can be conducted to directly address the concerns with pairwise comparison methodologies. Partial credit analyses involve grading the levels of the ordinal DOOR outcome similar to an academic test, i.e. from 0% to 100%. Consider the example of the simple three-level DOOR in Table 12. If the patient experiences the most desirable outcome (survival without a SAE), then they receive a score of 100%. If the patient has the least desirable result (e.g. death) then they receive a score of 0%. Partial credit is given for the intermediate category (survives with a SAE), directly accounting for the desired distance between categories. Assigning a partial credit of 100% provides full credit for surviving with a SAE. This would equate to an analysis of a binary endpoint of survival (full credit for survival regardless of SAE status; no credit for death). Assigning a partial credit of 0% provides no credit for surviving with a SAE. This would equate to an analysis of a binary endpoint of survival without a SAE.

Partial credit can be informed from patients using QoL instruments or from a survey of expert clinicians. Treatment comparisons can then be made by comparing mean partial credit scores e.g. using t-tests. The advantage of the partial credit scoring approach is that it strategically scores the DOOR categories to account for non-uniform steps between categories and can provide an evaluation of the robustness of the overall trial result. A disadvantage of the partial credit approach is that it is more challenging to score outcomes than to rank or prioritise them.

Although partial credit scoring can be pre-specified for transparency, the treatment contrast can be displayed as partial credit assignment varies (Figure 6). These sensitivity analyses allow visualisation of robustness, how the treatment effect varies as perspectives on the value of intermediate outcomes vary, proving patients the freedom to evaluate treatments based on how they value the intermediate categories. The approach can also identify a partial credit score that defines a tipping point for which there is a transition from favourability of one treatment to another.

Figure 6. Partial credit for survival with serious adverse event

Source:[57] (Figure reproduced with permission of Taylor & Francis Group)



Ordered priorities

An alternative strategy to constructing a composite outcome is through prioritising individual outcomes and then utilising the rank-based methods described above. For example, suppose two outcomes are considered: survival and whether an AE occurred. Further, suppose that survival is prioritised over the AE. When comparing two patients, if one survived but the other did not then the patient that survived had the most desirable outcome. If both patients survived, they would then be compared with regard to their AE experience. The win ratio, proportion in favour of treatment, and the DOOR probability could then be estimated. A score-based analysis such as partial credit would be more challenging to apply using the approach of ordered priorities.

Two examples of the application of this overall approach are presented in Case studies A.1 and B in Appendix I.

Conclusions

Increased focus on questions of a pragmatic origin is one of the most pressing needs and the most promising opportunities in BRA. Incorporating BRA into trial design and conduct rather than being viewed as a post-hoc exercise will improve the value of clinical trials for therapeutic decision making.

Pursuit of pragmatic real-world answers regarding the effects of interventions on patients, requires a paradigm shift from using patients to analyse outcomes, to using outcomes to analyse patients. This is accomplished by defining patient-centric BR outcomes. Patient-centric BR outcomes can become a standard, pre-specified along with efficacy and safety outcomes for transparency. Inclusion and analyses of such endpoints provides important information regarding the effects on patients, unable to be obtained by siloed marginal analyses of efficacy and safety. Pre-specified procedures to identify subgroups of patients with a positive BR profile will further advance clinical trial science.

3.2.2. Estimands in benefit-risk assessment

In the context of BRA, it is clearly important that treatment effects are set out precisely. The word 'estimand' has been used to describe this process within a clear framework. It does not necessarily introduce anything omitted in well-specified trials previously but encourages a precise description of the treatment effect reflecting the trial objectives. Although the word was suggested in 1939, and used by Tukey in 1968, it has only become part of mainstream statistical constructs since 2010.[71] Clearly defining the scientific question of interest is crucial to interpretation of a single trial and even more importantly, a set of similar trials. This affects planning, design, conduct, analysis, and interpretation. The estimand framework requires the population to be studied and the exact endpoint to be measured on each patient to be set out. It also includes ensuring that details of how events that may occur in the trial such as rescue medication are to be handled. Imprecision or omission of such details in a trial protocol leads to lack of comparability between trials and possibly between treatments in a single trial, resulting in confusion about the answer to the true clinical question. Recognising the need for clarity, the Steering Committee of the International Council for Harmonization (ICH) endorsed an addendum to ICH guideline E9 in 2019, which is denoted as ICH E9(R1) covering estimands and sensitivity analyses.[72]

While BRA potentially includes multiple trials or data sources, the addendum is focusing on articulating each pivotal trial's objective. Nevertheless, having a clear objective for each pivotal trial is a crucial building block in leading to a clear path to the BRA. The thinking process adopted in ICH E9(R1) [72] may also be helpful in bringing clarity to BRA in complex situations. Most of the emphasis on estimands has been in relation to efficacy though the concept also applies to outcomes related to harms and hence to BR. The study of harms is much more difficult to pre-define since there may be a limited range of hypotheses around the harms of a medicine and it is the unexpected effects that can be of greatest importance. The problems have been clear during the COVID-19 pandemic[73] and efforts have been made to apply the estimand paradigm to the analysis of AEs.[74]

The process of articulating the question of interest is a multidisciplinary task that requires cross-functional discussions with different stakeholders. The framework of estimand, which is proposed in ICH E9(R1),[72] aims to facilitate the discussion in a structured approach. Specifically, an estimand is a precise description of the treatment effect to be estimated from a trial, which reflects the clinical question posed by the trial objective. Given a clearly defined estimand, the planning, design, conduct, and analysis of the trial should be aligned to answer the same question to arrive at a clear interpretation of results. There are five attributes in an estimand—treatment, population, variable, intercurrent event, and population-level summary. Their definitions in ICH E9(R1) are as follows:

1. **The treatment condition of interest and, as appropriate, the alternative treatment condition to which comparison will be made**. For example, an investigational treatment and the placebo control;
2. **The population of patients targeted by the clinical question**. For example, adult patients with Type 2 Diabetes Mellitus;
3. **The variable to be obtained for each patient that is required to address the clinical question**. For example, change in hemoglobin A1c (HbA1c) from baseline to 24 weeks;
4. **Intercurrent events** are events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. For example, use of rescue medication and another example is discontinuation of treatment;
5. **The population-level summary for the variable** should be specified, providing a basis for comparison between treatment conditions. For example, difference in proportion of patients achieving a pre-specified HbA1c reduction.

In this framework, intercurrent events are crucial in clearly articulating estimands. Examples of intercurrent events include discontinuation of assigned treatment and the use of an additional or alternative therapy. There are five strategies suggested by ICH E9(R1)[72] to handle intercurrent events as follows.

1. Treatment policy strategy regards the occurrence of the intercurrent event as irrelevant and ignored in defining the treatment effect of interest. For example, when this strategy is applied to the use of additional medication as an intercurrent event, the treatment attribute effectively includes the investigational treatment plus additional medication versus the control plus additional medication. In this case, this strategy coincides with the ITT principle as the comparison is between two treatment policies based on a random assignment.
2. Hypothetical strategy envisages a scenario in which the intercurrent event would not occur. In this case, the value of the variable is the value which the variable would have taken in the hypothetical scenario. For example, when rescue medication must be made available for ethical reasons, it may be of interest to assess the treatment effect under the scenario where the rescue medication was not available. Predicting values of the variable in this hypothetical scenario is often needed for this strategy, which often relies on untestable assumptions, even under randomisation.
3. Composite variable strategy aims to incorporate an intercurrent event into the variable definition because the event is considered to be informative about the patient's outcome. For example, patients who need to use rescue medication may be regarded as not successfully treated. When the variable of interest is already a success or failure (e.g. clinical response or not), the use of rescue medication could be another case of failure. Thus, a composite variable could be a success for clinical response and no use of rescue medication, and failure otherwise.
4. While on treatment strategy is interested in the variable prior to the occurrence of intercurrent events, this strategy could be particularly relevant for safety analysis. For example, although patients may discontinue treatment prematurely, it may be of interest to assess the risk of an AR while the patient is exposed to treatment, i.e. before discontinuation or while on treatment. Thus, exposure time is often utilised to complement the analysis of the variable, e.g. exposure-adjusted analysis. Due to this added component, the interpretation of results needs care because of the potential imbalance of exposure between treatment groups, even under randomisation.
5. Principal stratum strategies focus the interest on a subpopulation, i.e. a principal stratum in which an intercurrent event would not occur. This is different from routine subgroup analysis because a principal stratum is defined by intercurrent events, which happen after randomisation. For example, in vaccine trials, it may be of interest to know the treatment effect on the severity of infection in the principal stratum of patients who are infected after vaccination.

In addition to the estimand concept, ICH E9(R1)[72] also provides the thinking process to align planning, design, conduct, analysis and interpretation. Starting from a clear trial objective, key clinical questions of interest should be translated into suitable estimands. With a clearly defined estimand, the design and the approach of estimation should be aligned. Recognising assumptions used in the main estimator, a sensitivity analysis could be planned to explore alternative assumptions but following the same estimand. Distinct from sensitivity analyses to address assumptions in the main estimator, a supplementary estimand could be utilised to more thoroughly investigate and understand additional trial objectives, which has a lower priority than the main estimand.

Although the principles outlined in ICH R9(R1) apply to efficacy or safety, most discussions in the literature are provided around assessing efficacy from RCTs. Different considerations may be needed for safety assessment for a complete and aligned BRA. Here we outline similar and different thinking for safety assessment and provide examples of estimands for BRA.

Among the five attributes of estimands, considerations are similar between efficacy and safety for treatment, variable, and population-level summary. For treatment, the selection for safety should be aligned with efficacy assessment. For variable, there could be more safety outcomes than efficacy

outcomes, and some AEs may not be clearly defined prior to the trial. For population-level summary, many safety outcomes are discrete variables and thus various summaries could be considered, e.g. risk difference, risk ratio or odds ratio (see Section 3.4 on Methodological considerations for addressing uncertainties in benefit-risk assessment for a more detailed discussion about suitability of these summaries for BRA). Care is needed to select the appropriate measure to strike a balance between clinical interpretability and statistical properties (e.g. rare events). In the BRA, it may be preferred to choose a summary measure that is suitable for both efficacy and safety. For example, consider both as time to event outcomes and use HR as population-level summary (see paragraphs on Absolute vs relative risk in Section 3.2.1 on Patient-level benefit-risk assessment – example of a novel paradigm through drug development and lifecycle management for a more detailed discussion about HR for BRA).

For the population defined in the protocol by inclusion and exclusion criteria, this should be the same target population for efficacy and safety. But in practice, as was highlighted earlier in this chapter, there are usually further difference between subsets of patients considered for efficacy and safety. The set of patients for efficacy usually follows the ITT principle and includes all randomised patients according to the randomised treatment assignment. But the set of patients for safety usually uses the actual treatment assignment to correct the assignment error which happens when a patient assigned to one treatment group received another treatment. This potential difference could lead to discrepancies between populations for efficacy and safety assessment (e.g. imbalance between treatment and control), if the occurrence of assignment errors is frequent with systematic trends. When choosing the population and the analysis set, it is important to be clear about what BR question is being answered and for which stakeholder the analyses are performed.

For intercurrent events, efficacy and safety assessments share many kinds of events, such as treatment discontinuation, use of rescue medication, and death. However, strategies to handle intercurrent events may be different for the efficacy or safety purpose. The treatment policy strategy follows the ITT principle and is one of the frequently used strategies for efficacy. It preserves randomisation for a causal interpretation and ignores intercurrent effects. However, when patients use treatments that are different from the assigned one, it would be difficult to interpret the safety profile using the ITT principle. For example, if a patient received an alternative treatment and had AEs, they would be more naturally attributable to the actual treatment, rather than the randomised treatment (see Section 3.2.1 on Patient-level benefit-risk assessment – example of a novel paradigm through drug development and lifecycle management for a more detailed discussion). In addition, if rescue medication was used and an AE happened, clinical judgement would be needed to find a causal link between the event and the assigned treatment or rescue medication. Because of these issues, the while on treatment strategy is often utilised for safety assessment. This strategy considers the actual treatment, as well as the duration of exposure and the mechanism of action. More specific discussions about intercurrent events include separate efficacy and safety estimands and varying exposures.[75]

In the last part, we illustrate the considerations for estimands that could be utilised in a BRA. Dapagliflozin was approved by the US FDA in 2014 for Type 2 Diabetes Mellitus. At the US FDA Advisory Committee meeting in 2011,[76] specific discussions were focused on different choices of estimands for efficacy analysis and the safety issues. Here, we retrospectively phrase the description using the estimand framework for a particular study.

In study MB102013, the efficacy estimand included the treatment attribute with dapagliflozin 2.5, 5, 10 mg, and placebo, with no background treatment. The population was drug-naïve patients with Type 2 Diabetes Mellitus. The primary variable of interest was change from baseline in HbA1c at 24 weeks. An important intercurrent event was defined as the use of rescue therapy for patients not reaching glycaemic control. If a patient used rescue therapy, the HbA1c data were still collected afterwards until the end of the study, or prematurely dropping out, but were excluded from the primary analyses. The primary analysis method was the last observation carried forward (LOCF)

approach and the analysis of covariance (ANCOVA). From this analysis, the strategy to handle rescue therapy as an intercurrent event was a hypothetical strategy answering the question about what would happen if the rescue therapy had not been made available. The population-level summary was the mean difference for the variable between dapagliflozin and placebo.

Although this estimand in study MB102013 was agreed with health authorities, the US FDA statistics review expressed concerns about the primary analysis during the Advisory Committee Meeting.[76] Instead, a sensitivity analysis was presented that included data after the use of rescue therapy and in this context, the magnitude of treatment effect was not as large as in the primary analysis. This discrepancy illustrated different preferences about intercurrent event strategies, and thus estimands. While the sponsor adopted a hypothetical strategy to answer a question of treatment effect on HbA1c without rescue therapy, the US FDA review stated a preference for a treatment policy strategy that was to compare dapagliflozin plus rescue therapy as needed versus placebo plus rescue therapy as needed.

For safety assessment, a short-term placebo-controlled pool was created including three Phase 2b studies and nine Phase 3 studies. Thus, the population attribute of the safety estimand is patients with Type 2 Diabetes Mellitus who received study drug and have at least one post-baseline safety assessment. The treatment attribute includes dapagliflozin 2.5, 5, 10 mg, and placebo. There are many variables of interest for safety signals for diabetes. The selected focus in this particular instance was hypoglycaemia and bladder cancer. For the variable of the occurrence of total hypoglycaemia, the intercurrent event was the use of rescue therapy. Because hypoglycaemia can be caused by rescue therapy, the primary analyses excluded data after rescue. This represented a hypothetical strategy to answer a question of effect on hypoglycaemia without rescue therapy. For the occurrence of bladder cancer, data after rescue therapy were included and thus this reflected the treatment policy strategy, which is interested in the comparison between dapagliflozin plus rescue as needed versus placebo plus rescue as needed. For other intercurrent events, e.g. treatment discontinuation, the while on treatment strategy was used to account for the different exposure to treatment. The population-level summary was proportions for both hypoglycaemia and bladder cancer with no formal comparison performed.

For the BRA, separate evaluations were done on the population level. Estimands were different between efficacy and safety mainly in strategies to handle intercurrent events. Because of the increased risk in bladder cancer and other safety variables, the majority of votes from the 2011 Advisory Committee were against approval of dapagliflozin. In addition, uncertainty in the efficacy estimands and the magnitude of treatment effect also made it harder to assess the BR balance. Following the Advisory Committee, additional safety data were generated and shared with the agency to address the safety concerns. Dapagliflozin was finally approved by US FDA in 2014 for Type 2 Diabetes Mellitus.

While this example illustrates estimands for the population level BRA, another approach could be evaluated on the patient level. Yuan and colleagues provide further examples in their chapter 'Estimands in Safety and Benefit-Risk Evaluation' in their book *In Quantitative drug safety and benefit-risk evaluation*.[77] Since estimands for safety and BRA are still being developed, the lesson learned from implementing estimands for efficacy can be very helpful. In general, clarity is gained with estimand discussions, and it provides a framework for communication within clinical trial teams and with health authorities and other stakeholders. Further references for safety and BR estimands are found in the literature[74,75,78,79] as well as a comprehensive review.[77]

3.2.3. Pragmatic and large simple trials as opportunities to better inform benefit-risk assessment

The inherent limitations regarding generalisability of efficacy and safety from controlled clinical trials conducted in the drug development program are well recognised, especially with respect to the identification of rare side effects, long-latency outcomes, or the under-represented populations in the pre-approval setting. Pragmatic Clinical Trials (PCTs) and Large Simple Trials (LSTs) can provide real-life BRA of increased reliability from broader and more diverse populations by overcoming the limitations of the traditional clinical trials. Such studies would still employ design elements to minimise bias (e.g. randomisation, intervention) but are distinguished by the intent to minimise interference with usual medical care, i.e. the population, setting, treatment risks and benefits that closely mirror the actual use of the drug in clinical practice (see Table 13).[80 ,81,82,83,84,85,86]

The concept of the pragmatic trial emerged decades ago from the general division of RCTs into groups classified by their intent as either mechanistic, to evaluate a biological or mechanistic hypothesis, or pragmatic trials aimed at answering questions that inform decision makers about health and health care. This fundamental division according to a trial's purpose remains a critical distinction[87] and becomes highly relevant for BRA purposes.

LSTs are defined as any randomised study with simplified study procedures permitting comparative assessment of medicines under real-world or routine clinical conditions. LST designs are similar to observational studies in that they can, in principle, be effectively used to study the safety of health interventions in patient populations not typically exposed in clinical trials, such as the elderly, very young or those with multiple comorbidities; determine if physicians prescribe according to their interpretation of the product label or clinical experience; and understand the safety of a health intervention as it is used with multiple concomitant prescriptions or OTC medications under routine medical care.[82]

There is a high degree of overlap between the definition of PCT and LST; formally and colloquially they are also referred to by many other names, such as large simplified trials/studies, large streamlined trials/studies, naturalistic trials/studies, practical clinical trials.[82] Pragmatic trials are generally classified according to the 'pragmatism' of their design with multiple tools available[85,88,89] whereas the LSTs are primarily characterised by their large sample size and simple and streamlined data collection processes.[82,90,91] A trial can meet both the pragmatic and LST definitions, but not always, hence for the purpose of this report, these studies are collectively referred to as 'pragmatic and large simple trials'.

'Pragmatic and large simple trials' are developed around patient-centric care and can help for investigating BRA questions and safety topics of interest, which would not be feasible to evaluate as part of a traditional trial due to the required duration of treatment or follow up (e.g. long-term effects, effects on growth and development, etc.) or due to characteristics or motivation of patients. They are generally conducted in post-marketing settings but may be useful in early development[81,92] or for label expansions.[93] Such innovative approaches are potentially useful when conducting long-term studies of pre-approval, investigational drugs, particularly when the safety and effectiveness outcomes of interest require longer follow-up durations.[94]

'Pragmatic and large simple trials' can generate RWE if they collect data from RWD sources,[95] although this is not a prerequisite. The regulatory framework for RWE along with new technology and data have created new opportunities for conducting streamlined safety and efficacy studies. The capture of RWD using methodologies such as decentralisation (e.g. trained nurses), direct-to-patient approaches (e.g. wearables, patient-reported outcomes), or databases (e.g. registries, claims) could be leveraged to capture long-term outcomes, and may be considered another step towards the adoption of innovative or hybrid study designs to improve clinical trial efficiencies.[95]

There are ongoing efforts to understand whether RCT results can be replicated using rigorous design and statistical methods in observational studies with RWD.[96] Until such methods become established and accepted for regulatory decisions, and for BRA matters that cannot be answered in a post-marketing observational study, the 'pragmatic and large simple trials' represent a valuable tool for evaluating drug BR in real-life conditions.

Table 13. High-level comparison of study types

Source: CIOMS Working Group XII

	Traditional pivotal Randomised Controlled Trials (RCTs)	Pragmatic Clinical Trial (PCT)/Large Simple Trial (LST)	Real-world evidence – Electronic Health Records	Real-world evidence – Real-world evidence administrative databases
Sample size	Approx. 500-10,000*	Larger, 1000 – 10,000*	1,000 to 100,000+	1,000 to Million+
Control for bias	Randomisation, blinding/masking	Randomisation	Matching (e.g. propensity score)	Matching (e.g. propensity score)
Treatment	Fixed pattern	Variable pattern	Variable pattern	Variable pattern
Comparator	Placebo/ selective alternative interventions	Many alternative interventions	Many alternative interventions	Many alternative interventions
Inclusion criteria	Robust and strict – inclusion/ exclusion criteria, i.e. exclude patients with co-morbid conditions, special populations or use of other concomitant drugs	Broader population included, i.e. according to the approved drug label	Broad, dependent on Electronic Health Records (EHRs) structured fields or systematic collection	Broad
Follow up after treatment discontinuation	Limited duration post-discontinuation	Longer	n/a	n/a
Setting primary source of investigators	Experimental setting Clinical research/ academic centres	General practitioners/ community-based	Real-world setting	Real-world setting
Site monitoring	Frequent	Minimal	n/a	n/a

* Does not include studies in orphan drug conditions, where sample size is much more limited, even below 100

We have just highlighted several established or evolving approaches that drive study design and statistical analysis, primarily in the area of pivotal studies. There are a number of additional innovative approaches that involve single arm studies often in combination with comparators derived from RWE information. These are particularly prevalent in the field of rare diseases and will be discussed in Chapter 4 (see Chapter 4 on Specificities of benefit-risk assessment methods for special situations).

3.2.4. Statistical approaches to enhance the benefit-risk assessment

As has been clearly outlined, there are robust and pre-defined statistical analyses applied to the data during clinical development. The opportunities to enhance the analytical process has been equally outlined through several examples of evolving methodologies. Another approach in the field of BRA has been to apply further statistical assessments to the BRA itself, historically referenced as quantitative BRA. As discussed already in this document, such additional analyses are not warranted on a routine basis but are nonetheless an important tool in the science of BRA. See Table 14 below. All of these tools are of great assistance in the right context, but which ones to use and when continues to be a matter of debate. It is beyond the scope of this document to detail these methods, but we provide detailed examples in the Appendices.

Table 14. Quantitative benefit-risk assessment methods

Source: CIOMS Working Group XII

(Example in Appendix if applicable)

- Multi-Criteria Decision Analysis (MCDA) (see Case study B - Introduction to the case study example).
- Stochastic multicriteria acceptability analysis.
- Simulations: Probabilistic Simulation or Monte Carlo Simulation (see Case study A.2 - Introduction).
- Metrics: number needed to treat (NNT), number needed to harm (NNH), maximum acceptable risk, impact numbers, and benefit-risk ratio.
- Estimation techniques:
  - Probabilistic simulation model;
  - Indirect/multiple treatment comparison;
  - Utility survey technique.

3.3. Methodological considerations to gain patient insights

As highlighted in Chapter 2, there is an increasing appreciation for the critical need to include patient input in all stages of drug development and lifecycle management, including input on clinical trial design and BRA. Patient experience data is information that captures patients' experiences, perspectives, needs, preferences and priorities related to a disease or condition.[97] There are recommendations to identify specific milestones in the drug development process where such input should be sought and incorporated, including those outlined in the CIOMS Working Group XI report.[25,98]

Figure 7. Patient involvement during a medicine lifecycle – pre-authorisation

Source: CIOMS Working Group XI[25]

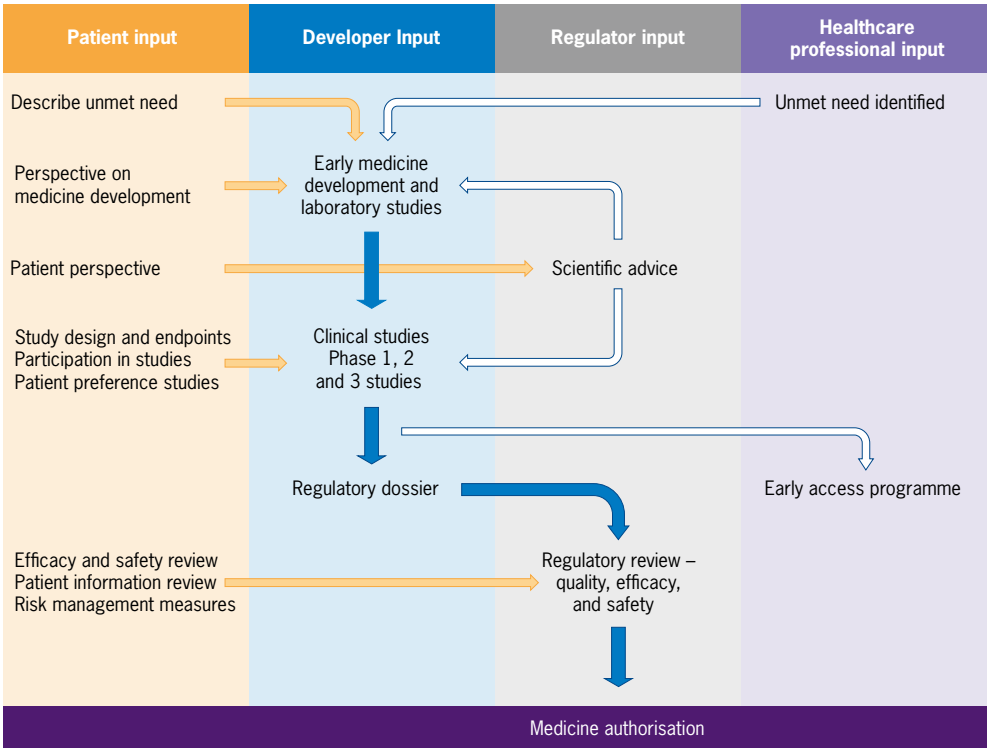
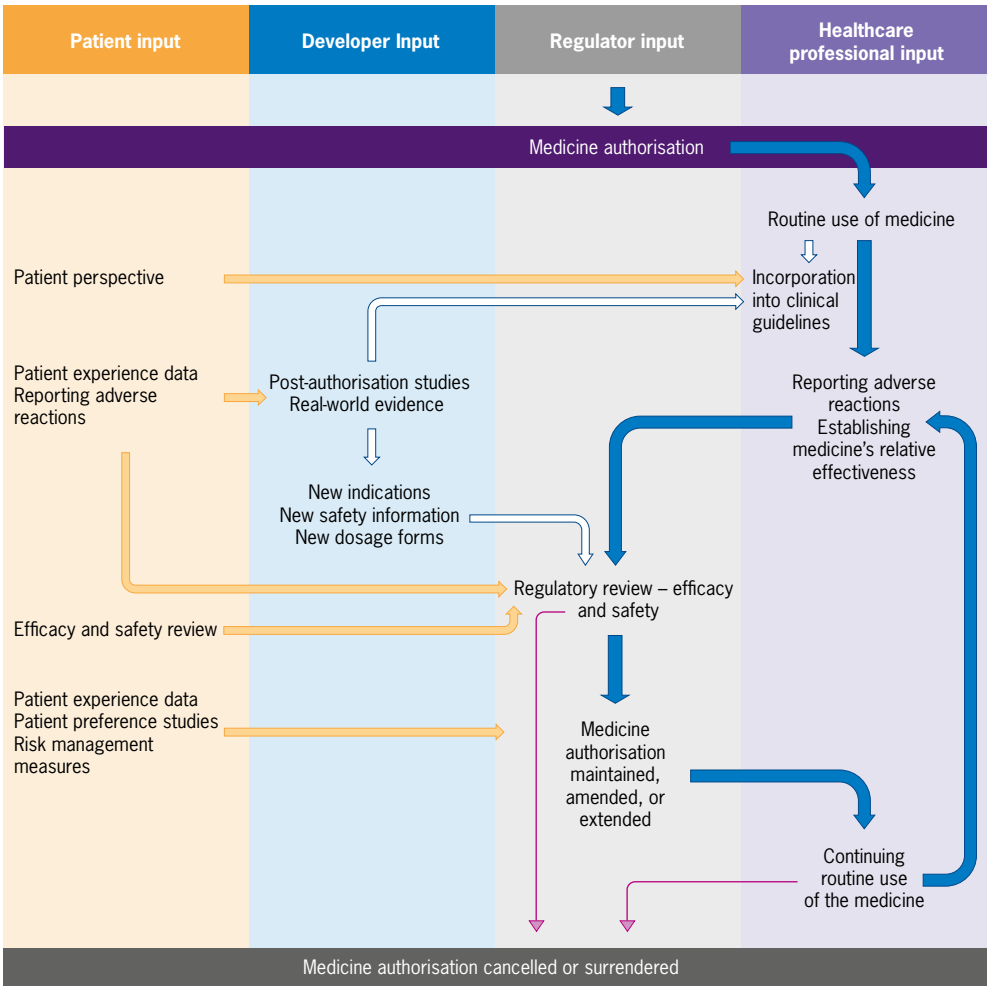


Figure 8. Patient involvement during a medicine lifecycle – post-authorisation

Source: CIOMS Working Group XI[25]



The CIOMS Working Group XI report provides a very useful framework for guiding principles, both in terms of the concepts and methods, for patient engagement as presented below.

KEY POINTS:

- The patient voice offers a valuable perspective throughout the development of a medicine. It should be fully incorporated in the decision-making process.
- Patients have expert knowledge and understanding of their diseases and conditions. This means they have equal credibility as those who are scientific and medical experts.
- Reimbursement of expenses and compensation for patients' time and contribution should be considered.
- Consider training of all stakeholders during the planning for patient engagement activities.
- Every effort should be made to maintain patients' independence.
- Balanced information, transparency and open communication are key. Written agreements should be easy to understand and complete.

With these key principles in mind, we will focus here on some of the specific methods to elicit such information as well as thoughts as to when in the overall lifecycle management these methods may be most suited.

Approaches to gain patient insights have evolved from contributions in many different fields including psychology, nursing, health outcomes research and marketing, ranging in approach from open interviews to highly structured questionnaires.

The CIOMS Working Group XI report Chapter 4 presents a number of opportunities on how and when to engage patients in the drug development process.[25] Despite great progress in establishing standard methodologies in the field, there continues to be a lack of consensus and alignment in which tools are best suited for what purpose and when to use them.[99]

As highlighted in the FDA guidance on *Benefit-Risk Assessment for New Drug and Biological Products*, different types of patient experience data can be collected to inform BRA.[100] Patient input collection covers a large spectrum of methods including, among others, collection of insights through panel discussion, patient reported measures (PRO) and patient preference elicitation.

We present here a brief overview of different methods used for patient preference elicitation but other methods of patient input collection remain also important to inform BRA; we invite the readers to consult more extensive references in the field for detailed and extensive reviews.

Patient preference information is defined as information resulting from 'assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions'.[101] Patient preference information can be determined through qualitative and quantitative methods, and includes the relative importance of what matters most to patients, enabling the examination of trade-offs that patients are willing to make between benefits and harms.[102] As highlighted in the CIOMS Working Group XI report, 'qualitative methods are used for insights into what matters most to patients' (e.g. their primary needs or clinical endpoints that are important to them). Quantitative methods, on the other hand 'are used to determine how much patients value different alternatives' (e.g. the relative importance of different clinical endpoints.) The CIOMS Working Group XI report further highlights the output from IMI-PREFER, which provides Principles for PPS.[25]

As described earlier, patients preference information are more likely to be needed to help inform decision making in specific situations also called preference-sensitive situations in the PREFER framework[103]. Below are displayed some key questions to be answered in these situations.

- What matters to patients – which decision criteria/endpoints are important to patients?
- How much it matters to patients – what is the relative importance of decision criteria/endpoints to patients? As an example, rating of the preferences to assess what patients prefer between benefits (e.g. between lowering weight or lowering blood sugar level) and between risks (e.g. between severe hypoglycaemic events or transient nausea).[104]
- The acceptability of trade-offs – how do patients weigh benefits versus risks and burdens. This might include different scenarios, for example:
  - a choice must be made between different benefits (different hypothetical health states);
  - a choice must be made between one available treatment versus no treatment (e.g. a treatment is available but has rare, serious, side-effects – some patients could choose to decline such a treatment, whereas others could choose to accept the treatment despite the side-effects);
  - a treatment is available that offers very moderate efficacy and has a very benign safety profile, and where it would be helpful for regulators to understand if the very moderate efficacy is something that patients value;
  - a choice is between two very different treatment options (e.g. surgery vs chronic treatment.

A helpful construct to consider methods that generate insights from patients has been published by Soekhai et al.[105] At a high level, they characterise methods into: a) patient preference exploration; and b) preference elicitation methods. The former includes methods applied to individual patients and groups of patients. The latter includes a broad range of methodologies that are primarily based on structured questionnaires in groups of patients.

3.3.1. Patient preference exploration

It is important to remember that valuable information may be gained from interactions with individual patients. A systematic approach to collecting this information can greatly enhance the process. Methods in this area include open-ended and semi-structured individual interviews as well as concept mapping and complaints procedures. While these methods offer insights from relatively few patients, they are often simpler to implement, require less resources, and may provide deep and private insights that may be difficult to elicit in group settings or through structured questionnaires. These methods offer a good starting point to build upon and develop the road map for other methodologies in the area.

A number of methods have been developed to elicit insights when a group of patients is brought together. These can range from focus groups to public meetings, at times leveraging specific processes such as the Delphi method or the dyadic interview method. Regardless of the method selected, it is important to derive the optimal amount of information from such activities. Of special interest is the level of concordance or divergence provided by the cohort. In some instances, there is a clear consensus opinion evolving from the group. In others, there are majority opinions but also very vocal and passionate dissenting perspectives provided by one or more subsets of patients. These may reflect important considerations for the future assessment of BRA across different populations; they should be clearly captured as part of final reports and considered for their evolution over time. Especially with the advent of social media, a minority perspective today can become a majority opinion in a short time period.

3.3.2. Preference elicitation methods

Preference elicitation methods refer to quantitative methods collecting quantifiable data for hypothesis testing and other statistical analyses used to measure patient preference information. These methods provide among others information about which benefits and risks are most important to patients or what maximal level of risk (known as maximum acceptable risk) patients are willing to accept for a given level of benefit.

These methods can be grouped in four categories:[105]

- discrete choice-based methods typically examine the importance of trade-offs between attributes and their alternatives through a series of choice sets that present (hypothetical) alternatives;
- ranking (or related) methods compare multiple pairs of attributes or alternatives where one of the two options is selected for each pairing presented - the selections are aggregated to yield an overall ranking of the proposed options;
- indifference techniques are methods that vary the value of one attribute in one of the alternatives until the participant is indifferent, or has no preference, between alternatives;
- rating (or related) methods usually allow participants to express the strength of their preferences along a labelled scale after which these ratings are compared.

Among the numerous preference elicitation methods, the most popular and more likely to address decision makers' needs are: Discrete Choice Experiment (DCE) a discrete choice-based method, best-worst scaling (BWS) a ranking method, threshold technique (TT) an indifference method, and swing weighting (SW) a rating method.[105] These methods have been recommended in the PREFER project.[103]

Details on the way to integrate patient preferences in quantitative BRA through selection of the preference elicitation method, framing attributes and how to present the risks, as well as analysis considerations including the need to normalise the preference weights and the need to consider the effect of preference heterogeneity can be found in the ISPOR good practice report for quantitative BRA, *Quantitative Benefit-Risk Assessment in Medical Product Decision Making*.[106]

Over the past years, DCE has been increasingly used to quantify patients' preferences for health outcomes, health services, and medical treatments.[105] DCE is a utility-theoretic method that can be used for eliciting preferences for medical interventions.[107] DCE allows simultaneous assessment of multiple attributes of a medicinal product using a choice-based questionnaire. The results of the questionnaire are then used to assess the relative importance of one attribute compared to another.

Participants are presented with a series of hypothetical choice scenarios. Each choice scenario includes two or more hypothetical alternatives. Each alternative is defined by attributes (e.g. benefits, risks, mode of administration) with varying levels. Participants then are asked to choose among the alternatives in each question and the pattern of choices allows the researcher to infer statistically the relative importance of each attribute and the trade-offs participants are willing to make among the attributes.

Table 15. List of selected attributes and levels in a preference study in early rheumatoid arthritis

Source: Hazlewood et al, 2016.[108] Reproduced with permission.

Attribute	Levels (possible options)
Chance of a major symptom improvement by 6 months	30 of 100 people 50 of 100 people 70 of 100 people
Chance of serious joint damage by 10 years	2 of 100 people 10 of 100 people 30 of 100 people
Chance of stopping the medication due to a side effect by 6 months	2 of 100 people 10 of 100 people 20 of 100 people
How you take the medication(s)	One medication: daily pills One medication: weekly tablets One medication: weekly injections Two medications: weekly tablets and daily tablets (two pills) Two medications: weekly tablets and injection at home every week Two medications: weekly tablets and i.v. Infusion in a clinic or hospital every 8 weeks Three medications: weekly tablets and daily tablets (six pills)
Possible rare lung or liver reaction (need regular blood work)	Yes no
Need for regular eye exams	Yes no
Small risk of serious infections and possible increased risk of certain cancers	Yes no
Need to limit alcohol	Yes no

Below is an example of DCE choice sets presented to diabetic patients asking them to choose. This is a version in tabulated text format[104] and on the next page is a version provided as figures to help patients better understand or visualise the different levels of attributes including the risks.[102] These examples illustrate that the complexity of DCE choice sets may vary across situations.

Table 16. Examples of discrete choice experiment choice sets: tabulated text format

Source: Bøgelund et al, 2011. Reprinted by permission of Taylor & Francis Ltd, https://www.tandfonline.com.[104]

	Treatment A	Treatment B
Hypoglycaemia	About once a month	About once a week
HbA_{1C}	About 7.5%	About 9.0%
Weight	Weight remained unchanged	Loss of 3kg weight
Nausea	Mild nausea for up to 3 months	No nausea
Additional payments	200 DKK per month	500 DKK per month

What treatment would you prefer?

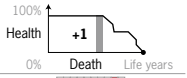
○ I prefer A	○ I might prefer B
○ I might prefer A	○ I prefer B

Figure 9. Examples of discrete choice experiment choice sets: visual format

Source: Mühlbacher et al, 2016.[102] (Figure reproduced with permission)

Time equivalent

You have been diagnosed with diabetes type 2. Your doctor asks you to decide between therapy A and therapy B. Which therapy would you choose?

Attribute	Therapy A	Therapy B
Additional **healthy** life years	+3 years 	+1 years 
Risk of urinary tract infection	Low 5 out of 100 (5%) 	High 10 out of 100 (10%) 
Risk of gastrointestinal problems	Low 4 out of 100 (4%) 	High 12 out of 100 (12%) 
Adjustment of long-term blood glucose level (HbA1c)	Good (7,0 – 7,5%) 	Very good (6,5 – 7,0%) 
Risk of genital infection	Low 10 out of 100 (10%) 	High 20 out of 100 (20%) 
Possible weight change	+4 kg 	+/- 0 kg 
Possible hypoglycemia	Severe (severe symptoms) 	Mild (without symptoms) 
		

Money equivalent

You have been diagnosed with diabetes type 2. Your doctor asks you to decide between therapy A and therapy B. Which therapy would you choose?

Attribute	Therapy A	Therapy B
Additional cost	15 € per month 	45 € per month 
Risk of urinary tract infection	Low 5 out of 100 (5%) 	High 10 out of 100 (10%) 
Risk of gastrointestinal problems	Low 4 out of 100 (4%) 	High 12 out of 100 (12%) 
Adjustment of long-term blood glucose level (HbA1c)	Good (7,0 – 7,5%) 	Very good (6,5 – 7,0%) 
Risk of genital infection	Low 10 out of 100 (10%) 	High 20 out of 100 (20%) 
Possible weight change	+4 kg 	+/- 0 kg 
Possible hypoglycemia	Severe (severe symptoms) 	Mild (without symptoms) 
		

As a result, when patients have answered all the possible scenarios, preferences can be quantified without participants explicitly being asked to state their preferred level for each individual attribute and each preference parameter indicates the relative contribution of each attribute level to the probability of choosing an alternative with that attribute level from all possible combinations of attribute levels.

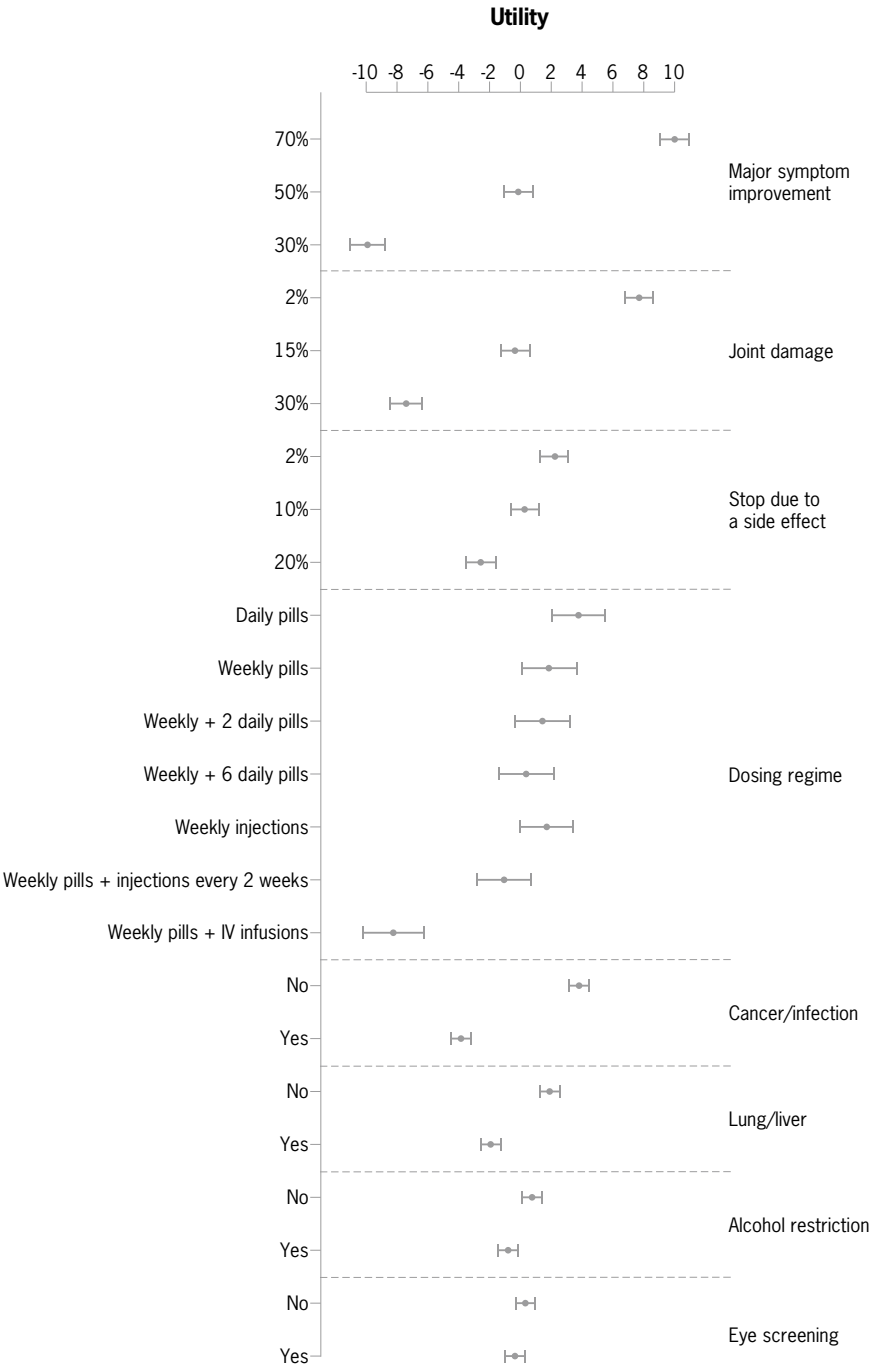
These measures can thus be used to estimate:

- the relative importance of treatment attributes;
- the maximum level of treatment-related risk that patients would be willing to accept to achieve a given level of treatment benefit or an improvement across a group of benefit attributes;
- the minimum level of treatment benefit patients would require to accept a given set of treatment-related risks;
- choice shares - the probability that the combinations of attribute levels defining a given treatment are preferred to the attribute levels defining a different treatment or standard of care, which can be interpreted as the probability that the benefits of that treatment exceed the risks relative to an alternative treatment or standard of care.

The figure opposite provides an illustration of measures from a preference study in patients with early-stage rheumatoid arthritis. The results display how much these patients value each level of treatment attribute. One of the key results of this study was that patients most valued (had the highest utility gain from) an increase in probability of a major symptom from 30% to 70% and a reduction in the risk of serious joint damage by 10 years from 30% to 2%.[108]

Figure 10. Part-worth utilities for each attribute and level

Source: Hazlewood et al, 2016.[108] (Figure reproduced with permission)

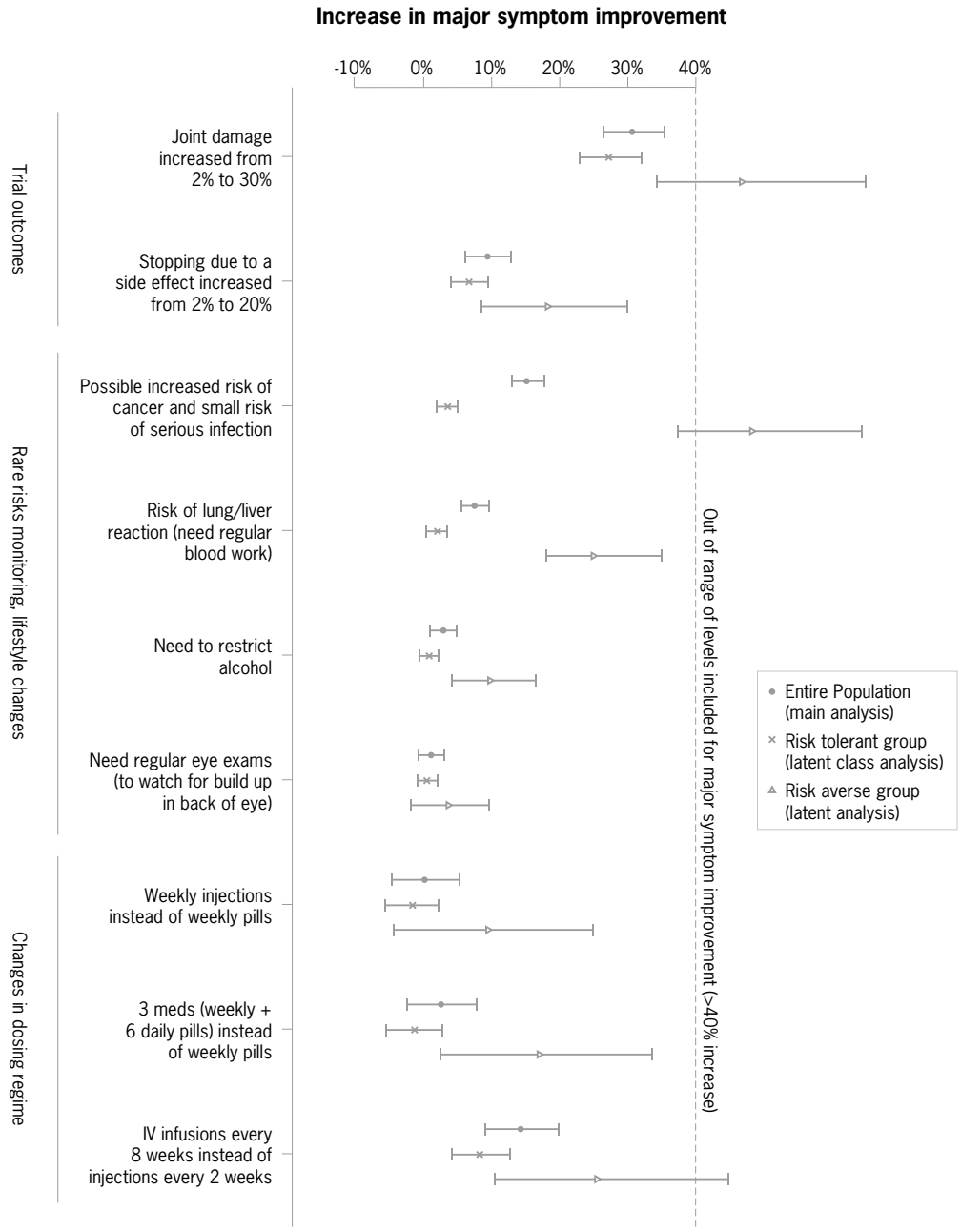


Utilities [mean (95% CI)] have been rescaled from −10 to + 10, with +10 indicating strong preference for the attribute level and −10 indicating strong aversion.

The figure opposite provides information on the minimum level of the treatment benefit that patients would require to accept undesirable features of treatment. Results are expressed as utility equivalence measures meaning that it is the change in the levels of one attribute that yield equal and opposite utility as the change in the levels of another attribute corresponding in this study to the percentage of increase in the chance of major symptom improvement required to accept undesirable features of treatment (such as treatment risks, dosing regimes). This study highlighted that patients were willing to accept a specific change in the risk of serious infections/possible risk of cancer for a treatment with 15% absolute increase in the chance of a major symptom improvement and would accept a change from injections at home every two weeks to intravenous infusions in a clinic every eight weeks for a treatment with 14% absolute increase in the chance of symptom improvement. In addition, the figure below also illustrates preferences heterogeneity between two groups of patients identified in the study (risk averse and risk tolerant). As a result, the risk averse group may prefer to avoid treatments with a possible increased risk of cancer/infection if other effective options are available.[108]

Figure 11. Comparison of preferences between the entire population and subgroups identified through latent class analysis

Source: Hazlewood et al, 2016.[108] (Figure reproduced with permission)



Results of the rate of trade-off for specific changes in undesirable attributes of treatment are presented as the absolute percentage increase [median (95% CI)] in the chance of major symptom improvement required for patients to accept change in undesirable features of treatments.

In conclusion, PPS provide the relevant patient preference information required for decision making where needed.

3.3.3. Additional considerations around patient insight methodologies

This field is rapidly evolving. Whichello et al,[109] in a study of relevant stakeholders, highlighted that nearly all the patient preference methodologies have a role to play in eliciting patient insights but they identified 13 methods that were clearly preferred and that these preferences could be in part linked to the lifecycle stage of a product. Importantly, these preferred methods included the full scope from individual patient interviews through complex elicitation methods.

Overall, the future of methods to elicit feedback from patients seems very bright. We see that the many methods can coexist in synergy and ultimately generate optimal patient insights. The relevance of the relatively simpler methods (individual or group methods) should not be lost. These can usually be implemented more easily, especially at a (smaller) country or regional level, as well as across multiple languages and socio-cultural contexts. The complexity of implementing effectively the more complex but robust elicitation methods across such a range of geographies and socioeconomic circumstances is much greater, and sometimes exceeds the resources available. Having some limited patient insights from a given area may often be more desirable than having to extrapolate from studies conducted in other geographic or socio-cultural contexts.

3.4. Methodological considerations for addressing uncertainties in benefit-risk assessment

Risk and uncertainty are two terms basic to any decision-making framework. Risk can be defined as imperfect knowledge where the probabilities of the possible outcomes are known, and uncertainty exists when these probabilities are not known. The difference between risk and uncertainty is often subjective: it relates to the information that is available to an individual.[110,111]

There are various sources of uncertainty to be considered in the BRA of a product and their importance depends on the extent to which they would affect the BR decisions.

- **Human variability**: Uncertainties can arise because clinical trials cannot fully represent a drug's effectiveness or harm in more heterogeneous real-world populations.
- **Statistical:** Uncertainty arises because clinical trials for product approval are designed to show that a drug works as intended, by evaluating the incremental difference in efficacy between a drug and a comparator, but not necessarily to quantify benefits and risks. In addition, clinical trials involve sampling which, by its nature, introduces the potential for error and thus uncertainty.
- **Clinical:** Uncertainty is a function of the research process itself. RCTs by definition must minimise biological variables in the study population, such as age, gender, genetic profiles, and other health issues or treatments. This reduces the value of RCT results outside the trial population. Also, the standard length of a clinical trial is generally too brief to anticipate AEs with long latency periods, such as in drugs that treat chronic conditions.

- **Methodological**: Uncertainties occur as RCT methods are tightly constrained to establish evidence in the pre-market setting, while observational studies are generally employed after the drug is approved to assess real-world risks. Additionally, some RCT methods that are intended to improve trial efficiency might be associated with a reduced ability to characterise all risks, such as randomised withdrawal designs.
- **'Unknown unknowns'**: Limits in our scientific understanding of a disease or a physical process make it difficult to know what to investigate and what could be an important 'domain of harm' to study.

Vaccines require considering additional uncertainties such as the disease transmission factor and the uncertainties related to vaccine policy and acceptance by individuals, introducing additional dimensions of complexity for a vaccine BRA.[110,112,113]

3.4.1. Approaches to address statistical uncertainty

Statistical uncertainty, which is present even in representative samples, is associated with the use of sample data to make statements about a wider population.

CIs are an approach to quantify the amount of statistical uncertainty present in a set of data. CIs may be seen as measures of uncertainty around effect estimates and are based only on the data observed in that study. An effect estimate could be for example, a difference in means, a difference in proportions, an odds ratio, a HR, etc. It is conventional to quote 95% CIs, though 99% or 99.5% intervals may be used. Using the usual 'frequentist' approach, the correct interpretation of a 95% CI is that 'if a very large number of studies were to be done, in the long run, 95% of such 95% CIs would contain the true value of the effect'. This is often loosely suggested as being equivalent to saying, 'one can be 95% confident that the true (unknown) estimate would lie within the lower and upper limits of the interval'. This would be true if instead a Bayesian approach were to be used, where probability is based on belief. The use of '95%' relates to the typical 5% significance level used in hypothesis tests. A 95% CI can be used to determine if a hypothesis test at a 5% level is 'statistically significant'. If the CI excludes the value derived from the NH (e.g. usually zero for a difference in means and one for an odds ratio), then the sample estimate is 'statistically significantly different from the null value' and the NH is rejected. In a frequentist approach, the NH is assumed to be true, and a P value can be calculated to say how likely such data would be observed if the NH were to be true. It does not address the probability that the NH is true, though that is a common misinterpretation.

The main point of this is that CIs, whatever the exact form of words used, are more useful than P values. It is often helpful to look at both ends of a CI to be aware of the range of values of the effect that are compatible with the observed data. The CI may also be used to select a distribution of possible effect sizes for use in a probabilistic BRA. It is not generally helpful, especially when looking at BR balance, to only use P values or hypothesis tests, but the range of uncertainty is an important consideration. If the range is compatible with no effect, what magnitude of effect is compatible with the observed data? Might that extreme value alter the balance of benefit and risk?

The larger the sample, the less the uncertainty, the narrower the CI, and hence the smaller the observed effect that can be declared statistically significant ($P < 0.05$). Thus, if a sample is very large, even a very small difference (which may be of no clinical relevance) may be statistically significant. The width of a CI is affected by both the sample size (n) and the sample variability. The larger the sample (and the smaller its variability), the greater the precision of the sample estimate and thus the narrower the CI. A wide CI can thus reflect either a small sample or one with large variability.[114] The use of CIs based on randomised data can have a clear interpretation. However, with any non-randomised data, such as with RWE, the assumptions that go into calculating a CI for a treatment effect usually do not take into account any uncertainty related to factors such as unmeasured

confounding. Hence, the CI presented will be underestimated and the true width of the interval could be dramatically greater. This is a special problem with large amounts of data such as with RWE, when the large sample size leads to extremely small CIs. There can be very great uncertainty in the uncertainty! Increasing sample size will usually reduce the range of the CI, but it will not reduce any bias that is present. It is possible to have a very precise estimate that may have substantial bias.

Bayesian analysis is firmly grounded in the science of probability and has been increasingly supplementing or replacing traditional approaches based on P values. Bayesian inference is a statistical approach aiming at assessing evidence (e.g. estimate of a parameter) provided by the observed data in light of the prior evidence about the same parameter. The prior evidence may be very limited and, in such circumstances, a so-called 'vague prior' may be used to reflect the ignorance of the science at that time. The Bayesian Credible Interval (CrI) is analogous to the CI in the frequentist approach and is usually very similar in value when there is no or very little prior information available. Bayesian CrI estimates the most likely values of the parameter of interest directly from the computed posterior distribution, which, combines the prior belief with the observed data. The interpretation of the Bayesian 95% CrI is the following: there is a 95% probability that the true (unknown) effect estimate would lie within the interval, given the evidence provided by the observed data and prior belief. The prior belief itself may be based on data from other studies. Bayesian methods may be useful not only for randomised trials but also for analysing observational studies, but they can be complex and challenging to implement. Their dependence on prior belief may in some circumstances be controversial, but making those beliefs explicit is always helpful.[115,116,117]

3.4.2. Probabilistic approaches using machine learning

The rapidly evolving big data analytics, Machine Learning (ML) and AI systems provide significant potential in global health and pharmaceutical development. ML is widely used to analyse big and complex datasets to uncover the hidden patterns and reach conclusive insights. Based on the observed data, ML systems form the basis for modelling, and then enable decision making. Uncertainty is fundamental to modelling, since any sensible model will be uncertain when predicting unobserved data.[118]

Uncertainties in the data make the decision-making process difficult, thus quantifying uncertainties in the data and the model help to enhance the confidence in the results obtained by different methods.[119] Probabilistic approaches are now emerging as a framework for modelling uncertainty in AI and ML. Probabilistic approaches to modelling, using probability theory, express all forms of uncertainty in the form of probability distributions to represent all the uncertain unobserved quantities in a model and how they relate to the data, and to provide the basis for inferring the unobserved quantities given the observed data.[118] In moving forward, improved precision of ML algorithms to quantify and model uncertainty in big data will be of great use in enabling decision making in BRA.

3.4.3. Recognising uncertainties in the Structured Benefit-Risk Framework

As described in Chapter 1 in Section 1.2 on New products and new data sources, the SBRF needs to incorporate and characterise uncertainties and discuss how they affect the interpretation of the evidence and their impact on the BRA. It is therefore essential that uncertainties are recognised early enough so they can be pro-actively managed and addressed in the lifecycle of the medicinal product. Table 17 below provides a non-exhaustive list of examples or sources of uncertainties that could be considered in the SBRF.

Table 17. Examples or source of uncertainties that could be considered in the Structured Benefit-Risk Framework

Source: Adapted from Mutanga et al, 2023.[120]

Therapeutic context	Clinical/scientific uncertainty about the condition.	▶ Limits on scientific understanding of the patient population and natural history of the condition, e.g. due to heterogeneity of disease manifestations and progression in the patient population. ▶ Lack of identification of risk factors or prognostic biomarkers.
	Uncertainty about the patient preference.	▶ Burden of current treatment/product on patients. ▶ Patient input data about the unmet medical need.
	Uncertainties about the place in the armamentarium for the proposed treatment.	Uncertainty about the place of the proposed treatment in the current approved treatments and standard of care, including their efficacy, safety, tolerability, and other limitations (e.g. subpopulations who do not respond to or do not tolerate treatment, curative versus palliative intent).
Product profile - benefits	Uncertainty in clinical relevance of the endpoint.	▶ Relevancy of the primary endpoint to patients and appropriateness of the primary endpoint. ▶ Uncertainty in nature of the effect (e.g. survival, reduction of serious outcomes). ▶ The trial(s) use of a surrogate endpoint that may not be widely established.
	Uncertainty about assessment of the benefit based on clinical trial data.	▶ Uncertainties due to statistical analyses including effect size and associated uncertainty (e.g. a CI). ▶ Uncertainty about data quality and integrity. ▶ Insufficient enrolment of trial patients. ▶ Attribution of benefit to the product when studied in combination with other therapies. ▶ Uncertainty in time course and durability of effect. ▶ Uncertainties due to exclusion of a significant subpopulation from the trial.
	Uncertainty about real-world benefit.	▶ Concerns regarding the sufficiency and generalisability of clinical trial results as to judging the clinical meaningfulness of benefit for indicated patients in real-world settings (e.g. older patients or patients with comorbidities not extensively studied in the clinical trials). ▶ Additional benefits of the product not immediately captured by the clinical trial results in: — Less restrictive or less frequent dosing schedule, or improvements to patient adherence due to reduced burden; — Uncertainty due modelling of benefit and public health outcomes that could be expected in the real-world setting (e.g. vaccines), accounting for aspects regarding the patient population or setting of use may extend upon the clinical trial setting (e.g. the public health impacts of false negative diagnoses).

Product profile - risks	Uncertainty in clinical relevance of the safety endpoint.	▶ Relevancy of the primary safety endpoint to patients and appropriateness of the primary endpoint. ▶ The trial(s) use of a surrogate endpoint that may not be widely established.
	Uncertainty about assessment of the safety profile.	▶ Uncertainties about trial results and their analysis including: ▶ Small or statistically insufficient safety database; ▶ Uncertainty in AE reversibility; ▶ Uncertainties in the ability to predict, monitor for, and/or prevent the AE; ▶ Limited exposure duration; ▶ Uncertainty of AEs in the specific product-class; ▶ Uncertainties regarding prevalence and severity of risks; ▶ Exclusion of a subpopulation from clinical trials; ▶ Uncertainty for a causal association between drug exposure and risk; ▶ Toxicity or other safety concern identified outside of human trials including manufacturing or product quality concerns.
	Uncertainty about product use safety in the post-market period.	▶ Uncertainty about the use in real-world, within-the-indication patients that may be at higher risk of the safety event. ▶ Uncertainties due to modelling of risks and public health outcomes that could be expected in the real-world setting, accounting for aspects regarding the patient population or setting of use may extend upon the clinical trial setting (e.g. the public health impacts of false negative diagnoses). ▶ Medication error or error in use of product (for example, at home COVID test kits use). ▶ Drug adherence on the potential consequences (including AEs and less effectiveness of the drugs). ▶ Concern for off-label use or abuse.
Product optimisation	Uncertainty in effectiveness of risk management options.	▶ Labelling. ▶ Boxed warning. ▶ Post-market surveillance concerns. ▶ Post-market requirements (such as new clinical trials/ observational studies). ▶ RMP and/or REMS. ▶ Value and burden of risk mitigation efforts to patients.
	Uncertainty in trade-off between effectiveness and burden of risk management options.	Uncertainty in trade-off between effectiveness and burden of risk management options.
Benefit-risk trade-off	Uncertainty in BR trade-offs/ weights.	▶ Uncertainty about assigning weights to individual benefit and risk endpoints for the BRA. ▶ Uncertainties about importance of potential benefit and risk trade-offs to patients. ▶ Uncertainties regarding BR for subgroups. ▶ Uncertainties regarding individualised decision making, such as patient/physician acceptance of a BR balance.

3.4.4. Strategies to address uncertainties of benefit-risk profile

The standard terminology BR balance implies an equality between the two opposing components – the benefits and the risks, or a net of all benefits against the side effects. However, arguably, the BR of drugs is not a zero-sum situation, thus BR management should be rather focused on optimising or expanding benefits, whilst managing the risks and addressing the uncertainties. In following with well-established concepts from other fields,[114] the BR optimisation and uncertainty management is presented as a three-dimensional function of decision, control and valuation, with the ultimate objective being to affect and control the BR balance.

Decisions - For uncertainties that could carry a significant negative impact on BRA, uncertainties can be reduced through the form of authoritative decisions to limit or eliminate their consequences on BRA. Such decisions may consist of safety restrictions or absolute contraindications for example, when the uncertainty regarding the magnitude and consequences of the risk do not justify further evaluation in human trials to elucidate the risk of uncertainty, or whilst characterisation of such risks is underway.

There are many examples of uncertainty reduction measures in the form of *decisions* in BRA that are routinely applied, such as could be the exclusion of women of childbearing potential in early studies when the reproductive toxicity assessment is not complete, or contraindication of use in patients with ventricular arrhythmia of drugs with suspected potential to prolong QT interval. Similarly, from the benefit side, when benefit in some populations has not been assessed, decisions to exclude those populations from the product's indications are made until further benefit information becomes available.

Decisions, in their pure form, are unambiguous, there is no doubt, as long as the decision is clear. Stakeholders such as health care providers and patients then react to the decision and adjust their behaviour, showing that the decision has consequences.[114] Although such strategic 'decisions' will not resolve or better characterise the uncertainties themselves, (i.e. will not improve knowledge, nor will promote the uncertainty to a 'risk' or 'benefit' classification), the impact of uncertainties on BR balance, of the drug, or at patient level, is greatly mitigated.

Control – Most uncertainties cannot be subject to a simple, binary BR decision such as safe/unsafe, indicated/contraindicated, nor their elucidation justifies delay in access to the treatment. With time, from expanding knowledge and experience with a treatment, an uncertainty that led to a BR decision, can now be managed or mitigated with less restrictive measures, i.e. can be controlled. Although still, the knowledge is imperfect to qualify and quantify an uncertainty as a risk or established benefit, controlling the circumstances in which the uncertainty is expected to occur could mitigate the worst predicted consequences. Examples of uncertainty controls include specific diagnostic procedures to confirm that the patient is a suitable candidate for treatment, monitoring, and assessment of hepatic function for drugs with hepatotoxic potential, etc. In clinical studies, such controls would be described in the protocol and schedule of activities, whereas for approved drugs, several sections of the product label provide control measures to address residual uncertainties and optimise the BR balance (e.g. dosage and administration, warnings and precautions, etc.).

Valuation - Valuation of the BR profile, taking into account objective information regarding benefit and risks, as well as patients' values and preferences, is an important tool to guide uncertainty reduction strategies. Reflecting the value of the decision makers in the BR can help prioritise strategies to reduce uncertainties for those patients who are most likely to benefit from treatment and/or with the most optimal tolerance profile.

3.4.5. Understanding uncertainty from the patient perspective

From a practical standpoint, individuals struggle with uncertainty in their lives. Uncertainty can lead to suboptimal decision making, negative affect, diminished well-being, and psychopathology.[121] Uncertainties relevant to health issues can be considered along several dimensions. How the uncertainty may be perceived differently by the patient and the HCP. Another dimension is the source of information, including the nature of the information relative to probability, ambiguity and complexity. A further dimension is the context in which the uncertainty is perceived: scientific (e.g. I do not know how this drug works), practical (e.g. I do not know how to diagnose the right patient for this treatment) or personal (e.g. I do not know if I will be able to tolerate this treatment).[122, 123]

In assessing uncertainties for SBRF, we therefore need to understand how patients could perceive the BRA and its uncertainties. Ambiguity in health information – that is, uncertainty elicited from believing that information lacks credibility, reliability, or adequacy – is typically associated with pessimistic appraisals (e.g. high perceived risk) and behavioural avoidance.[124] Ambiguity also arises when risk-related information is incomplete or missing, and has been shown to have several distinct effects on individuals, promoting pessimistic judgments of the risks and benefits of actions, and avoidance of decision making.[121] In patients, ambiguity can lead to cognitive, affective, and behavioural responses, for example, heightened perceptions of the risk of the intervention, diminished perceptions of the efficacy, heightened worry or fear or avoidance of decision making and diminished uptake of the intervention.[121] One key feature of ambiguity is that it can be partially resolved by gathering information about how outcomes unfold: as more information becomes available, the decision space for patients becomes more akin to outcomes with known probabilities.[125]

Patients' appraisals of uncertainty influence their ways of coping, which can in turn influence health outcomes such as QoL. When a situation is or appears to be highly uncertain, patients' coping strategies can be very limited and could result in decreased QoL and wellbeing.[126]

Another factor to consider is the patient's intolerance to uncertainty – a dispositional characteristic resulting from negative beliefs about uncertainty and its implications. At the core of this intolerance to uncertainty is the fear of unknown and leads to interpretation of ambiguous information in a more threatening, negative, manner that ultimately affects decision making.[127, 128]

The Uncertainty Reduction Theory (URT) holds that since uncertainty evokes discomfort and anxiety, individuals are strongly motivated to engage in specific behaviours to reduce it. URT originally addressed the initial interactions between strangers from a communication science perspective, as a state in which a person is confronted with several alternatives concerning a stranger's behaviour, and thus, more alternatives make the individuals feel more uncomfortable because the other person's behaviour is harder to predict. Although URT was initially developed to explain initial interactions between individuals, the theory has been applied to other contexts.[129,130]

Individuals reduce uncertainties through the use of passive, active, and interactive information-seeking approaches, and thus, uncertainties can be reduced by appropriate means such as transparent communication, social influence, and trust. The application of URT in BR management is thus a useful tool to understand and pro-actively manage the patient-level implication due to far-reaching uncertainties in various phases of the drug lifecycle.

Individuals rely on information that is accessible and valuable. Therefore, transparency is an enabler for information-seeking strategies and should target the disclosure, clarity, and accuracy of information.

- **Disclosure** is the perception that sufficient relevant information is timely and accessible.
- **Clarity** is the perception that the received information is comprehensible and lucid. For instance, the disclosure of a huge amount of information cannot be considered transparent if the information

is not understandable by individuals (e.g. because the information is cryptic and only consists of technical information). This information would hinder an individual's ability to effectively perform active and passive information seeking.

- **Accuracy** is the perception that the information is correct. The apparent incorrectness of information would not lower uncertainty but might lead to concerns about hidden intentions.[130]

Transparent BR communications thus serve as a tool for patients and stakeholders to reduce uncertainty through observation or targeted research. The primary means for communicating drug BR and associated uncertainties is represented by the product label. The approved label can facilitate uncertainty reduction by providing accurate, timely and relevant information and help patients to differentiate between risks (i.e. known probabilities) and uncertainties (i.e. unknown probabilities). The product label can also guide patients to directly reduce uncertainties and their impact by providing information regarding what actions are warranted to elucidate uncertainties (e.g. laboratory tests in the case of specific signs and symptoms, direction to discuss with HCPs).

Information from the approved drug label can be complemented with a suite of other tools to facilitate stakeholder information seeking strategies, such as:

- Publication of clinical trial results in scientific literature;
- Disclosure of study results in regulatory portals;
- Scientific and professional communications and interactions (e.g. congresses, symposia and workshops);
- Public disclosure of regulatory approval packages;
- Company interaction with stakeholders through medical information channels;
- Publication of emerging safety information in regulatory portals (e.g. signal assessments);
- Educational materials and related tools for patients and/or HCPs.

3.5. Approaches to visualisation of benefit-risk assessment

Visualisation is a very effective tool in helping to quickly convey data and enhance the understanding across stakeholders. A number of methods have been developed in the area of BRA, often derived from standardised visualisation tools that have been further customised for the purpose of BR communication. A selection of these standard methods are discussed below.

3.5.1. Attribute tree (value tree)

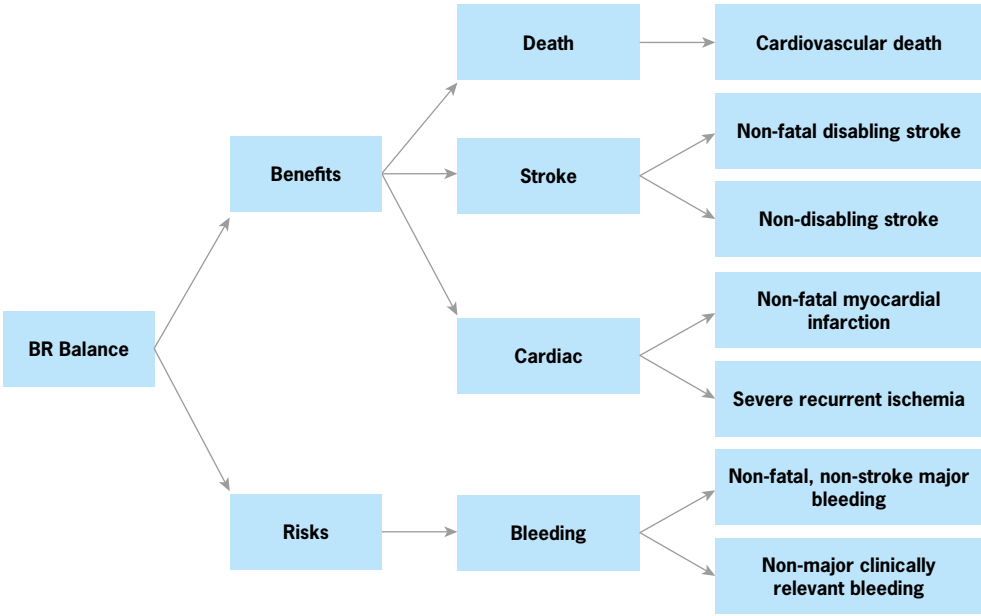
An attribute tree, also referred to as a value tree, is a helpful visualisation method in performing a BRA. In its simplest form, the attribute tree conveys clearly how the BRA depends on the benefits, with the key component(s), and the risks, with their key components. It is frequently constructed during multidisciplinary BR team meetings, where it provides an opportunity to brainstorm and capture the most essential components of the BRA.

The attribute tree focuses on key events in terms of the BRA. It is not intended to capture an exhaustive list of events, either for the benefit or the risk dimension. An important principle is that an event can only be represented in one category. Further refinements can be applied, such as categorising reversible and irreversible events. It is also important to ensure that the events captured

in the attribute tree correspond to the events formally captured and analysed in clinical studies. Figure 12 provides an example of an attribute tree.

Figure 12. Attribute tree for the treatment of acute coronary syndrome

Source: Modified from Levitan B and Cross J[131] (Figure reproduced with permission)



3.5.2. Effects table

An effects table provides a simple way to clearly present key data as they pertain to the BRA. It has been a required element for submission dossiers by the EMA. The table closely reflects the attribute tree, but it provides the actual data, and conveys the data in a way that enhances the comparison between elements. Table 18 provides an example of an effects table, aligned with the attribute tree in Figure 12.

Table 18. Effects table for the attribute tree in Figure 12

Source: CIOMS Working Group XII, based on the original work by Levitan B and Cross J[131]

	No. events / 10,000 patient-years		Risk difference/10,000 patient-years (study drug – comparator)	
Endpoint	Study Drug	Comparator	N	95% CI
Cardiovascular death	400	423	-23	(-118, 72)
Non-fatal disabling stroke	44	66	-22	(-43, -1)
Non-disabling stroke	70	63	7	(-32, 46)
Non-fatal MI	450	644	-194	(-311, -77)
Severe recurrent ischemia	586	620	-34	(-137, 69)
Non-fatal, non-stroke major bleeding	155	51	104	(66,142)
Non-major clinically relevant bleeding	1960	1011	949	(801, 1097)

3.5.3. Graphical display tools – visual displays

Visual displays to effectively communicate results continue to evolve and offer a broad range of options, with their respective strengths and limitations.[132] The PROTECT Benefit-risk group (Work Package 5) provided an in-depth analysis of visual representations to convey the results of BRAs of medicinal products.[133] They provided clear recommendations around addressing considerations for the audience targeted as well as the type of information being conveyed, highlighting that there can be potential shifts in the target audience perspectives and knowledge over time so the specific message to be conveyed may need to evolve, to reduce the risk of misunderstanding.

There are a number of visualisation methods that are very effective in communicating BRA, as shown in Figures 13-16 below. A comprehensive summary of these tools are not provided in this report however, some of the more commonly used tools are presented below.

Figure 13. Example of benefit-risk assessment visual: Forest Plot

Source:[134] (Figure reproduced with permission)

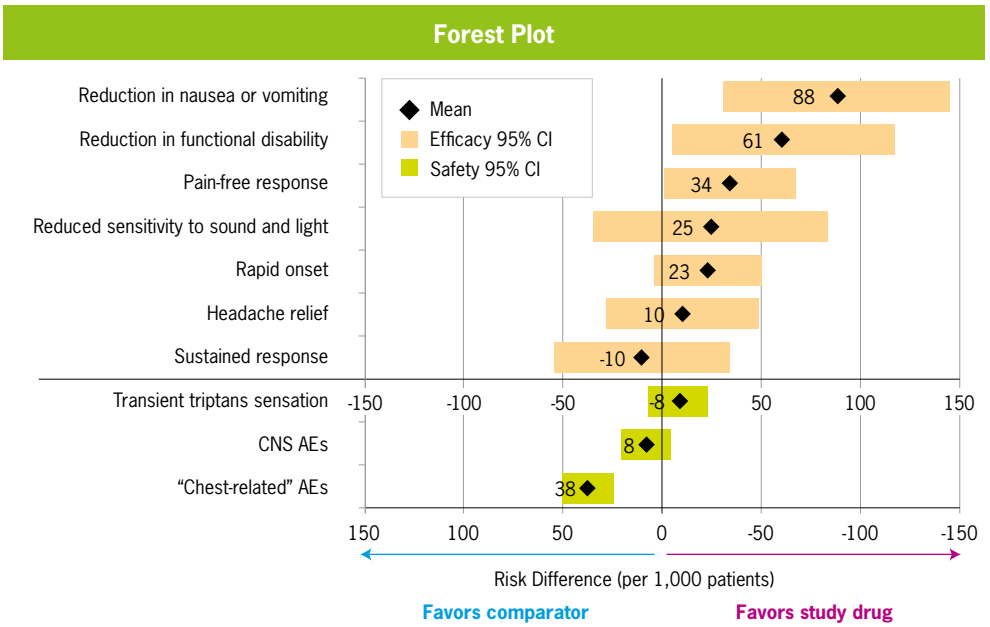


Figure 13. Risk-difference per 1,000 patients in using a constructed triptan vs. another constructed triptan for treating acute migraine. Point estimates for all efficacy outcomes, except sustained response, favor the study drug. Estimates for central nervous system and chest-related AEs favor the comparator, while those for transient triptan sensations favor the study drug. Visual displays, such as a forest plot, help to summarize and communicate information about multiple outcomes in a concise and understandable format.

Figure 14. Example of benefit-risk assessment visual: Waterfall Plot

Source:[135] (Figure reproduced with permission)

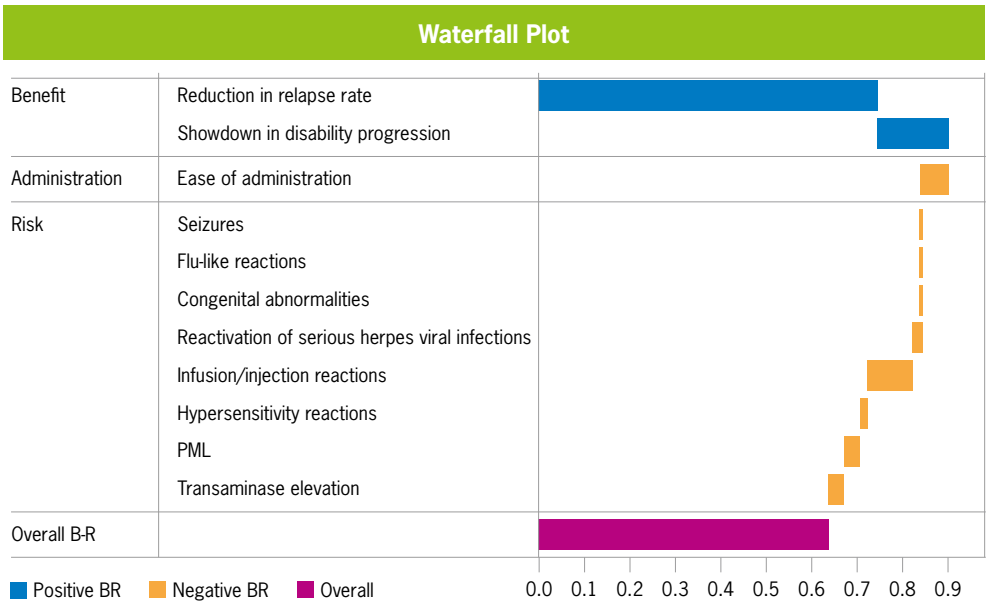


Figure 14. Difference between natalizumab treatment vs. placebo in the PROTECT natalizumab case study. The overall benefits (B-R score) of natalizumab treatment outweigh the risks suggesting a favorable treatment option in this context. Waterfall plots like this can summarize the contribution of each benefit and risk to the overall benefit-risk assessment.

Figure 15. Example of benefit-risk assessment visual: Heatmap

Source:[136] (Figure reproduced with permission)

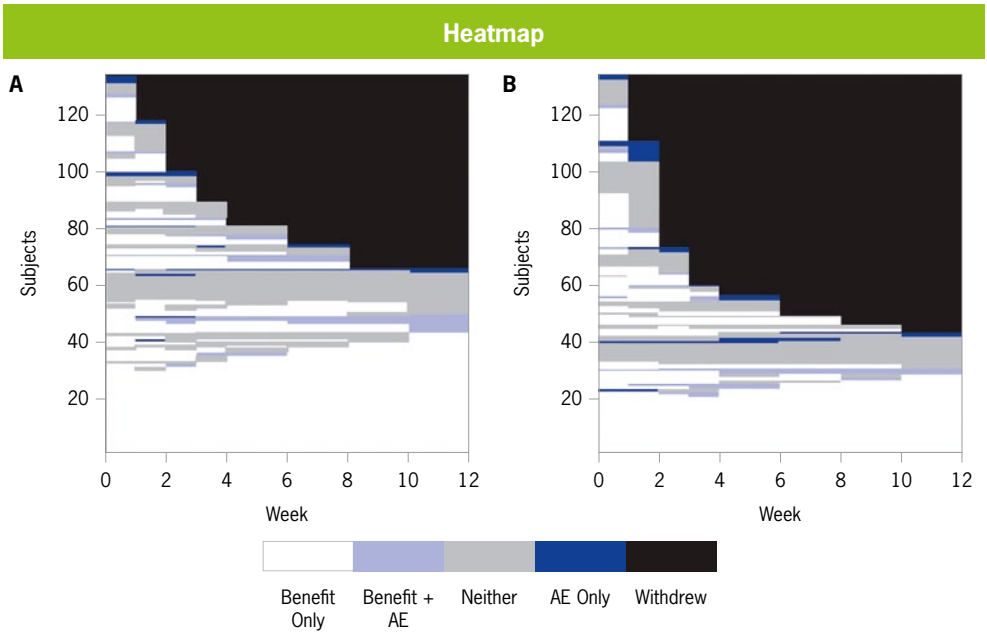


Figure 15. Individual response profiles for patients randomized to (A) hydromorphone or (B) placebo. N = 134 in each arm. By comparison, the hydromorphone arm had more AE-free benefit (white), fewer dropouts (black) at the end of the study (last vertical slice), and few moderate-to-severe AEs were observed. These kinds of heatmaps allow readers to see how each patient received benefits or was harmed by the intervention and can reveal patterns about individual patient responses.

Figure 16. Example of benefit-risk assessment visual: Tornado Plot

Source:[137] (Figure reproduced with permission)

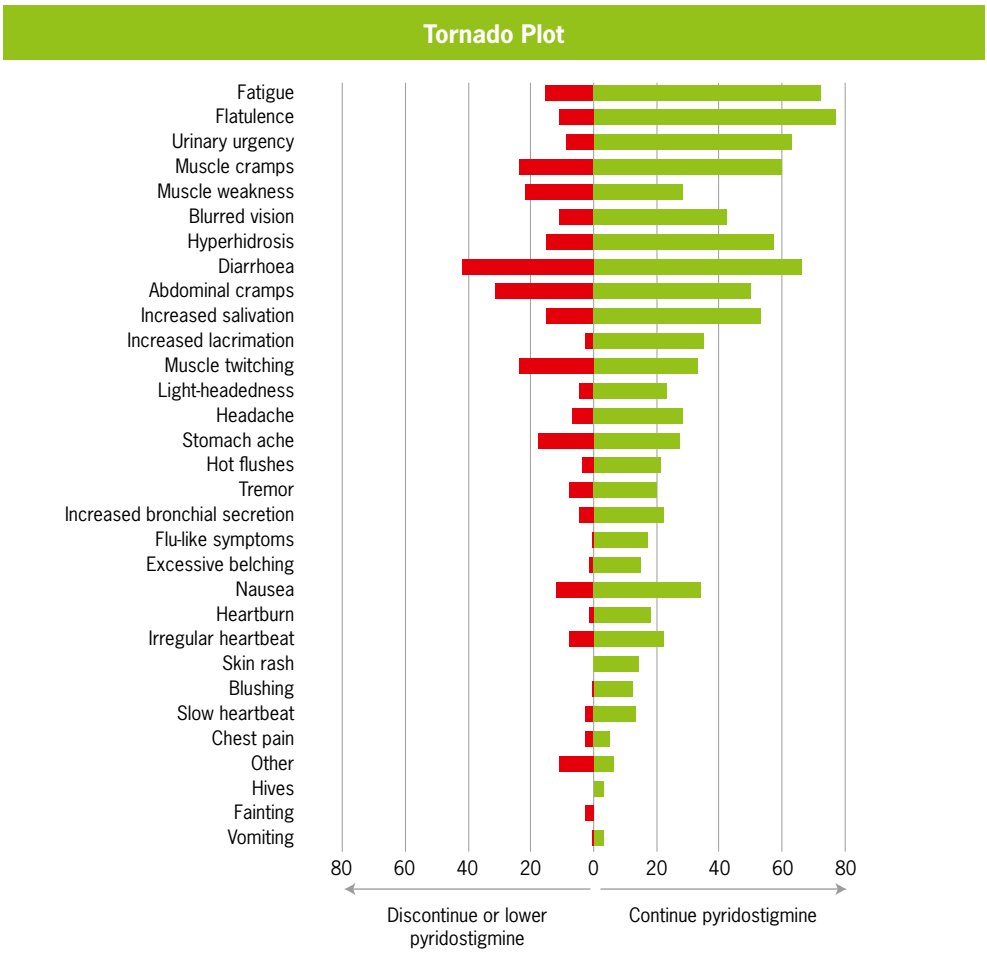


Figure 16. Number of patients considering the side effect a reason to discontinue or lower the dose of pyridostigmine. The most frequently considered side effects for which treatment was stopped or dose was lowered were diarrhea, abdominal cramps and muscle twitching.

A BRA forest plot is frequently used, however, other types of visualisations may also be used if they contextualise the data better.[138,133,139,140,141] In the example of the BRA forest plot, the endpoints used in the forest plot are based on the value tree. The text summarising clinical importance and key evidence should summarise the endpoints used in the BRA forest plot. However, the text of the BRA may include additional key evidence which are not included in the BRA forest plot. Determination of which endpoints are included in the BRA visual should be made and the cross-functional team should be selective.

A visual has impact only if it is easy to follow and provides a clear message without clutter. Figure 14 shows a Waterfall plot summarising how each key benefit and risk contributes to the overall BR profile of natalizumab treatment vs placebo in the PROTECT natalizumab case study. The largest contribution to benefits was from the reduction in the relapse rate, and the largest contribution to risk was infusion/injection reactions. The overall BR is summarised at the bottom of the chart with the purple bar.

Figure 15 shows an example of a heatmap. Heatmaps show each individual as a row and use different colours to show the status of the patient over the time they are observed in a study. This tool has the potential to display each individual patient in a study in a limited graphical space. In this example, individual response profiles for patients randomized to (A) hydromorphone or (B) placebo are shown over time. The status of a patient at any given time is colour-coded as benefit only, benefit+AE, Neither, AE only, or withdraw. By carefully sorting the patients, heatmaps can reveal important patterns at the patient level. In this example, the hydromorphone arm had more AE-free benefit (white), fewer dropouts (black) at the end of the study (last vertical slice), and few moderate-to-severe AEs were observed. These kinds of heatmaps allow readers to see how each patient received benefits or was harmed by the intervention and can reveal patterns about individual patient responses. Linking back to the patient-centric approach to BRA (see Section 3.2.1 on Patient-level benefit-risk assessment – example of a novel paradigm through drug development and lifecycle management), a well-designed heatmap may optimally display a large amount of information about the individual patient experience in a concise and easily understood manner.

Finally, Figure 16 shows an example of a tornado plot. Tornado plots attempt to show the overall contribution of a set of variables to the BRA. This example shows the number of patients considering the side effect a reason to discontinue or lower the dose of pyridostigmine. The most frequently considered side effects for which treatment was stopped or lowered the dose was diarrhoea, abdominal cramps, and muscle twitching. They are called tornado plots because they are typically sorted to have the widest bars at the top and the smallest bars at the bottom generating a shape reminiscent of the funnel shape of a tornado.

3.6. The multidisciplinary Benefit-Risk Management Team

As stated at the beginning of this chapter, we wish to cover aspects of BRA beyond the statistical or technical elements of the BRA methods. The elements that foster cross-functional collaboration and input are just as essential to drive a state-of-the-art BRA as are statistical or methodological considerations. This will be highlighted in this section. Equally important is to acknowledge the specific capabilities needed to conduct a comprehensive BRA. These capabilities may occasionally be mastered by a single individual; however, usually, they are an aggregate of many skilled team members, that may belong to a wide range of functional components within an organisation.

3.6.1. Responsible party and the benefit-risk assessment and decision

Responsible party and decision-making models may vary in pharmaceutical companies. In most companies, the BRA is made at multiple levels depending on the information under review.

Ongoing evaluation of safety information is a key component of BRA. Safety physicians and scientists lead the effort of monitoring and evaluating safety information throughout the lifecycle of a product to detect any potential safety signal/issue. The sources include, but are not limited to, non-clinical and clinical study data, individual case safety reports, epidemiology study results, post-marketing study or solicited program data, published literature, product quality reports, medical information queries, regulatory agency requests and assessments, and disproportional analysis generated from regulatory agency or WHO databases; e.g. FAERS, EVDAS, and WHO global database VigiBase. Once a safety signal is validated, a thorough signal evaluation report will be written to assess relevant information. The report will be brought to a safety team within the global safety department for further signal assessment to determine whether a signal is refuted or requires further action.

If escalation is warranted for a safety signal/issue, it will be brought to a cross-functional safety group, commonly called Safety Management Team (SMT). However, if a safety signal/issue requires immediate action to ensure patient safety, through a decision from senior management, it can be directly brought to the highest level of committee.

The SMT is usually product- or therapeutic-specific and consists of functional experts or leads involved in the product/therapeutic area including representatives from clinical development, safety pharmacovigilance, and regulatory affairs. The SMT is led by a safety physician/scientist. The team adjudicates safety signals/issues, confirms or refutes signals, determines escalation of safety signals/issues, or recommends further action such as label or IB update. If escalation is required, the team submits its recommendation to the appropriate decision-making committee, as described in the sponsor's procedural documents.

In many companies, the highest level of governance is the committee that makes the final decision for products across all therapeutic areas and consists of department heads. The committee is chaired by a senior, medically qualified individual, generally the Chief Medical Officer (CMO) and/or the head of the patient safety department. The committee reviews safety signals/issues that may impact the BRA of a product; it may require immediate notification to the regulatory agency, investigators, health care providers, and patients; it may require urgent safety measures or suspending or stopping of the clinical trials outside of protocol-defined stopping criteria or changing conduct of the clinical development; or it may require the company core label change. In some companies, responsibility for the contents of company core label resides with a separate committee. The committee makes the final decision on risk mitigation measures if warranted.

When the efficacy of a product has not been proven, e.g. an investigational product prior to marketing approval or a marketed product under investigation of new indication, ongoing BRA is also conducted by multi-level product development teams focusing on both the efficacy and safety of a product. A study team analyses study efficacy and safety data. A product team assesses a BRA based on all relevant information including efficacy and safety data from clinical trials, non-clinical data, the treatment landscape, and emerging data from the same drug class, and makes decisions for the product development program. If escalation is warranted, the product team submits its recommendation to the next level, a therapeutic area leadership team. The therapeutic area leadership team makes a recommendation of go/no-go, or modification of a clinical development program to the highest level of committee. The highest level of committee, frequently led by the CMO, makes the final decision on a product clinical development program based on the BR profile of the product and the company portfolio and strategy.

As most companies generally have at least two cross-functional teams to evaluate safety information: one is a multidisciplinary SMT (see the CIOMS Working Group VI report[142]) and one is a senior leadership team, the same teams can be refocused to encompass the expanded role of the BRA.

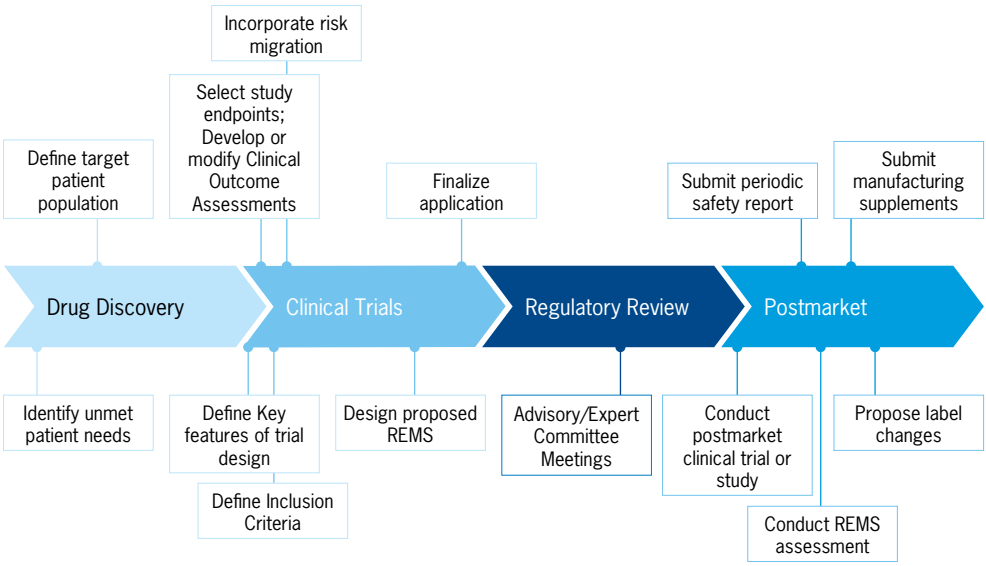
3.6.2. Company Benefit-Risk Assessment Document

A number of key events during the drug development process impact the BR profile (Figure 17). These events start early in the development process and highlight the opportunity to initiate the BRA process early in a product's lifecycle. See Section 2.3 on Lifecycle approach to benefit-risk assessment. Several companies have introduced a company SBRF and management process, captured in a document containing the company's comprehensive BRA of a product at a given timepoint in the product's lifecycle. This company-internal document captures the core position of the company on the BRA and management at given milestones in the product development. This is generally driven by a BRMT and starts sometimes as early as prior to first-in-human studies. See Section 3.6 on The multidisciplinary Benefit-Risk Management Team. The BRAD, introduced in Section 2.2 on Components of a Structured Benefit-Risk Framework, gives a company a clear picture of a product's key benefits,

risks and uncertainties to help develop strategic plans and establish go/no-go criteria. The BRAD also enables a company to develop risk mitigation strategies early in a product's lifecycle and implement them consistently across different programs or studies throughout a product's lifecycle, thus protecting trial participants and increasing the possibility of a product's success. For example, during the product development stage, the BRAD could mandate the implementation of risk mitigation measures such as product-specific inclusion/exclusion criteria and toxicity management in all clinical trials. In addition, the BRAD assists a company to build effective, consistent and transparent communication with regulatory agencies, investigators, and trial participants; for example, while the BRAD is an internal document that is not shared externally, its structured content facilitates a company's preparation for an end of phase meeting with regulatory agencies. In summary, the BRAD will be vital for a product's development program planning, execution, strategic decision making, and communication. See Appendix II: Example of a company Benefit Risk Assessment Document.

Figure 17. Key events that have an impact on the benefit-risk assessment of a product

Source:[143] (Figure modified with permission of Taylor & Francis Group)



The BRAD contains key elements including the characteristics of the targeted disease and the patient population; a description of the unmet medical need; the key benefits and key risks with a discussion of the strengths, limitations and uncertainties of the available data; the risk management activities to characterise and mitigate risks; and a conclusion. If appropriate, a value tree, an effects table, and/or other visualised BRA analyses may be included. See Section 3.5 on Approaches to visualisation of benefit-risk assessment. The BRAD would need to discuss special populations, such as paediatrics, pregnant women and the elderly. Also, if more than one indication is investigated for a product, a separate BRAD may be considered when development for subsequent indications pass the proof-of-concept stage and the disease and patient population are significantly different from those of the first indication.

The BRAD is a living document throughout a product's lifecycle. Creation of the BRAD prior to an IND helps the company to make investment decisions, develop strategic plans, and align on the key safety messages in the IB and toxicity management in the first-in-human protocol. However, a company may choose to develop the BRAD at a later stage (e.g. end of Phase 1 or 2 clinical trials)

due to reasons such as scanty data and substantial uncertainty. The important milestones for BRAD updates include prior to Phase 2 clinical trial or equivalent, prior to pivotal clinical trials, and prior to regulatory submission such as NDA/MAA. BRAD updates can also be triggered by new information impacting BRA such as availability of efficacy data, newly identified serious ARs associated with the product or with the product class, results from a risk mitigation effectiveness check, and a change in the treatment landscape due to results from competitive products. It is critical not only to create the BRAD, but to maintain its currency throughout the product's lifecycle.

Developing and maintaining the BRAD should involve a cross-functional team, as outlined in the next section. The results are reviewed by the cross-functional team, who will then develop or refine the value tree, the effects table, and/or other visualised analyses. Afterwards, the BRAD will be drafted or updated by a medical writer, a SBRF specialist, or a risk management scientist, depending on a company's organisational structure. Final approval of the BRAD may involve therapeutic heads within clinical research, patient safety and regulatory affairs departments.

Each function that constitutes the cross-functional team that contributes to the BRAD must consistently ensure that the appropriate elements of the BRAD are incorporated into the relevant documents and practices. For example, the BRA section of the following documents should be in alignment with the BRAD: the Investigational Medicinal Product (IMP) Dossier, study protocols, IB, Clinical Overview Section 2.5.6, regulatory agency meeting briefing documents, DSUR, and PBRER.

Understanding the inter-relationship between the BRAD and other company core documents such as the Development Core Data Sheet (DCDS)/CCDS and Developmental Risk Management Plan (DRMP)/RMP is crucial to the full utilisation of these dynamic documents throughout a product's lifecycle. The DCDS/CCDS contains both core efficacy and safety information along with other key elements of a product label, and it is a reference source for the development of local labels and the BRAD. Unlike the BRAD, the DCDS/CCDS usually does not contain non-label-enabling efficacy data, potential risks, and all risk mitigation measures. For well-established products on the market for years, the benefits presented in the BRAD and CCDS should be similar, while risks in the BRAD must be part of AEs listed in the CCDS. The DRMP/core RMP mainly focuses on safety specifications and the pharmacovigilance plan. An RMP is required at and beyond the license application in some regions, while a DRMP is an internal document for a product under development. Since the BRAD evaluates both key benefits and key risks, it often encompasses the key elements of a DRMP/core RMP. Unlike the BRAD, a DRMP/core RMP does not contain efficacy information. Furthermore, the risks specified in the DRMP/core RMP could be a subset of risks in the BRAD because the risks within a DRMP/RMP require further evaluation and/or additional risk minimisation activities, while risks in the BRAD could include those with no additional mitigation available or required (e.g. malignancies). Thus, some experts and companies conclude that a DRMP serves little purpose and can be omitted in the presence of the BRAD. In short, with the increasing emphasis on BR balance during a product's lifecycle, the BRAD is an important addition to the pool of company core documents and its existence could make certain company core documents such as a DRMP obsolete.

3.6.3. Cross-functional Benefit-Risk Management Team in the pharmaceutical industry

This team includes representation from functional lines that contribute to the evaluation of the BR profile. It must be acknowledged from the start that pharmaceutical companies vary in how they are organized functionally, driven in part by the size and scope of the company as well as other considerations, such as divisions between the stages of development, e.g. Phase 1, Phase 2-3 and post-marketing vs single integrated structure. In this context, we provide general guidelines focusing primarily on the capabilities of the individuals contributing to the process. Typically, this team includes representatives with expertise in safety/pharmacovigilance, clinical development, regulatory matters, medical affairs, epidemiology, statistics, clinical pharmacology, non-clinical aspects, and others. The team may also include a project manager or process expert to facilitate meeting conduct and documentation of the discussion and decisions.

The responsibility for the on-going BRA of the product, including the creation and update of the BRAD, can rest with different individuals, depending on the construct within the company. It may be the safety/pharmacovigilance lead, clinical lead, or an individual from a separate group dedicated to BRA. In all instances, there is usually a clear process to endorse the BRA at the primary team level, and escalate through the governance process to final approval. Last but not least, regular updates to the BRA are commonly mandated, usually associated with key milestones (e.g. first-in-human, end of Phases 1-2-3, prior to first major submission for regulatory approval).

Product lead/clinical lead

The product lead is responsible for designing and conducting the product development program and submission for regulatory approval. Oftentimes, the product lead is a global product physician in the clinical development department. A key contribution to the BRA centres on the efficacy, defining relevant endpoints, and characterising the level of uncertainty.

Safety physician and pharmacovigilance scientist

The safety/pharmacovigilance lead and team members have the responsibility for identifying and evaluating risks relating to the product, how to optimally balance benefit and risk, as well as working with the team to develop risk mitigation plans. They frequently lead the work to develop key outputs, such as value trees or graphic depiction of the BR profile. They also ensure that regulatory pharmacovigilance requirements are met and that safety information is appropriately included in the CCDS and IB. As stated above, in many instances, the safety/pharmacovigilance function is the lead for the BRA process and routing through appropriate governance.

Regulatory affairs representative

The regulatory affairs representative has the responsibility for advising the team on regulatory policy and requirements, guiding the team in accordance with regulatory process and the timeline through the lifecycle of the product development, and serving as a liaison between the pharmaceutical company and regulatory agencies.

Medical affairs representative

The medical affairs group provides key input relative to the perceived needs of the clinical community, including country level variations. Their deep knowledge of the physician and patient communities, as well as access challenges provide key insights that drive the design and conduct the product development program and submission for regulatory approval. Similarly, the medical affairs group provides very relevant input to the BRA, and how the key decision makers, including patients,

may perceive the benefits, risks and BR profile of the product in development. Following approval of the product, the medical affairs group may become the lead in future development and data generation activities, substituting for the development/clinical lead.

Epidemiology / real-world evidence / health economics and outcomes research

This is one area where there are marked differences between companies in terms of structure and division of work. In some instances, separate teams cover the range of these activities, while in other entities, a single team covers all dimensions. We will focus here on the key deliverables related to this broad field of science, focusing on the contributions to the BRA.

A key contribution to the BRA is a clear depiction of the disease state relative to a clear quantitation (e.g. incidence, prevalence) of the events which are being targeted by the benefit and risk profile. Epidemiology can generate detailed insights into the current use of current therapeutic alternatives, including their BR profile in the real-world setting, compared to results derived from pivotal clinical studies. It can also identify key differences between regions and countries. Another important contribution relative to the BRA is the ability to leverage RWE in determining baseline events (e.g. incidence of neutropenia) in the target population, to assist in determining the discrete impact of the therapy on this clinical event.

Individuals with insights into health economics and outcomes research can provide many of the insights listed above but frequently focus more on the economics considerations and generating HTAs. Early involvement in the BRA process brings in the great insights they have gathered and also enhances the likelihood of long-term alignment between the BRA and the HTA outputs generated later in the product lifecycle.

Statistician

Just as outlined above for the field of epidemiology, statistics is another area where there are marked differences between companies in terms of structure and division of work. It ranges from a single group covering all dimensions, to separate groups, including individuals fully dedicated to safety and BR considerations. Regardless, key activities in supporting the BRA are essential.

The statisticians are key to a wide range to decisions including study design, definition of endpoints, powering and handling of interim analyses. Leadership from the statistics group may drive the adoption of some of the novel methodological approaches outlined (see Section 3.2.1 on Patient-level benefit-risk assessment – example of a novel paradigm through drug development and lifecycle management and Section 3.2.2 on Estimands in benefit-risk assessment). The statistics team is responsible for the generation and primary analyses of the data to be assessed for the BRA throughout the product development.

Statisticians will usually take the lead in conducting additional analyses on data, when needed to conduct the BRA. Similarly, they are generally in charge of generating many of the data visualizations. In those companies where all BRAs follow a pre-specified analytical framework, e.g. MCDA, a group of individuals with a specialised statistical background (sometimes from the epidemiology group) usually drive the process and analyses.

Clinical pharmacologist

The clinical pharmacologist is responsible for designing, conducting and evaluating drug pharmacokinetic (PK) and pharmacodynamic (PD) studies, assessing DDIs, and providing dosing recommendations. A clinical pharmacologist's in-depth knowledge in mechanisms of action, PK PD, and potential DDIs are critical to a team's BRA assessment. This includes deep knowledge on how the product's profile relating to DDIs may differ from therapeutic alternatives.

Non-clinical/toxicology representative

The non-clinical/toxicology representative is in charge of generating the necessary non-clinical data to enable and inform the clinical development. This includes in-vitro and in-vivo toxicity testing, determining a safe initial dose level for the first-in-human exposure and understanding the toxicological profile of a pharmaceutical therapy (e.g. identification of target organs, exposure-response relationships, and reversibility). All of these insights are vital in the early assessment of BRA, and continue to be highly relevant to the BRA as the product progresses through the stages of development, while further non-clinical data may become available.

Other

A number of additional individuals may be included in the cross-functional team. This may include a representative from the legal team sometimes to understand potential future liability issues or to ensure the confidentiality of the discussions during the BRA (e.g. attorney client privileged communications). The EU Qualified Person Responsible (EU QPPV) may be included, especially during the late stages of development, with critical input into potential risk management measures. Where there is a team dedicated to eliciting patient input, their contribution may be invaluable especially with the great focus on incorporating patient insights in the BRA process. In those instances where the product is a combination product, especially if it involves a device, the device vigilance team may become a key contributor.

In all instances, the composition of the cross-functional team should be carefully considered. It is general to have a core group of functions that are consistently involved. The opportunity to implement flexibility and draw in a wider group of competencies, depending on the need, should be considered a best practice.

Senior leadership team/governance

The senior leadership team or governance body includes department heads, e.g. the therapeutic area head, the global safety head, and the regulatory affairs head, and is often chaired by the CMO or co-chaired by the CMO and the head of the safety department. The senior leadership team may provide the final endorsement of the BRA. It also makes decisions on emerging safety issues that require immediate actions, e.g. notifying a regulator of a safety finding, issuing a dear health care provider letter, changing a development program, and/or updating the safety section of the CCDS and/or IB.

3.6.4. Cross-functional Benefit-Risk Management Team in regulatory agency

The cross-functional team should include representatives as listed below. At the stage of the BRA for new drugs, most or all representatives should be included in the cross-functional team, on the other hand, representatives would be chosen based on the issue at the stage of the post-marketing BRA. As detailed below, most regulatory agencies have an individual designated as the Team Leader to drive the BRA process.

In the EU, a cross-functional team includes a non-clinical reviewer, a clinical reviewer, epidemiologist, policy reviewer and others *to be decided*. At the US FDA, a cross-functional team includes a regulatory project manager; a clinical reviewer; a chemistry, manufacturing and control (CMC) reviewer; a statistician; a toxicologist; an epidemiologist; a biologist, and others.

Team leader

The team leader is in charge of managing the BRA schedule and staying in close communication with each team member, related divisions and related organisations such as pharmaceutical companies.

Pharmacokinetics

The representative of PK is in charge of data assessment about drug absorption, distribution, metabolism and excretion and provides supportive information to consider the dosage and administration in package inserts.

Toxicology

The representative of toxicology is in charge of data assessment of non-clinical data such as toxicity testing with animals and cells to identify the pharmacologic properties of a pharmaceutical therapy, establishing a safe initial dose level for the first-in-human exposure and understanding the toxicological profile of a pharmaceutical therapy, e.g. identification of target organs, exposure-response relationships, and reversibility.

Chemistry, manufacturing and control

The representative of chemistry, manufacturing and control (CMC) is in charge of data assessment related to physicochemical properties and pharmaceutical quality to ensure the efficacy and safety confirmed in clinical trials. In addition, the CMC reviewer should confirm a system that can consistently produce quality equivalent to the investigational drug used in clinical trials.

Pharmacology

The representative of pharmacology is in charge of data assessment about pharmacology to scientifically consider drug efficacy and adverse effects in human administration from the point of view of working mechanism.

Clinical

The representative of clinical is in charge of data assessment related to efficacy and safety of human administration from the point of view of generalisability of clinical trial results and status of drug administration in clinical settings.

Statistics

The representative of statistics is in charge of data assessment related to its suitability for collecting and analysing, and contributes to informed decision making via quantitative statistical methods to interpret study data.

Safety Risk Manager

The Risk Manager is in charge of the central management of safety information such as concerns before approval and similar drug information throughout the lifecycle to establish a system to provide guidance and advice on safety measures from an earlier stage of the lifecycle and to ensure consistent safety measures from the development/approval stage through to post-marketing.

3.6.5. Expert consultations

During the lifecycle of a drug, BRAs are conducted by sponsors and health authorities. In order to address certain topics related to BRA aspects, both sponsors and health authorities may seek advice from different expert groups. For example, US FDA may conduct an Advisory Committee Meeting prior to the approval of a molecule with a new mode of action to receive independent advice from outside experts. These may include consultations with:

- External experts; and
- Internal experts.

External advice may be sought to provide independent recommendations to optimise and strengthen the research and clinical development efforts on existing and new products and may concern:

- Thorough understanding and assessment of the efficacy and safety profile and potential of the compound;
- Evaluation of compounds and existing and emerging alternative treatment options, scrutinising the competitive environment on the basis of publicly available information;
- Recently published scientific data relevant to the therapeutic area;
- Appropriateness of efficacy and safety endpoints.

Furthermore, sponsors may establish internal expert groups to evaluate or advise on specific safety topics, especially those considered rare, medically severe, and associated with a high drug-attributable risk. These may include drug-induced liver injury, immunogenicity, QT prolongation, and severe cutaneous ARs.

As comprehensively covered in the CIOMS Working Group XI report, patients are the subjects ultimately affected by benefits and risks of a drug and decide on the start, continuation or discontinuation of a medicinal therapy in consultation with prescribers. Patients may have different views on the benefits and risks of drugs compared to HCPs. Hence, the value of patients' active participation in health care systems including the reflection of their needs and expectations in the pharmaceutical development across the product lifecycle has been recognised. Delivering on patients' needs and expectations in clinical development may increase participant satisfaction, patients' compliance during therapy, and ensure that medicines address patients' needs. There are multiple types of formats for patient input. Individual patients, groups of patients, or patient advocacy groups can provide advice and participate in decision making. In addition, patient input can be evidence that is included in decision making. Such evidence can be in the form of patient preference information and other forms of patient experience data[25] (see Section 2.4 on Role of the patient in the Structured Benefit-Risk Framework).

Furthermore, regulatory health authorities are increasingly engaging patients and more actively including patients' experiences, perspectives, needs and priorities into their decision making. While some initiatives soliciting input from patients are facilitated directly by regulatory health authorities, there is also a growing expectation that clinical research sponsors are collecting and utilising patient input more systematically in the design of their clinical development programmes. The topics benefitting from information on the patients' perspective may include:

- Endpoints including PROs reflective of patients' most burdensome symptoms and unmet needs;
- Target population should consider patients' unmet needs and treatment goals;
- Background treatments, comparators;
- Most burdensome risks including information on most relevant characteristics from patients' perspective;

- Options to increase appropriateness and effectiveness of RMMs;
- Presentation of data on benefits and risks.

3.6.6. Capability needs at regulatory agencies, sponsors, and in academia

All of the capabilities listed below (Table 19) are necessary, at some point, in the conduct of comprehensive BRAs. The CIOMS Working Group XII does not provide any recommendation as to who, or how any one organisation should ensure that these capabilities are on-hand. Most of the key elements for each of these capabilities has been covered in this chapter or elsewhere in this report. We wish to comment here on the structured, strategic stakeholder engagement architectures/approaches. This is an often-overlooked component in the journey to producing a comprehensive BRA. It is as critical for regulators and sponsors to have on-hand expertise in eliciting input (systematic approaches and good practices) from stakeholders. Established methods include Provocative Questions Initiative, parallel scientific advice, and the Delphi process. The same methods can be used to collect patient preferences and incorporate input into the BR analysis. Linked with this capability are activities such as training patients on product development and regulatory approval so that they can effectively participate in the BRAs. The capability also encompasses how to effectively communicate on benefits, risk, uncertainties, and probabilities to the different stakeholders.

Table 19. Capabilities to support benefit-risk assessment

Source: CIOMS Working Group XII

Stakeholders will need to have expertise in:

- Benefit-risk frameworks (see Chapter 2 on Structured benefit-risk approach/framework);
- Structured strategic stakeholder engagement/Benefit-risk cross-functional workshops;
- Statistics;
- Real-world data and evidence;
- Patient preference elicitation and/or patient preference data;
- Patient engagement;
- Data visualisation;
- Decision-science.

CHAPTER 3 ANNEX: EXAMPLES OF FIVE-LEVEL DESIRABILITY OF OUTCOME RANKINGS

Example i

Cardiovascular event prevention trials typically evaluate efficacy based on the time-to-first event where the event could be death, myocardial infarction (MI), or stroke. Safety is evaluated based on the time-to-the first major bleeding event.

Though standard analyses are quite informative, they have several limitations when trying to comprehensively understand how interventions affect patients. A paradoxical property to the analyses above is that a patient with MI at 40 days is considered a worse outcome than a patient who dies at 60 days despite the differential importance of the events. The standard analyses do not recognise that patients can have multiple events with cumulative consequences on individual patients. The approach does not recognise the association between events, or effectively deal with the complexities induced by competing risks, for example, with death informatively censoring the time to stroke. A typical BRA conducted by separately estimating an effect for each important event, for example, death, MI, stroke, and bleeding, and then combining the marginal effects on these outcomes in some way, is difficult to interpret. Since events may not be mutually exclusive (e.g. fatal bleeding event), events can be double counted.

To effectively address these issues, a five-level DOOR could be constructed based on three principles: (i) death is more important than non-fatal events, (ii) events with permanent or disabling sequelae are more important than events with transient sequelae, and (iii) more events are worse than fewer events (Table 20).

Table 20. Five-level Desirability of Outcome Ranking based on three principles

Source: Adapted from Table 3 from the article by Evans SR, Knutsson M, Amarenco P, Albers GW, Bath PM, Denison H, et al [144]

Desirability of outcome rank	Patient-centric outcome
1 (most desirable)	Survived with no events
2	Survived with 1 event (stroke, MI, major bleed) with transient sequelae
3	Survived with >1 event with transient sequelae
4	Survived with event with permanent sequelae
5 (least desirable)	Death

This version of the DOOR outcome was applied in a RCT for acute stroke or transient ischemic attack treated with aspirin or Ticagrelor.[145] For longer duration trials where event times are important, the timing of events can be incorporated into analyses via tie-breaker analyses or by evaluating DOOR states longitudinally.

Example ii

Carbapenem-Resistant Enterobacteriaceae (CRE) are a family of bacteria that commonly cause infections in health care settings. These superbugs have become resistant to powerful carbapenem antibiotics.

An analysis[146] compared ceftazidime-avibactam, a relatively new antibiotic drug combination vs colistin, an older (control) drug, for the initial treatment of infections caused by CRE. A four-level DOOR was created based on survival status, whether the patient was discharged home, and whether they experienced renal failure, a serious toxicity by Day 30 (Table 21).

Table 21. A four-level Desirability of Outcome Ranking

Source: Derived from Van Duin, et.al, 2018[146]

Desirability of outcome rank	Patient-centric outcome	Colistin (N=46)	Ceftazidime-avibactam (N=26)
1 (most desirable)	Alive; Discharged home	4 (9%)	6 (23%)
2	Alive; Not discharged home; No renal failure	25 (54%)	17 (65%)
3	Alive; Not discharged home; Renal failure	5 (11%)	1 (4%)
4 (least desirable)	Death	12 (26%)	2(8%)

The DOOR probability (inverse probability of treatment weighting (IPTW)-adjusted) i.e. the probability of a more desirable result for a randomly selected patient treated with ceftazidime-avibactam vs colistin was 64% with a 95% CI of (53%, 75%). Partial credit analyses were also conducted with sensitivity analyses for all possible combinations of partial credit scoring for intermediate categories.[146]

Example iii

Recent regulatory-industry-academic collaborations have developed and applied DOOR outcomes for complicated intra-abdominal infections (cIAI) [147] based on a US FDA ORISE fellowship[148]and (cUTI) [67] and hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia.[149] For example, a DOOR outcome for cUTI was formed on the basis of absence of clinical response, infectious complications, SAEs, and mortality (Table 22). DOOR outcomes have been developed in other diseases such as obstetrics[150] and status epilepticus.[151]

Table 22. A generalised Desirability of Outcome Ranking analysis strategy

Source: Howard-Anderson J et al. 2023.[149] Reproduced with permission.

Rank[a]	Alive	How many of the following events: 1. Absence of clinical response[b] 2. Infectious complications[c] 3. Serious adverse events[d]
1 (most desirable)	Yes	0 of 3
2	Yes	1 of 3
3	Yes	2 of 3
4	Yes	3 of 3
5 (least desirable)	No (death)	Any

Table 23. Definitions for complicated Urinary Tract Infection trials

Source: Howard-Anderson J. et al, 2023.[149] Reproduced with permission.

Event category	ARLG criteria for cUTI trials
Absence of clinical response[b]	▶ Did not meet clinical success or cure as assessed by study investigator at test of cure ▶ Recurrent cUTI prior to test of cure
Infectous [*sic*] complications[c]	▶ Renal or intraabdominal abscess ▶ Septic shock ▶ Bacteremia due to the same bacteria identified in original urine culture ▶ Recurrent UTI or pyelonephritis after test of cure ▶ Clostridioides difficile ▶ Epididymo-orchitis[e] ▶ Prostatic abscess[e]
Serious adverse events[d]	▶ Any untoward medical event that: ▶ Results in death; ▶ Is life-threatening; ▶ Requires inpatient hospitalisation or prolongation of existing hospitalisation; ▶ Results in persistent or significant disability/incapacity; or ▶ Is a congenital anomaly/birth defect.

DOOR analysis strategy. A, The generalised DOOR analysis strategy that could be applied to any infectious diseases clinical trial. B, Details of how the DOOR component events were defined a priori for cUTI trials. Abbreviations: ARLG, Antibacterial Resistance Leadership Group; cUTI, complicated urinary tract infection; DOOR, desirability of outcome ranking; UTI, urinary tract infection. [a]Quality-of-life markers, when available, could be used as a tiebreaker for patients with the same rank. [b]Defined as lack of global resolution of index infection or recurrence of index infection before test of cure. [c]Defined as a newly identified complication or progression of the original infection that was not present at enrollment, including the development of Clostridioides difficile. [d]Defined according to ICH E6 Good Clinical Practice guidelines. [e]Added after the initial review of adverse events from the cUTI trials with agreement by the ARLG Innovations Committee.

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CHAPTER 4.
SPECIFICITIES OF BENEFIT-RISK ASSESSMENT METHODS FOR SPECIAL SITUATIONS

4.1. Introduction

This chapter addresses situations with an important lack of information on benefits and risks, and where uncertainty related to them is so high that there is a need to consider the BR balance in a different way. These situations are not rare and may cover up to half of recently approved drugs and vaccines. In addition, other situations are described to detail the specific challenges and considerations for legacy products and non-prescription medicinal products.

This chapter also covers situations impacting the way we evaluate the BR balance due to the medicinal product itself, the targeted population or the regulatory status.

4.2. Public Health emergency use and/or repurposing

Managing with lack of evidence and urgency

The essential principles of evidence-based medicine and regulatory decision making remain key also in times of public health emergencies. As has been the case with the COVID-19 pandemic, such emergencies can develop rapidly, and much-needed, robust, scientific data may not be immediately available to close the knowledge gaps. Pressures to make decisions without proper evidence have the potential to overcome sound scientific judgement and lead to unjustifiable conclusions, as well as the use of unproven therapies that may be ineffective or harmful, and have a further negative impact on public health.

Specific considerations

One of the most complex, scientific activities during public health emergencies is to determine whether a candidate medicine intended to prevent or treat the disease is effective and establish whether its expected benefits outweigh its potential risks to patients. This assessment is based on all available evidence about the medicinal product and the surrounding situation including: the severity of the disease; how well patients' medical needs are addressed by alternative, available therapies; the uncertainty around how data from clinical trials or testing environments extrapolate to real-life situations; and whether specific risk management measures need to be applied to mitigate known and/or potential risks. In the case of a public health emergency, such information is often not readily available in sufficient quantity or quality to adequately support evidence-based decision making, and the urgency of the decision context magnifies the potential consequences of action or inaction.

When decision making in the face of high uncertainty cannot be avoided, increased focus on reducing uncertainty through the monitoring of safety and effectiveness of such new therapies, once they are approved for use in the public domain, is critical. Considerations for expanded surveillance should include appropriate, evidence-generating or AE-monitoring strategies such as: Phase 4 clinical studies; observational studies; manufacturer-run patient registries and/or patient support programs; and patient focus groups to determine patient experiences. The monitoring of repurposed medicines is also important and necessary under the different uses made in a pandemic situation, since their efficacy/effectiveness remain to be confirmed and their safety profile may well be different when used for an indication other than that or those the drug was originally approved for. In addition, the acceptability of potential risks may be different than in non-emergency use circumstances. As an example, during the COVID-19 pandemic, initial safety monitoring efforts by regulators and other stakeholders were focused on the use of medicinal products that were not approved for treating the COVID-19 infection but that had been approved for some other indications. To support these efforts, the Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial, a large multi-arm adaptive international trial, was launched to evaluate possible treatments for patients admitted to hospital with COVID-19[1].

When the public health emergency is lifted, the standard measures of monitoring should be applied for the approved indications. See more details in the considerations for legacy products.

4.3. Accelerated pathways for approvals based on surrogate endpoints

Managing with uncertainty and pending evidence

Some drugs addressing unmet medical needs, where the benefit of the immediate availability of the medicine outweighs the risk inherent in the fact that additional data are still required, come to MAs with less comprehensive clinical data (i.e. benefits measured with surrogate endpoints) than are normally required. Due to limited evidence on benefits and risks, and a high level of uncertainty for external generalisability, an approval may be granted conditional on the provision of comprehensive data post-marketing under procedures either called 'accelerated approval' and/or 'conditional approval'.

Specific considerations

One of the major challenges at the time of the initial evaluation is the limited data on benefits and risks. This challenge is even greater because there is generally more uncertainty associated with risks, especially rare events. The methods described in Section 2.5 on Additional quantitative analysis to simulate effects and sensitivity analysis should be considered to reduce uncertainty. Regarding the uncertainty of a treatment effect, the focus should be on providing a quantitative measure of sampling variability associated with estimates from a single trial or a meta-analysis of trials. Additionally, the methods to extrapolate the available measures (e.g. surrogate endpoints) into clinical outcomes are applied to characterise uncertainty. See Case study A2, which illustrates how simulation characterises uncertainty by providing a range of potential outcomes.

In the post-marketing setting, when evidence on treatment effect and risks accrue, the reassessment of BR based on new data collected through planned post-marketing activities (clinical trials, observational studies, etc…) is conducted on a regular basis. For this purpose, the synthesis of data from multiple sources is implemented.

4.4. Special populations

4.4.1. Patients with rare diseases

Managing with limited data and known heterogeneity

While overall the BRAs for common diseases can also be applied to rare diseases, rare diseases products require more tailored considerations throughout the assessment process for multiple reasons including limited knowledge of the disease, small patient populations with limited data and high heterogeneity, and – for many – a lack of alternative treatment options. The acceptability of potential harms may also be different than in common disease BRAs. Rare diseases is an area where understanding patient preferences brings additional value to the assessments.

Specific considerations

At the time of an initial evaluation, the focus should be on addressing multiple uncertainties. In the context of an absence of an approved treatment and a comparator, RWD can be used, such as in the form of patient registries, and methods can be deployed to build e.g. a synthetic control arm (retrospective natural history disease registry) such as described in regulatory guidance.[2] The lack of knowledge on epidemiology of disease and of frequency of background risks can be reduced through the use of RWD such as patient registries and methods to predict the natural history of disease. While data on benefits, risks and comparisons are limited, several methods can be considered (such as sensitivity analysis and Monte Carlo simulation (for more details, refer to Case study A2).[3] As efficacy endpoints may be laboratory values or imaging data that are not validated as surrogates of clinical benefits, methods to validate endpoints or post-market studies to validate clinical benefit can be implemented. When heterogeneity in disease phenotypes is identified, the BR evaluation can be conducted by disease phenotype subgroup and may include the use of biomarker/measurement to identify individuals with greater benefits or risks.

Another important consideration in this context is the important unmet medical need and the lack of alternative treatment. In the BRA, it is important to get a measurement of the risk acceptance with a threshold of tolerability of the patient's perceptions and expectations. Considerations to conduct a patient-focused BRA as a key decision-making factor that integrates benefit expectations and risk acceptance from a patients' perspective should be undertaken.

When a product has been marketed for some years and there remain uncertainties over its benefits and risks, a continuous collection of data to document the risks in treated and untreated patients (epidemiology and case reports); the continued measurement of beneficial effects in RWD; the synthesis of data from multiple sources; and an evaluation of the risks monitoring and risk mitigation strategy should be undertaken.

4.4.2. Paediatric population

Managing with uncertainty and heterogeneity

The BRA for the paediatric population draws more uncertainty than that for adult populations due to limited exposure of the paediatric population and heterogeneity of this population from infants to adolescents. Various ethical considerations must also be taken into account when enrolling children in clinical trials.

Specific considerations

At the time of the initial evaluation, due to the limited data on benefits and risks, and the potential for heterogeneity in the expected effect of the product, methods to address the remaining uncertainties should be implemented such as evaluation of long-term effectiveness to confirm the durability and persistence of the treatment response. It is also important to consider any potential impact of the formulation of the product on children's compliance, risks of overdose and of medication error. One other important challenge is related to specificities of paediatric forms of the disease as progression may differ as compared to the adult form (more severe, harder to manage, more complications, and so forth). Alternative treatments approved in the paediatric population may be more limited than in adults and off-label use may also be an important part of the assessment of the unmet medical need. Use of clinical registries of off-label use in paediatrics may bring sufficient evidence or may help to identify a knowledge gap in the unmet medical need where more data are required. Moreover, dependent on indications, the data in routine clinical databases may be heavily influenced by parents' behaviour/experience. Some parents may tend to over-report AEs that may bias the analysis. Methodologies to identify and address such biases would prove worthy when dealing with these types of data.

When the product is marketed, there may be remaining uncertainties on the benefits and risks that warrant continued collection of data on risks in treated and untreated patients (epidemiology and case reports), continued measurement of treatment effects in RWD, risk monitoring and risk management activities.

4.5. Advanced Therapy Medicinal Products

Managing with uncertainty and lack of guidance

Advanced Therapy Medicinal Products (ATMPs) are novel medicines for human use that are based on genes, tissues or cells. They offer groundbreaking new opportunities for the treatment of disease and injury.[4] The BRA of ATMPs draws more uncertainty regarding long-term efficacy and long-term safety potentially related to the product itself, the associated administration procedures, the required conditioning measures and/or the background disease to treat. BRA is also impacted by a lack of standards for these novel therapeutic products and their huge uncertainty of risks.

Specific considerations

At the time of the initial evaluation, the level of evidence may be insufficient due to the limited number of patients included in the trials, the potential use of non-validated endpoints and there may be a lack of representativity of the population when clinical trials were conducted in a limited number of sites and countries. Uncertainties linked to limited data on risks and an understanding of potential mechanisms of risks should be addressed with methods such as sensitivity analysis and Monte Carlo simulation (for more details please refer to Case study A2**.** in the Appendix). In the case of the eTRANSAFE Project on Translational Safety Assessment through Integrative Knowledge Management, translational safety methods for comprehensive analysis of correspondence and validity of animal data was used to better identify potential risks.[3]

When the product is marketed, evaluating the remaining uncertainties on benefits and risks warrants the continued collection of data on risks in treated and untreated patients (epidemiology and case reports), the continued measurement of treatment effects in RWD with a synthesis of multiple sources of data, risk monitoring and assessment of risk mitigation strategies.

4.6. Legacy products

Managing with data from a different era for standard of care and missing information

For legacy products, previously approved prior to current day regulatory requirements, a treatment paradigm, data standards and clinical guidelines may have evolved over time since the MA of the product was granted.

Another big challenge with legacy products can be missing information. The regulatory paradigm was likely not as robust as it is today, resulting in less comprehensive documentation of evidence at the time of approval. In addition, there can be practicalities, such as the loss of archived information, that impact the ability to introduce data into a BRA. Conventions and standards for recoding efficacy and safety endpoints may have also evolved over time, making the like-for-like comparisons more difficult. For example, MedDRA – the dictionary for AEs – became more widely adopted as a standard in AE reporting in 1999 when it was first implemented in Europe, Japan and the US and has since been revised more than 20 times to add new terms that characterise and describe AEs.

In the post-marketing setting, new information may come from a wide range of sources of information such as systematic collection (post-marketing studies, REMS assessment reports) or surveillance and pharmacovigilance (AEs reports, medication error reports, product quality reports, patient experience data, literature, etc.).

In the situation where information on new, but rare, risks may arise while limited information on benefits is available, only RWD can be leveraged.

Specific considerations

For these legacy compounds, in post-marketing settings, the methods to address the limited or absent comparative efficacy data should focus on leveraging real-world effectiveness data to estimate treatment effect. While upcoming post-marketing information may be limited to risks, different activities can be implemented including methods to address uncertainties regarding drug use in special populations (such as the elderly, pregnant women, children), the synthesis of RWD from multiple sources (e.g. network meta-analysis) and integration of the impact of the results on effectiveness of RMMs.

One of the important considerations for such products is to define which new information is relevant enough to trigger the need for re-evaluation of BR. As an example, an important new risk can trigger the re-evaluation of BR.

4.7. Non-prescription medicinal products

Consumer responsible for a range of decisions about the medicine's selection and use

The BRA of non-prescription products draw a strong need to focus on the patient perspective as patients play a major role in the decision making. In the non-prescription setting, consumers are able to self-select an appropriate medication for treatment of minor ailments with minimal, if any, health care professional input. Consideration of patient and/or consumers' behaviour is critical in the assessment of clinical outcomes for non-prescription medicines.

BRA will be required most frequently in two types of situations: either when the drug is intended to move from a prescription to a non-prescription status, or when a new important risk that may impact the BR balance is identified.

Specific considerations

In the situation of a prescription product to a non-prescription product switch, the key challenge is to understand the impact of the switch in terms of benefits and risks, through recognition and consideration of the incremental benefits and risks of non-prescription use. For this purpose, the criteria described by Brass and colleagues[5] cover the BR domains to be considered including the improved access to effective drugs and the risk of unintended misuse. The synthesis of data from multiple sources using RWD may help to define the current use, benefits and risks. Moreover, collection of patient insights using methods described in Section 3.3 would help to measure the patient's perspective.

In case of BRA, re-evaluation due to a new identified risk, the methods described for legacy products should be considered taking into account that non-prescription drug use may be partially or not at all recorded in RWD.

4.8. Summary

The table below summarises for each situation key challenges and where uncertainty is the most important when an assessment is done and the specific considerations and/or methods that can be applied to address them.

Table 24. Overview of benefit-risk assessment challenges in special situations

Source: CIOMS Working Group XII

Situation	Major issues/ challenges	Specific considerations/methods
Emergency use and/or repurposing	Urgency, no specific study designed for the indication	Real-life and real-time monitoring of the product's effectiveness and safety using Real-World Data (RWD) based on recommendations of CIOMS Working Group XIII report on *Real-world data and real-world evidence in regulatory decision making*.[6]
Accelerated/ conditional approval	Pending more mature efficacy data	Simulation and extrapolation methods (for more details on methods refer to Section 2.5 on Additional quantitative analysis).
Special population: Rare disease	Limited number of patients exposed, limited knowledge on risks	Use of RWD to complement evidence in post-marketing and to build a historical cohort as a comparison group.
Special population: paediatric	Limited exposure and heterogeneity	Use of RWD to complement evidence and to address uncertainties (for more details on methods refer to Section 3.4 on Methodological considerations for addressing uncertainties in benefit-risk assessment).

Situation	Major issues/ challenges	Specific considerations/methods
Advanced Therapy Medicinal Products	Uncertainty on benefits and risks	Simulation and extrapolation methods combined with enhanced post-marketing monitoring (for more details on methods refer to Section 2.5 on Additional quantitative analysis).
Legacy product	Absence of recent clinical data or comparative data, missing information and heterogeneity of available sources of information in post-marketing setting.	Synthetise data from multiple sources (from systematic collection and spontaneous reports) and use of RWD evaluation methods.
Non-prescription medicinal products	Consumers responsible for a range of decisions about the medicine's selection and use.	Synthetise data from multiple data sources using RWD including patient insights (for more details on methods refer to Section 3.3 on Methodological considerations to gain patient insights). Recognition and consideration of the incremental benefits and risks of non-prescription use.

Chapter 4 – References

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APPENDIX I.
CASE STUDIES A - E

A1. Rotavirus vaccine: how to inform benefit-risk assessment with an emergence of risk of intussusception

Summary table of the case study

TOPIC	SUMMARY INFORMATION
Purpose/Objective of the case study example	This study uses quantitative analysis to inform BR of Rotavirus Vaccine (RV) in the US.[1] This case study provides a good example for post-market BRA and application of computational models to incorporate different sources of data for BRA when there is an uncertain severe risk emerging in a post-marketing setting and the BR profile cannot be determined based on clinical trial data alone.
Information on the disease or condition being treated	Rotavirus (RT) is the most common cause of severe gastroenteritis (GE) among children <5 years of age worldwide. Before the introduction of RV in 2006 in US, Rotavirus-associated Gastroenteritis (RTGE) caused nearly 20-60 deaths, 55000-70,000 hospitalisations and 200,000 Emergency Department (ED) visits in children <5 years of age every year.[1]
Information on the drug being used to treat the patient	Two RVs have been approved in US since 2006, including: 4. RotaTeq™: a live oral pentavalent (RV5) vaccine composed of five human-bovine reassortant strains which include G1, G2, G3, G4 and P1A to prevent RTGE caused by types G1, G2, G3 and G4, manufactured by Merck & Co. Inc., and approved by US FDA in 2006. 5. Rotarix™: a live, oral, monovalent RV (RV1) indicated for the prevention of RTGE caused by G1, G3, G4 and G9 types, manufactured by GlaxoSmithKline. Inc. and approved by US FDA in 2008. Rare cases of intussusception, a potentially life-threatening intestinal blockage, have been reported worldwide in the post-marketing setting for both vaccines.
Pharmacology	RV5 is administered orally as a 3-dose series to healthy infants between ages week 6 to 32 weeks. Doses are administered at 4- to 10-week intervals. RV1 is given as a 2-dose series to healthy infants of 6-24 weeks of age with doses separated by a minimum of 4-week interval.
Benefits endpoints	Prevention of RT-associated deaths, hospitalisations and ED visits.
Risks endpoints	Excess deaths, hospitalisations and short-stay or ED visits due to RV-associated intussusception.
Integrated benefit-risk endpoints (if applicable)	The study estimates the BR ratio, i.e. the ratio of deaths, hospitalisations and ED visits prevented by RV to accordingly those events caused by RV-associated intussusception.

TOPIC	SUMMARY INFORMATION
Benefit-risk assessment principle/method and reference	Two Probabilistic Monte Carlo models were used to evaluate the BR of RV in children from birth to 5 years of age. The models incorporate vaccine efficacy data from a post-market study, US data on vaccine coverage, US baseline intussusception rate and vaccine-associated intussusception rate reported in Mexico. Model 1 was used to first estimate the RT disease burden such as deaths, hospitalisations and ED visits under scenarios without vaccination and with a fully implemented vaccine program, then to calculate the vaccine efficacy. Model 2 calculates the excess intussusception associated with RV and the ratio of the number of deaths, hospitalisation and ED visits prevented by fully implemented vaccine program to those events caused by vaccine-associated intussusception.
Benefit-risk assessment results	The BR ratio, i.e. the deaths, hospitalisations and ED visits due to RT infections prevented by vaccination compared with the vaccine-associated intussusception related deaths, hospitalisations and ED visits were largely favourable 71:1, 1093:1, and 12115:1, respectively.
Strengths & limitations of the benefit-risk assessment	This study evaluates the BR of licensed RVs using computational models to incorporate clinical trial and other epidemiologic data. However, this study did not include outpatient visits, herd immunity and other societal benefits.[2]
Benefit-risk conclusion and risk minimisation strategies	The analysis concludes that the benefits of receiving a RV- substantially exceed its potential risk in children <5 years of age.

Introduction to the case study example

A RT infection is the most common cause of diarrhoea in infants and young children resulting in over 215,000 deaths annually worldwide. Before the RVs were developed, most children in the US and other countries had been infected with the RT at least once before the age of two.[3]

Two RVs were approved by US FDA, Rotateq™ (RV5, three-dose schedule) in February 2006 and Rotarix™ (RV1, 2-dose schedule) in April 2008. Based on their respective clinical trial data, these RVs were found to be safe and efficacious in preventing RTGE and reducing the severity of cases.[4,5] By the time this analysis was published,[1] the US post-marketing data had not documented any RV-associated intussusception cases. However, international data showed a low-level of increase in incidence of intussusception post-RV vaccination.[1] A similar risk could not be ruled out due to insufficient US data. To evaluate the BR of RV, computational models, specifically probabilistic Monte Carlo models were developed by the US Centers for Disease Control & Prevention (CDC) researchers to incorporate different sources of data. The number of deaths, hospitalisations and ED visits due to vaccine-associated intussusception were compared with the estimated corresponding events prevented in a fully implemented US vaccination program. The study helps to inform the real-world BR of RV. This case study example illustrates how quantitative analysis could be helpful in BRA when there is uncertain severe risk and the real-world BR cannot be determined based on clinical trial data alone.

Benefit-risk assessment methodology

Probabilistic Monte Carlo simulations were performed to:

- Estimate the RT disease burden such as: number of deaths, hospitalisations and ED visits, with, verses without a fully implemented vaccine program (Model-1);
- Calculate the ratio of the number of deaths, hospitalisations and ED visits prevented by the RV (benefit estimated from model-1) to the number of events caused by RV-associated intussusception (risk) (Model-2).

Model 1: A previously published Monte Carlo probabilistic model[6] developed for a cost-benefit analyses of a vaccination program, was used to estimate the RT disease burden with and without a vaccine program for a 2009 US birth cohort of 4,261,494 infants ranging in age from birth to five years of age.

The RV vaccine effectiveness for full (three doses) and incomplete doses (< three doses) were estimated based on RV5 data from a large post-licensure study[7] since RV5 accounted for more than 90% of all US RV vaccinations through August 2010. In this study, RV effectiveness was assessed using case-control methodology and data from the electronic immunisation information system (IISs) [8] of three states (Minnesota, Georgia and Connecticut) in the Emergent Infections Program Network. [9] Specifically, the children with GE were defined as either case-subject (with vaccination) or control (without vaccination). The odds ratios of incidence of death, hospitalisation, and ED for case-subject compared to the control were estimated using unconditional logistic regression by vaccine dose group. Triangular probability distributions of vaccine protection against death/hospitalisation and ED visits due to RT disease were derived from the results of model 1 (Table-25).

The RV vaccination of 2009 birth cohort with number of doses completed under a hypothetical fully mature vaccine program (Table-26) was assumed based on the data from the 2009 National Immunization Schedule (NIS) on RV vaccine (either RV5 or RV1), DTaP (Diphtheria, Tetanus, Pertussis Vaccine)/diphtheria and tetanus toxoid vaccines.

Table 25. Model input variables for vaccine effectiveness

Source: Derived from from Desai R, Cortese MM, Meltzer MI, Shankar M, et al [1]

Model input variable *vaccine effectiveness*	Point estimate with [95% CIs] or (Ranges)		
	Dose 1	Dose 2	Dose 3
Hospitalisation/death	66% [16-86%]	90% [75-96%]	92% [86-96%]
Emergency Department visits	55% (5-75%)	79% (64-85%)	81% [52-92%]

Table 26. Model input variables for birth cohort and vaccine coverage

Source: Derived from Desai R, Cortese MM, Meltzer MI, Shankar M, et al.[1]

Model input variable	Point estimate		
	Dose 1	Dose 2	Dose 3
Portion of birth cohort vaccinated	95.8%	92.7%	81.8%
Number of 2009 US live births was 4,261,494			

Model 2: The second Monte Carlo model was used to calculate the ratio of the number of deaths, hospitalisation and ED visits prevented by RV to the number of those events from RV-associated intussusception. The model ran for 10,000 iterations using probability distributions of RV effectiveness derived from Model 1 to estimate the prevented numbers of deaths, hospitalisations, and ED visits (vaccine benefits). The probability distributions of RV-associated intussusception were calculated based on baseline intussusception rates in the US calculated from hospital and ED discharge databases for US infants, vaccine coverage under a fully mature vaccination program, and the RR of vaccine-associated intussusception found in Mexico (point estimate of 5.3).

Vaccine-associated Intussusception risk: the increased risk of intussusception was assumed to occur only in week 1 after dose 1 and the risk does not change with age and there was no risk after dose 2 or 3. The study estimates the numbers of infants who would receive RV dose 1 for each week before one year of age (all doses of RV are expected to complete by one year of age based on vaccine schedule) based on the US vaccine coverage data for a fully implemented vaccine program. Baseline intussusception hospitalisation rates were obtained from the State Inpatient Databases from 22 states comprising about 67% of the US birth cohort before vaccine introduction, from 2000-2005. To capture the intussusception cases managed in short-stay or ED visits, State Emergency Department Databases from 14 states accounting for 20% of the US birth cohort from 2003-2005 were analysed. The RV-related excess cases of intussusception were calculated based on the RR observed in Mexico (point estimate of 5.3) and weekly baseline incidence of intussusception during the first year of life. Table 27 shows the point estimates used in the model to evaluate the potential vaccine-associated intussusception risk. The total number of hospitalisations from RV-associated intussusception was the sum of RV-related surgery and death episodes.

Table 27. Model input variables for intussusception risk

Source: Derived from Desai R, Cortese MM, Meltzer MI, Shankar M, et al.[1]

Model input variable *Potential* rotavirus vaccine *intussusception risk*	Point estimate with [95% CIs] or (ranges)
Excess risk of intussusception in week 1 after dose 1	5.3 [3.0-9.3]
Percent of intussusception hospitalisations requiring surgery	52.8% (51.1-55.4%)
Percent of intussusception hospitalisations resulting in death	0.3% (0-0.5%)

Two computational models were developed in this study to incorporate vaccine efficacy data from a post-marketing study, vaccine coverage data from NIS, baseline intussusception rate derived from hospital and ED discharge database and RV-associated intussusception rate reported from Mexico.

Computational techniques can be used to capture data uncertainty and assess its impact on the benefits and risks of the product.

The CDC researchers conducted Monte Carlo simulations to calculate the BR ratio and associated uncertainty. A sensitivity analysis was conducted to examine the impact on the BR ratio of uncertainty in the RR of RV-associated intussusception, a key model input assumed based on international data. The study indicates even with a conservative assumption about RR of RV-associated intussusception, the benefits of RV outweigh its risks, which help increase confidence in decision making under the uncertainty.

One of the limitations of the study is uncertainty about the RV-associated intussusception rate. The available data is limited. Also, some potential benefits of RV were not included, such as reduced outpatient visits and indirect benefits of herd immunity,[2] which make the estimates of vaccination benefits conservative. However, this study is informative for BRA of RV and management of a RV program.

Conclusion and risk minimisation

This quantitative BR analysis showed that the number of prevented deaths, hospitalisations and ED visits in young children receiving a RV far exceeds the number of deaths, hospitalisations, and ED visits caused by RV-associated intussusception.

Appendix I – Case study A1 – References

1 Desai R, Cortese MM, Meltzer MI, Shankar M, Tate JE, Yen C, et al. Potential intussusception risk versus benefits of rotavirus vaccination in the United States. The Pediatric Infectious Disease Journal. 2013;32(1):1. https://doi.org/10.1097/INF.0b013e318270362c (PDF accessed 7 September 2024).

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A2. Rotavirus vaccine: focusing on benefit-risk assessment methods including Monte Carlo simulation

Introduction

In this case study A.2, we build on case study A.1 to elaborate on the BRA methods used.

Benefit evaluation

The Model 1 determined the number of RT-associated deaths, hospitalisations and ED visits that could be prevented with a fully mature vaccination program in infants up to the age of five years. Vaccine benefits were estimated based on the effectiveness data of RV5, which accounted for more than 90% of all RV vaccinations from February 2006 through to August 2010 and vaccine coverage for an assumptive matured vaccine program based on the 2009 NIS on RV (either RV5 or RV1), DTaP (Diphtheria, Tetanus, Pertussis Vaccine)/diphtheria and tetanus toxoid vaccines. Model inputs for vaccine effectiveness used for this estimation are shown in Table 25.

Risk evaluation

The vaccine risks were evaluated by the death, hospitalisation and ED visits as a result of RV-associated intussusception. Baseline rates of intussusception in US infants were calculated from a hospital and ED discharge database. Baseline intussusception hospitalisation rates by week of age during the first year of life were obtained from the US State Inpatient Databases maintained by the Healthcare Cost and Utilisation Project containing data from 22 US states, which comprises about 67% of the US birth cohort from 2000 to 2005. The ED databases from 14 US states include nearly 20% of the US birth cohort from 2003 to 2005.

The RR of RV-associated intussusception was assumed same as the RR reported in Mexico (point estimate of 5.3, see Table 27). The intussusception incidence was calculated by multiplying baseline incidence of intussusception in the 2009 US birth cohort with the RR.

Integrated benefit-risk assessment of the benefit-risk profile

Monte Carlo model 2 was used to calculate the BR ratio, i.e. the ratio of the number of deaths, hospitalisations and ED visits prevented by RV to the number of corresponding excess events from RV-associated intussusception. The impact on the BR ratio of uncertainty associated with the assumption about the RR was examined through sensitivity analysis with incremental change of RR by 0.1 within a range from 3.0 to 9.3 (95% CI estimate from Mexico). The results of sensitivity analysis were used to calculate the 95% CIs of the overall BR ratios.

Results

Results from model 1 showed the benefits from an assumptive fully implemented vaccination program by comparing the numbers of events (deaths, hospitalisations and ED visits) associated with RT disease, in 2009 birth cohort followed to five years of age, that would occur if a vaccination program was not implemented and the numbers of those events that would be prevented if a vaccination

program was fully implemented. The vaccination would prevent 14 deaths, 53,444 hospitalisations and 169,949 ED visits (Benefit Column in Table 28).

Results from model 2 showed an estimate of 1856 intussusception cases (baseline number) would occur among the 2009 birth cohort during the first year of life in the absence of a RV program. The model estimated 58 excess intussusception cases among the same study cohort with a fully implemented RV vaccination program which will lead to excess 0.2 deaths, 45 hospitalisations and 13 ED visits (Risk column in Table 28). The BR ratio column in Table 28 shows the median number of vaccine-adverted events for each vaccine-caused event.

Table 28. Benefits and potential risks of a rotavirus vaccine program in a birth cohort for a period up to age five

Source: Derived from Desai R, Cortese MM, Meltzer MI, Shankar M, et al.[1]

Events	Benefit RT-associated sequalae prevented with vaccine [95% CIs]	Risk Excess intussusception cases and sequalae with vaccine	Benefit-risk ratio
Deaths	14 [10-19]	0.2 (0.1-0.3)*	71 (48-112)+
Hospitalisations	53,444 [37,622-72,882]	45 (21-86)*	1093 (688-1902)+
Emergency Department visits	169,949 [118,161-238,630]	13 (6-25)**	12,115 (7528-21,448)+

*Range based on 5-95% limits of the vaccine-associated intussusception relative risk estimate.
+Point estimates (RV disease burden prevented per each intussusception case potentially caused). 5-95% CI based upon the median and 5-95% distributions obtained from 10,000 Monte Carlo simulation sampling from the benefit and risk for each clinical setting.

Lastly, results from sensitivity analysis showed that if the RR of intussusception for RV were 9.3 (upper limit of the 95% CI from the risk evaluation in Mexico), the BR ratio, i.e. the number of prevented death, hospitalisation and ED visit, for each RV-associated excess event would be 48, 618 and 6922 respectively. Even with this most conservative assumption, the benefits of RV still outweigh its potential risks.

Discussion

This case study is a good example of using quantitative analysis to assist post-marketing BRA of a licensed product. Three main lessons can be learnt from this case study:

1. Continuing evaluation of BRA post-marketing is warranted when there is concern about an emerging uncertain severe risk associated with a licensed drug or vaccine in any geographical location.

Up until August 2010, more than 90% of approximately 35 million doses of RV5 vaccine were distributed in the US and no vaccine-associated intussusception cases had been documented in the Vaccine Adverse Event Reporting System (passive reporting) or the Vaccine Safety Datalink (active reporting) in the US. However, given the level of risk seen in Australia and Mexico with RVs, the US CDC conducted this study to continuously assess the BR of RVs used post-licensure in a real-world setting. The model results indicate that the benefits of RVs outweigh their risks, which helped to

inform the management of the RV vaccination program in the United States. Later CDC's update of safety data from US showed a small increase of intussusception incidence following RV vaccination.[2,3,4] However, the BR conclusion from this study remains unchanged.

2. Computational models can be used as a tool to incorporate different sources of data to inform BRA.

Two computational models were developed in this study to incorporate vaccine efficacy data from a post-marketing study, vaccine coverage data from NIS, baseline intussusception rate derived from hospital and ED discharge database and RV-associated intussusception rate reported from Mexico.

3. Computational techniques can be used to capture the data uncertainty and assess their impact on the benefits and risks of the product.

The CDC researchers conducted Monte Carlo simulations to calculate the BR ratio and associated uncertainty. A sensitivity analysis was conducted to examine the impact on the BR ratio of uncertainty in the RR of RV-associated intussusception, a key model input assumed based on international data. The study indicates even with a conservative assumption about RR of RV-associated intussusception, the benefits of RV outweigh its risks, which help increase confidence in decision making under the uncertainty.

One of the limitations of the study was the uncertainty about the RV-associated intussusception rate given the available data was limited. Also, some potential benefits of RV were not included, such as reduced outpatient visits and indirect benefits of herd immunity,[5] which make the estimates of vaccination benefits conservative.

Conclusion and risk minimisation

The quantitative BR analysis showed that the number of prevented deaths, hospitalisations and ED visits by RV far exceeds the number of deaths, hospitalisations, and ED visits caused by RV-associated intussusception. This case study highlights how quantitative methods can be informative for the BRA of vaccines and the subsequent management of a vaccination program.

Appendix I – Case study A2 – References

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B. Benefit-risk balance for oral anticoagulants

This case study demonstrates how MCDA can help inform a decision associated with a complex BR trade-off using an example for use of Oral Anticoagulants (OACs) among a general population (70- to 79-years-olds) from a publication by Hsu et al.[1] Hsu et al. compared BRAs of different OACs (warfarin, dabigatran etexilate, rivaroxaban and apixaban) and different dosages for treatment of Non-Valvular Atrial Fibrillation (NVAF) using MCDA. The key benefits of the OACs include prevention of stroke and systemic embolism, and the risks include increased episodes of bleeding. The consequences of clinical events that drugs can prevent (benefits), or cause (risks) are severe. The BR trade-off for different OACs is difficult.

TOPIC	SUMMARY INFORMATION
Purpose/Objective of the case study example	To demonstrate the use of MCDA to compare BRAs of different drugs to inform clinicians and patient's decisions about treatment options in situations of complex BR trade-off.
Drug indication	OACs are for the treatment of NVAF, which include Novel Oral Anticoagulants (NOACs) (dabigatran, rivaroxaban and apixaban) and vitamin K antagonist (VKA) warfarin.
Pharmacology	▶ Warfarin is a VKA used to treat venous thromboembolism, pulmonary embolism, thromboembolism with Atrial Fibrillation (AF), thromboembolism with cardiac valve replacement, and thromboembolic events post MI. ▶ Dabigatran is an oral reversible, potent, competitive direct thrombin inhibitor. It can bind free thrombin and is capable of binding and inhibiting both free and clot-bound thrombin.[2] ▶ Rivaroxaban is a new oral, direct, and selective inhibitor of the Factor Xa of the coagulation cascade.[3] ▶ Apixaban is an oral, direct factor Xa inhibitor that inhibits both free and clot-bound factor Xa.[4]
Information on the disease or condition being treated	OACs are used for prevention of ischemic stroke resulting from AF. The prevalence and incidence of AF have increased in part due to the aging population. By 2015, in the US, more than 6.5 million patients have been diagnosed with AF. This number is expected to double by 2050.
Benefits/endpoints	Prevention of ischemic stroke and prevention of systemic embolism.
Risks/endpoints	Intracranial bleeding and extracranial bleeding.
Integrated benefit-risk endpoints (if applicable)	Using MCDA to calculate the BR scores of different OACs integrating effect sizes of selected key benefit and risk endpoints and respective weights determined based on the health utility.
Benefit-risk assessment principle/method and reference	This study used a value tree to summarise the key benefits and key risks of the drugs (warfarin, dabigatran, rivaroxaban, and apixaban), and used the effect tables to summarise the measures of BR endpoints of drug/dosage combinations. The health utility was used to calculate the weights for BR endpoints of interest. The MCDA was used to integrate the benefits and risks and generate overall performance scores for individual drugs.

TOPIC	SUMMARY INFORMATION
Benefit-risk assessment results	Results suggest that overall, NOACs had a higher performance score than warfarin for patients of 70-79 years of age.
Strengths & limitations of the benefit-risk assessment	The MCDA approach allows to integrate multiple criteria explicitly for BR trade-offs; thus, to inform a decision on the use of drugs under different clinical conditions. This study used a published health utility index to determine the weights for selected key BR endpoints. A PPS may be conducted to help fill in the gaps or replace the health utilities to better reflect a patient's preference in the BR trade-off. A methodological drawback of this study is using HR to represent the effect sizes of benefits and risks. This can be misleading without considering the magnitude of a baseline. An absolute risk may be more appropriate (see more discussion in Chapter 3 on Benefit-risk assessment methodology considerations).
Benefit-risk conclusion and risk minimisation strategies	For use among the general population of 70–79-year-olds to treat NVAF, Dabigatran 150 mg BID had the highest performance score followed by Rivaroxaban 20 mg QD and Apixaban 5 mg BID. Warfarin had the lowest BR performance score for this indication.

Introduction to the case study example

AF is the most common type of heart arrhythmia.[5] Currently in the US, more than 454,000 hospitalisations occur each year with AF as the primary diagnosis.[5] It is estimated that more than 12 million people in the United States will have AF by 2030.[6,7] European descent people are more likely to have AF than African Americans. The risk of experiencing a stroke increases with AF and up to 125,000 Americans experience a stroke annually.[8] Some patients' characteristics and comorbidities increase the risk of stroke in patients with AF.[9]

There are different treatments for AF such as medicines to control the heart's rhythm and rate, surgery (when AF is valvular related), and OACs to prevent the formation of blood clots and reduce the risk of a stroke. Due to the high number of AF diagnosis in the US, OACs are commonly prescribed for stroke prevention in patients with NVAF.[10] Available OACs include warfarin and NOACs such as apixaban, dabigatran and rivaroxaban, which became available subsequently. Warfarin has been used for decades and has been known to be highly effective for stroke prevention in AF. However, the NOACs have become the primary choice of therapy due to their efficacy, ease of use, and primarily low risk of bleeding complications.[10] In this case study, we describe how MCDA was used to compare the benefits and risk of warfarin and other NOACs alternatives (dabigatran, rivaroxaban, and apixaban) for treatment of NVAF. Although approaches to MCDA analysis may be slightly different depending on the risks and benefits selected, endpoints chosen and their assigned weights, four common steps are described below, and are applied to this case study.

1. Map a value tree (specifying decision criteria). Identify key benefit and risk endpoints and comparators.
2. Summarise benefit and risk evidence. Obtain effect size values of each endpoint (sub-criteria).
3. Weight the sub-criteria. Derive weights for each endpoint.
4. Calculate overall BR performance score of each comparator. Performance score of each comparator is calculated by integrating scaled and normalised effect sizes and respective weights encompassing all BR sub-criteria.

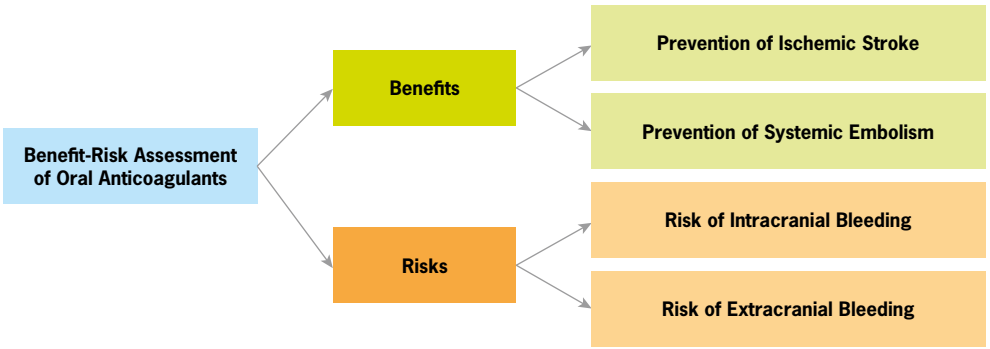
Benefit-risk assessment methodology

In this study, MCDA was used to assess and compare the benefits and risks of different OACs for treatment of NVAF.

The first step of the study is to map a value tree (Figure 18) representing the key benefits and key risks of NOACs and warfarin for uses among the general population (70–79-year-olds). In the value tree, the selected decision criteria and specific endpoints were plotted. In this study, selected key endpoints for benefit included 'Prevention of Ischemic Stroke' and 'Prevention of Systemic Embolism' and the selected key endpoints for risk included 'Risk of Intracranial Bleeding' and 'Risk of Extracranial Bleeding'.

Figure 18. Benefit-risk value tree for use of oral anticoagulants among the general population (70–79-year-olds)

Source: Modified from Hsu JC, Hsieh CY, Yang YH, and Lu CY [1]



The second step of the study is to obtain the effect size values (with 95% CIs) of each BR endpoint of the drugs. The authors obtained these values from a cost-effectiveness study.[11] The effect size values of all NOACs are represented as reciprocal of HR relative to warfarin for benefit endpoints, while represented as HR relative to warfarin for risk endpoints (Table 29). The MCDA model used mean effect size values and their respective 2.5th and 97.5th percentile as the lowest and highest values of model inputs.

At the third step, the weight for each benefit and risk sub-criteria is estimated using the values of health utilities[1] (Table 29). Health utility is a rating scale used to measure general health status and health-related QoL. The health utilities (mean and ranges) used in this study were obtained by the stroke Patient Outcomes Research Team (PORT). For example, the weight for prevention of ischemic stroke is obtained by using the reciprocal of the respective health utility (3.70) divided by the sum of the reciprocal of health utilities for all selected key benefit and risk endpoints (8.61), i.e. 3.70/8.61 = 0.43.

The last step is to calculate the overall BR performance score for each drug using the MCDA method to integrate effect sizes and respective weights encompassing all BR endpoints. The drugs with higher performance scores are more preferred.

Table 29. Health utilities and weights for benefit and risk endpoints for the general population (70–79-year-olds)

Source: Modified from Hsu JC, Hsieh CY, Yang YH, and Lu CY[1]

Criteria	Endpoints	Health utility	Reciprocal of health utility	Weight	
Benefit	Prevention of Ischemic stroke	0.27 (0.22-0.32)	3.70 (3.12-4.55)	0.43	0.631
	Prevention of Systemic embolism	0.575 (0.45-0.7)	1.74 (1.43-2.22)	0.202	
Risk	Risk of intracranial bleeding	0.46 (0.22-0.9)	2.17 (1.11-4.55)	0.252	0.369
	Risk of extracranial bleeding	0.997 (0.98-1.00)	1.00 (1.00-1.02)	0.116	

Benefit evaluation

The effect sizes in Table 30 are the reciprocal of HR obtained from Canestaro et al. 2013.[11] In this case study, the effect sizes of all BR endpoints for warfarin are defined as 1, since the effect sizes of respective endpoints for other NOACs are taken from HRs calculated in referenced studies using warfarin as the control. The effect sizes of NOACs are estimated as ratios relative to warfarin.

Table 30. Effect sizes for benefit endpoints as model inputs

Source: Modified from Hsu JC, Hsieh CY, Yang YH, and Lu CY [1]

Endpoint	Units	Oral anticoagulant agents			
Prevention of		Warfarin	Dabigatran 150 mg BID	Rivaroxaban 20 mg QD	Apixaban 5 mg BID
Ischemic stroke	1/HR	1	1.32 (1.02-1.67)	1.06 (0.85-1.33)	1.09 (0.89-1.35)
Systemic embolism	1/HR	1	1.20 (0.93-1.72)	4.35 (1.64-11.11)	1.15 (0.57-2.27)

HR = Hazard Ratio; 1/HR = the reciprocal of hazard ratio.
QD: Once a day; BID: twice per day.

Risk evaluation

Table 31 contains the effect size for each risk endpoint, HRs obtained from Canestaro et al. 2013.[11]

Table 31. Effect size for risk endpoint as model inputs

Source: Modified from Hsu et al, 2015.[1]

Endpoint	Units	Oral anticoagulant agents			
Risk of		Warfarin	Dabigatran 150 mg BID	Rivaroxaban 20 mg QD	Apixaban 5 mg BID
Intracranial bleeding	HR	1	0.40 (0.27-0.60)	0.67 (0.47-0.93)	0.42 (0.30-0.58)
Extracranial bleeding	HR	1	1.07 (0.92-1.25)	0.42 (0.29-0.55)	0.79 (0.68-0.93)

HR = hazard ratio
QD: Once a day; BID: twice a day.

Integrated benefit-risk assessment

The BR performance score and ranking of integrated benefits and risks of the drugs are summarised in Table 32. These performance scores are the sum of scaled and normalised effect sizes for all benefits (Table 30) and risks (Table 31) multiplied by the respective weights (Table 29). Overall Dabigatran 150 mg BID had the highest performance score, and Warfarin has the lowest (Table 32) for use among the general population of 70–79-year-olds for treatment of NVAF.

Table 32. Calculated performance scores of drugs by integrated benefit-risk assessment

Source: Modified from Hsu JC, Hsieh CY, Yang YH, and Lu CY [1]

	Warfarin	Dabigatran 150 mg BID	Rivaroxaban 20 mg QD	Apixaban 5 mg BID
Score	0.191	0.529	0.462	0.426
ranking	4	1	2	3

Discussion

This case study demonstrates the use of of multiple BRA tools. For example, use of the value tree to define BR criteria, the use of the effect table to summarise the data/evidence (effect size) for benefits and risks, the use of health utility to calculate the weights for benefit and risk endpoints, and the use of MCDA to integrate effect sizes and respective weights of all BR endpoints to calculate performance score assisting BR trade-off decision.

The study has several limitations. In general, decision models are a simplification of decision making in real-life scenarios. For example, interactions with other drugs, patient adherence rate, risk of switching medications, off-label or inappropriate use of drugs, availability of a reversal agent, administration frequency or food interactions, which may have an impact on the BR balance,[10] but are not considered in the model. Lastly, time-dependent risks and benefits may need to be considered.

This study used a published health utility index to determine the weights for selected key BR endpoints. A PPS may be conducted to help to fill in the gaps or replace the health utilities to provide weights of BR endpoints and better reflect patient's preference in the BR trade-off.

A methodological drawback of this study is using HR in the analysis. This can be misleading without considering the magnitude of baseline risks. Absolute risks may be more appropriate (see more discussion in Chapter 3 on Benefit-risk assessment methodology considerations).

Conclusion and risk minimisation

The MCDA quantitative method can be used to compare the BR balance of multiple treatment options when the BR trade-off is complex by integrating the effect sizes and weights of multiple benefit and risk endpoints of the drugs. This type of study helps clinicians and patients to make a better choice of drug/treatment options for patients with different clinical conditions and risk factors.

Appendix I – Case study B – References

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C. Two regulatory agencies conduct benefit-risk assessment differently on neratinib (Nerlynx)

Summary table of the case study[1]

Pharmacology	Tyrosine kinase inhibitor. Irreversible pan-erythroblastic leukaemia viral oncogene homolog (ERBB) tyrosine kinase inhibitor (ATC code: L01XE45).
Indication/ Disease treated	On 17 July 2017, the US FDA approved neratinib (Nerlynx) as a single agent for the extended adjuvant treatment of adult patients with early stage HER2[i]-positive breast cancer to follow adjuvant trastuzumab based therapy. In the same year, the MAH also applied for the following indication in Europe: 'Nerlynx as a single agent for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer at high risk of recurrence who have received prior adjuvant trastuzumab based therapy'. The indication was restricted during the assessment procedure to 'Nerlynx as a single agent as indicated for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer at high risk of recurrence (node positive and within one year of completion of prior adjuvant trastuzumab based therapy'). On 28 June 2018, the EMA, following a re-examination procedure, adopted a positive opinion, for the medicinal product neratinib, intended 'for the extended adjuvant treatment of adult patients with early-stage hormone receptor positive HER2-overexpressed/amplified breast cancer and who are less than one year from the completion of prior adjuvant trastuzumab based therapy'.
Benefits	The benefits with neratinib are its ability to reduce the risk of invasive disease recurrence after two years compared with placebo. This is based on a randomised, double-blind, placebo-controlled, Phase 3 study that included 2840 patients with early-stage, HER2-positive breast cancer who had completed adjuvant treatment with a trastuzumab-based regimen within the previous two years. Around 94% of the women given a year's treatment with neratinib lived for one further year after stopping neratinib without their cancer coming back versus 92% of those given placebo. When only women with hormone-receptor positive cancer were considered, about 95% of those given neratinib lived another year without the cancer coming back versus 91% of those given placebo.
Known risks	The most common, serious side effect with neratinib is diarrhoea, which affects nearly all patients. Other common side effects, which may affect more than one in 10 people, are: nausea, abdominal pain, fatigue, vomiting, rash, stomatitis, decreased appetite and muscle spasms. Neratinib must not be used in patients with severely reduced liver function. It must also not be used with certain medicines that affect the way neratinib is broken down in the body. For the full list of restrictions, see the package leaflet.

[i] HER2: human epidermal growth factor receptor 2

Benefit-risk assessment method	The US FDA approval of neratinib was based on the safety and efficacy data from the pivotal clinical trial, a randomised, double-blind, placebo-controlled, Phase 3 study that included 2840 patients with early-stage, HER2-positive breast cancer who had completed adjuvant treatment with a trastuzumab-based regimen within the previous two years. Patients were randomised to receive neratinib (N = 1420) or placebo (N = 1420). The majority (81%) of patients were enrolled in the study within one year of completing trastuzumab therapy. The median patient age was 52 years (range, 23-83 years); 10% of the patients had stage I disease, 41% had stage II disease, and 31% had stage III disease. After two years, 94.2% of patients who received neratinib did not have disease recurrence and did not die compared with 91.9% of patients who received placebo. In an exploratory subgroup analysis of patients who were reconsented for extended follow-up beyond 24 months, the invasive Disease-Free Survival (iDFS) rates at five years were consistent with those of the two-year findings from the pivotal study. The Committee for Medicinal Products for Human Use (CHMP) of the EMA however initially had a different view on the BR balance of the product. Using the effects table to assess the BR (which includes the favourable effects and the uncertainties and limitations for the favourable effects; and the unfavourable effects and the uncertainties and limitations for the unfavourable effects), the CHMP concluded that although a greater proportion of women given neratinib in the study lived for two years without their disease coming back than women given placebo (around 94% versus 92% respectively), it is uncertain that this difference in benefit would be seen in clinical practice. Furthermore, neratinib causes gastrointestinal side effects, particularly diarrhoea, which affected most patients and might be difficult to manage. The Committee therefore concluded that the benefits were not enough to outweigh the risk of side effects and recommended that neratinib be refused MA. Major efficacy findings (CHMP's initial assessment) For the primary endpoint of iDFS in the ITT population, the two-year and five-year point estimates for absolute difference (2.3-2.5%) are rather small, but could be accepted as representing a clinically relevant benefit. However, the point estimates for the HRs are imprecise as demonstrated by wide 95% CIs including values close to unity. Importantly, the five-year efficacy estimate may be subject to bias due to incomplete re-consent for longer term follow-up. There was a lack of strong support from clinically relevant secondary endpoints including distant disease-free survival. Furthermore, there is internal inconsistency in the outcomes, as the isolation of the measured effect to hormone receptor positive patients lacks a clear rationale, contributing to uncertainty. Therefore, for a number of reasons there is considerable uncertainty in the magnitude of the treatment effect demonstrated by this single pivotal trial. Given these uncertainties, the lack of supportive evidence of a clinically useful anti-tumour effect from confirmatory studies in the neoadjuvant or metastatic breast cancer settings is notable. A proposal to restrict the indication to patients at high risk of recurrence has some rationale from the BR perspective but the evidence of efficacy in such a population was not more compelling than in the full ITT population.

Benefit-risk assessment method	Major safety findings (CHMP initial assessment) Neratinib causes significant gastrointestinal toxicity. Diarrhoea affects most patients, is severe in a high proportion, and can be expected to affect QoL. Based on available data from study 6201, it is uncertain at this time whether the diarrhoea can be adequately managed by prophylactic anti-diarrhoeals. The very high rate of early discontinuations from this trial despite intensive loperamide prophylaxis is of concern. It is also unclear to what extent diarrhoea may improve over time for the individual patient who decides to remain on treatment after experiencing severe diarrhoea. In routine clinical practice, there may be an even greater rate of treatment discontinuations due to diarrhoea, leading to a reduction in efficacy. In the presence of a robustly demonstrated important clinical benefit, the side effect profile might be considered acceptable, but is of major concern in the context of the deficiencies in the demonstration of efficacy. Balance of benefits and risks (CHMP initial assessment) A clinically relevant benefit on iDFS has not been established with an acceptable degree of certainty and the gastrointestinal toxicity is substantial. For these reasons, it is considered that the benefits of neratinib do not outweigh the risks. Re-examination procedure The sponsor requested a re-examination on detailed grounds. Clinical ground 1. The sponsor argued that the absolute iDFS benefit seen in pivotal study with neratinib is well within the range of iDFS benefits seen with other drugs that are currently approved for adjuvant use in early stage breast cancer in Europe (such as anastrozole, letrozole, exemestane). The sponsor considers that the enhanced neratinib treatment benefit observed in hormone receptor positive patients can be explained by: 1) the difference in the risk recurrence profile of HR-positive patients compared to HR-negative patients; and 2) the mechanism of action of neratinib on inhibiting the cross talk between the Estrogen Receptor (ER) and with HER2 and Epidermal Growth Factor Receptor (EGFR). Endocrine therapies which solely block ER have limited effectiveness in tumours with HER2 signalling. Conversely, blockade of amplified or overexpressed HER2 with HER2 inhibitors induces ER expression, which serves as an adaptive mechanism for tumour survival. Clinical ground 2. Other than diarrhoea, neratinib is associated with a low incidence of severe or SAEs and, with a safety database of over 3000 cancer patients (early stage and metastatic), there is no evidence for irreversible or cumulative toxicity associated with neratinib, with some patients receiving neratinib for more than five years. Data from Study 6201 demonstrate that anti-diarrhoeal prophylaxis helps decrease the incidence and severity of diarrhoea and reduces the duration of the severe diarrhoea episodes. The addition of budesonide or colestipol to the loperamide antidiarrhoea prophylaxis regimen appears to further reduce the incidence and severity of neratinib-related diarrhoea and appears to improve the tolerability of neratinib with less patients discontinuing neratinib treatment. Data from the post-marketing setting in the US demonstrate that use of improved and proactive diarrhoea management techniques for both physicians and patients and the introduction of a comprehensive education and support program results in reduced diarrhoea rates. The implementation of the support program reduced discontinuation rate due to diarrhoea to 7% (from 17% in the confirmatory study).

Benefit-risk assessment method	Clinical ground 3. Extended adjuvant therapy with neratinib provides a clinically meaningful and statistically significant reduction in risk of disease recurrence. The magnitude of the benefit seen in a pivotal study is in line with other drugs that are currently approved in Europe for the adjuvant treatment of early stage breast cancer and a single pivotal trial has typically been used as the basis for the approval of cancer drugs in Europe. Additionally, patients within pre-stratified subgroups (including node-positive and HR-positive breast cancer) had an observed benefit that was substantially increased relative to the ITT population. Diarrhoea is the most frequently reported AE, however it can be managed with antidiarrhoeal agents and/or reducing or temporarily holding the dose of neratinib. Using these diarrhoea management techniques, 95-97% of the patients with diarrhoea due to neratinib achieved resolution of their diarrhoea. The MAH committed to further investigate optimal diarrhoea management post approval (see RMP).
Assessment results	The first assessment outcome of CHMP concluded that the benefits of neratinib did not outweigh the risks. During the meeting on 19-22 February 2018, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a MA to neratinib. During the re-examination, the CHMP looked again at all the data and considered whether there would be a group of patients where the benefits outweighed the risks. During the meeting on 25-28 June 2018, the CHMP re-examined its initial opinion and in its final opinion recommended the granting of the MA. The EMA considered that although the side effects, particularly diarrhoea, can be severe and lead to treatment being stopped, there would be patients with HER2-positive, hormone-receptor positive early breast cancer for whom treatment with neratinib after surgery and trastuzumab would be a reasonable option. The agency therefore decided that neratinib's benefits are greater than its risks in this group and it can be authorised for use in the EU.
Conclusion	On 28 June 2018 the EMA's CHMP adopted a positive opinion recommending MA for the medicinal product neratinib for the extended adjuvant treatment of adult patients with early-stage hormone receptor positive, HER2-overexpressed/amplified breast cancer and who are less than one year from the completion of prior adjuvant trastuzumab based therapy.

Appendix I – Case study C – Reference

1 European Medicines Agency (EMA). Nerlynx Summary of product characteristics (Website accessed 29 May 2023).

D. Example of cell therapy and a theoretical risk of oncogenesis: Axicabtagene ciloleucel

The field of cell therapy presents many interesting insights into the BRA. The following example illustrates how a potential risk, based on theoretical concerns, presents a significant unknown for evaluation and characterisation. The EMAs approach to assessing the risk of oncogenesis and the evolution in the perception of this risk up to this point are described in this case study.

Summary Table of the case study

Pharmacology	Axicabtagene ciloleucel (YESCARTA) is a genetically modified autologous cell-based product containing T cells transduced ex vivo using a retroviral vector expressing an antibody to CD19 protein on B cell membranes (anti-CD19) Chimeric Antigen Receptor (CAR) comprising a murine anti-CD19 Single Chain Variable Fragment (ScFv) linked to CD28 co-stimulatory domain and CD3-zeta signalling domain.
Indication/Disease treated	▶ Adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy. ▶ Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including Diffuse Large B-cell Lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from Follicular Lymphoma (FL). ▶ Limitations of use: not indicated for the treatment of patients with primary central nervous system lymphoma. ▶ Adult patients with relapsed or refractory FL after two or more lines of systemic therapy. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Benefits	▶ Relapsed or Refractory Large B-Cell Lymphoma (axicabtagene ciloleucel).[1] ▶ In a study of adult patients with relapsed or refractory LBCL after first-line chemoimmunotherapy that included rituximab and anthracycline, the primary efficacy measure was event-free survival (EFS) as determined by an independent review committee. The estimated EFS rate at 18 months was 41.5% [95% CI: 34.2, 48.6] in the axicabtagene ciloleucel arm and 17.0% [95% CI: 11.8, 23.0] in the standard therapy arm. An interim analysis of overall survival was conducted at the time of the primary EFS analysis. The interim analysis of overall survival has not met the criteria for statistical significance. ▶ In a single-arm, open-label, multicentre trial, the efficacy of a single infusion of axicabtagene ciloleucel[1] was evaluated in adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma, where the median time to response was 0.9 months (range: 0.8 to 6.2 months). Response durations were longer in patients who achieved complete remission (CR), as compared to patients with a best response of partial remission (PR). Of the 52 patients who achieved CR, 14 initially had stable disease (seven patients) or PR (seven patients), with a median time to improvement of 2.1 months (range: 1.6 to 5.3 months). ▶ Relapsed or Refractory Follicular Lymphoma (axicabtagene ciloleucel). ▶ Efficacy in FL is based on a single-arm, open-label, multicentre trial that evaluated a single infusion of axicabtagene ciloleucel in adult patients with relapsed or refractory FL after two or more lines of systemic therapy, including the combination of an anti-CD20 monoclonal antibody and an alkylating agent. Efficacy was established based on objective response rate and duration of response as determined by an independent review committee. The median time to response in the primary efficacy population was 1.0 month (range: 0.8 to 3.1 months). The overall Objective Response Rate was 91% [95% CI 83-96].
Known Risks	▶ The known risks – important identified risks – include Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions; neurologic toxicities, including fatal or life-threatening reactions; hypersensitivity reactions; serious infections; prolonged cytopenias; and hypogammaglobulinemia. ▶ Secondary malignancies and Replication-Competent Retrovirus (RCR) are considered important potential risks in the EU RMP based on theoretical mechanisms as thus far no causal association has been established. See full text below.
Benefit-risk assessment method	Basic/Judgement-based

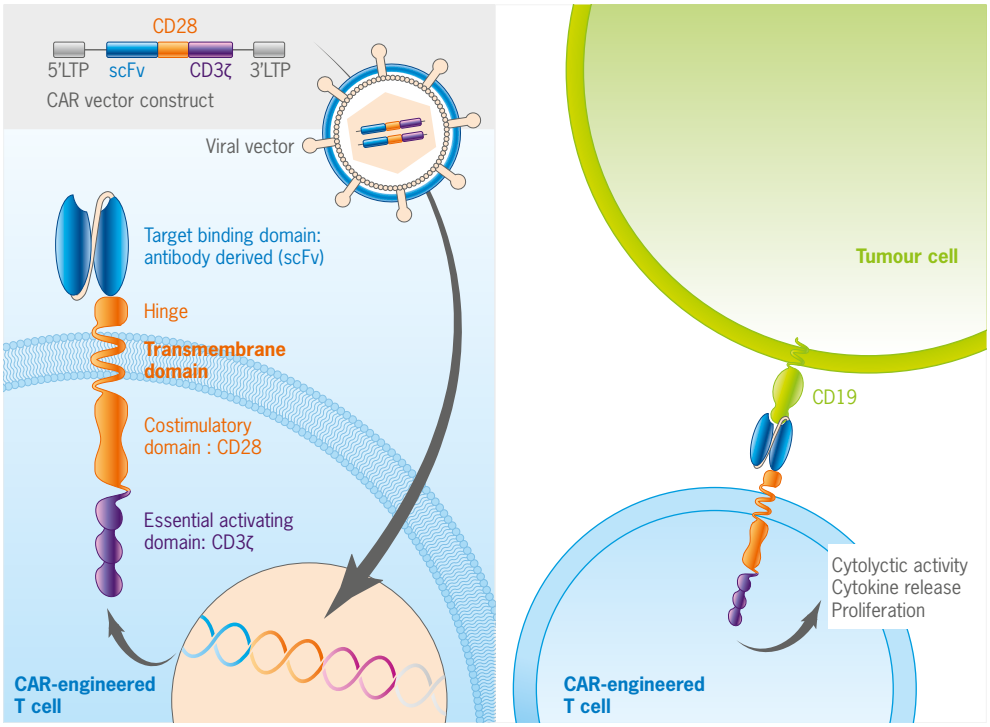
Assessment results	▶ The EMA and US FDA requested to conduct a long-term (15-year), non-interventional study of recipients of axicabtagene ciloleucel for the treatment of relapsed or refractory DLBCL, Primary mediastinal large B cell lymphoma (PMBCL) and FL utilising registries established by the European Society for Blood and Marrow Transplantation (EBMT) and the Center for International Blood and Marrow Transplant Research (CIBMTR), respectively. One of the objectives of these registries is to assess the rate of secondary malignancies and the generation of RCR in samples of patients with secondary malignancies. ▶ Per definition, a secondary malignancy is the development of a new malignancy suspected to be possibly related to gene-modified cell therapy (i.e. temporally associated with gene-modified cell therapy and without compelling alternate aetiologies). Consistent with the definition above, no cases of secondary malignancies were reported in the registries and post-marketing cases. ▶ A positive BR profile in the approved indications was established and the EMA granted a renewal of the license following the five-year MA renewal procedure.
Conclusion	Cell therapies present complex and extensive BRAs, sometimes associated with a high-level of scientific uncertainty that requires constant analysis, learning and readjusting over time. See full text below.

Background

Axicabtagene ciloleucel is a genetically modified autologous cell-based product containing T cells transduced ex vivo using a retroviral vector expressing an anti-CD19 CAR comprising a murine anti-CD19 ScFv linked to CD28 co-stimulatory domain and CD3-zeta signalling domain. Axicabtagene ciloleucel manufacturing relies on a replication-deficient murine γ-retroviral vector to stably integrate the anti-CD19 CAR transgene into the T cell genome (see Figure 19). As a result of this genomic integration, there is a theoretical risk of oncogenesis via insertional mutagenesis (for example, by disruption of gene expression (oncogenes or tumour suppressor genes) or alteration of gene expression by the regulatory regions within the vector). Since the vector is replication-defective, this integration to the genome can only happen once per viral vector. The potential for multiple integrations in the same cell is reduced by minimising the number of vector copies per cell during manufacturing.

Figure 19. Replication-deficient murine γ-retroviral vector stably integrates the anti-CD19 CAR transgene into the T cell genome

Source: Reproduced courtesy of Gilead Sciences, Inc.©



The vector packaging systems used in the early days of gene therapy were not designed to completely prevent recombination events between the vector and viral genes used to assemble the virions, and thus, rarely, RCRs were generated during manufacturing. These RCRs had properties similar to those of the wild-type virus, including the ability to cause malignancies by increasing the rate of integration events and, thus, the likelihood of oncogenic events. Although the process was improved since (i.e. the viral genes were separated into different plasmids, and the homology between the vector and packaging sequences were minimised to reduce the likelihood of any recombination events), these findings have been the basis for the RCR screening requirements issued by the US FDA and other regulatory bodies.

Therefore, when axicabtagene ciloleucel was granted MA in the EU on 23 August 2018, the EMA requested that secondary malignancy and RCR be included as important potential risks in the EU RMP. In addition, the EMA imposed a non-interventional Post-Authorisation Safety Study (PASS) as an additional pharmacovigilance activity to further characterise these risks. The Summary of Product Characteristic (SmPC) included instructions that patients should be monitored lifelong for secondary malignancies. If a secondary malignancy occurs, the company is to be contacted to obtain instructions on patient samples to be collected for testing.

Characterisation of the risks during clinical development

Kite clinical studies of axicabtagene ciloleucel employed a monitoring plan to assess the presence of RCR and the expansion and persistence of anti-CD19 CAR T cells in the peripheral blood of subjects treated with axicabtagene ciloleucel aiming to monitor the occurrence of engineered T-cell expansion and allow for retrospective analysis to determine whether a transformational event due to gretroviral insertion underlies the increased proliferative capacity of a particular T cell clone. The clinical monitoring plan included follow-up assessments for RCR at months 3, 6, and 12 for all subjects; additionally, subjects with positive RCR test results during the first year were to be monitored annually for 15 years. Further, quantitative polymerase chain reaction (PCR) was to be utilised to monitor for secondary expansion of anti-CD19 CAR T cells in the blood at multiple time points after infusion as defined in the study-specific protocol schedule of assessments. Should such an event occur, insertional sites were to be characterised in detail utilising methods such as linear amplification-mediated PCR and next-generation sequencing to fully characterise the location and nature of the integration site(s).

In addition, some clinical development protocols included instructions that if a subject were to develop a secondary malignancy during the study, every effort should be made to test for RCR in their blood and a biopsy sample of the neoplastic tissue.

Characterisation of the risks post-marketing and reflections from the five-year marketing authorisation renewal by the EMA

Post-marketing experience

Replication-Competent Retrovirus

Notably, the regulators were comfortable with the RCR safety of axicabtagene ciloleucel, and Kite was not required to test the commercial products for RCR during manufacturing. So the same scheduled testing performed during the clinical development program was no longer applicable to the post-marketing setting. Moreover, the PASS was not an adequate tool to address the RCR risk as it used secondary data from the EBMT registry and depended on the variables collected in the EBMT Cellular and Gene Therapy Form. It was revealed that certain variables might not be generated as part of routine medical practice, or local regulations limit the ability to collect the information. As a result, sampling for RCR testing was not collected in the EBMT Cellular and Gene Therapy Form. Eventually, only the incidence rate of secondary malignancies could be collected without the ability to determine a causal association with RCR.

After five years on the market, the question remains whether RCR could happen post-infusion due to a random recombination event with endogenous retroviral elements or following viral infections. Overall, no cases of RCR have been reported in Kite's clinical trials or post-marketing, as well as the literature that could establish a causal association between axicabtagene ciloleucel and the risk for RCR. Likewise, no RCR or replication-competent lentivirus cases have been reported in other CAR T cell products. With hindsight, there was no pre-defined mechanism to characterise the risk of RCR through routine or enhanced pharmacovigilance activities, and it was apparent that there is a need to develop a testing algorithm and a standard operating procedure to characterise the risk further if regulators wish to keep this risk highlighted in the RMP.

Secondary malignancies

To characterise the risk post-marketing, a secondary malignancy was defined as developing a new malignancy suspected to be possibly related to gene-modified cell therapy (i.e. temporally associated with gene-modified cell therapy without compelling alternate aetiology). As mentioned previously, the most plausible mechanism is insertional mutagenesis. However, it was realised that the PASS was not suited to characterise the risk, and in the post-marketing setting, there was neither a testing algorithm to prove a causal association nor a process to follow.

EU Risk Management Plan update during the five-year marketing authorisation renewal

The five-year MA renewal in Europe was a good opportunity to reflect on the EU-RMP and determine whether the risks made sense and if the pharmacovigilance plan and RMMs fit the purpose.

As mentioned previously, the main mechanism by which secondary malignancy can theoretically occur following axicabtagene ciloleucel treatment is insertional mutagenesis of the CAR construct into regions of the T-cell genome resulting in an oncogenic event or generation of RCR. The undesirable clinical outcome of both scenarios is a secondary malignancy of T cell origin; thus, combining the two risks to an important potential risk of secondary hematologic malignancy (including due to RCR) was proposed in the RMP during the five-year MA renewal. The rationale that was provided in the RMP was as follows:

1.) *The level of CAR T cells decreases and reaches near-undetectable levels over time;*

2.) *Thus far, no evidence of the occurrence of recombination events that led to the generation of replication-competent endogenous retroviruses has been reported, although 8% of the genome is composed of retroviral elements; if such a recombination event occurs, the probability of initiating a solid tumour oncogenic event is negligible as the emergent RCR would require appropriate tropism and pseudotyping (ability to recognise target cells through compatible viral envelope glycoproteins) to infect non-hematopoietic cells.*

Since genetic recombination events were not expected to occur outside T-cells, there was a limited rationale for testing non-haematological cancers. Therefore, secondary hematologic malignancy (including due to RCR) was considered the most appropriate risk to follow in the post-marketing setting.

To begin with, it was assumed that the risk of insertional mutagenesis and RCR is extremely low, and compared to the excellent efficacy, there was no doubt that the BR ratio is positive. Supportive evidence for this notion accumulated over time, and more publications demonstrated no increased risk of subsequent malignancy in patients treated with CAR T products. Long-term results from clinical trials to evaluate gammaretroviral vector engineered T-cells for HIV showed that CAR T-cells were detected in 98% of samples tested for at least 11 years post-infusion; however, there was no evidence for any suspected or documented occurrences of hematologic disorders suggestive of retroviral genotoxicity. The clinical data set represented over 540 patient years without integration mediated toxicity, therefore, based on a Poisson distribution assumption, they were 95% confident that the true AE rate is less than 0.0068 per person-year, or equivalently, no more than one event in every ~147 years.[2] As a result, more investigators questioned whether relaxing the uniquely intensive and prolonged monitoring is warranted. Thus, at the time of MA renewal, it was apparent that it is debatable if these risks should even be considered important in the context of the RMP.

The Committee for Advanced Therapies response

The Committee for Advanced Therapies (CAT) acknowledged that the undesirable clinical outcome of RCR is a secondary hematologic malignancy and combining RCR with the risk of secondary malignancy was acceptable. However, they raised a concern that while insertional mutagenesis and, thus, secondary malignancies of T cell origin are the primary concern, the risk for non-hematologic malignancies cannot be fully excluded. For example, a theoretical concern is that CAR-T-mediated prolonged depletion of normal CD19-expressing B-cells may render patients more susceptible to tumorigenesis due to impaired anti-tumour immunity. As such, the mechanism would not be limited to haematological malignancies; thus, the risk should reflect the general concern of secondary malignancy.

Although prolonged B-cell depletion can, in theory, be pro-tumorigenic, recent studies show no increase in the rate of malignancies in other patient populations treated with B-cell depletion.[3,4,5] Also, it would be extremely hard to establish a causal association with axicabtagene ciloleucel as all patients are treated with prior chemotherapies, including anti-CD20 antibody therapy, which will impair the ability to determine with absolute certainty the cause of the secondary malignancy, especially with the low incidence of secondary malignancies seen with axicabtagene ciloleucel during the last five years. The pharmacovigilance plan, as mandated by the regulators, is very unlikely to further the benefit-risk profile of the product, particularly in terms of patient risks linked to the treatment as opposed to background events.

Following Kite's pushback, the EMA agreed that there is no evidence to suspect a causal relationship between axicabtagene ciloleucel and non-haematological secondary malignancy and the proposed rephrasing of the safety concern to 'Secondary hematologic malignancy (including due to RCR)' was accepted.

Summary

This example shows the complexity of defining cell-therapy risks, foreseeing their appropriate pharmacovigilance activities, and the learnings acquired over time. It also emphasises the importance of the five-year MA renewal as a time to reflect, gain a better understanding and readjust the RMP for a better BRA that is more suited to characterise the risks post-marketing. Even before the MA renewal, there was a realisation that using secondary data from registries has limitations regarding controlling the variables to be collected, access to patient-level data, and satisfying the regulators that had much higher expectations regarding the data collection and what could be provided. Another lesson is that much more thinking and planning must be exercised in the transition from clinical trials to the post-marketing setting in determining the appropriate and feasible routine and enhanced pharmacovigilance activities for an optimal BRA. For example, developing processes for sampling and testing, identifying vendors/laboratories that would be able to provide standardised testing across all territories, and identifying responsibilities within the company to liaise with health care professionals, all of which require intense cross-functional collaboration ranging from drafting scientific position papers to execution of the plan by the field teams. In conclusion, cell therapies have more complex and extensive BRA that require constant analysis, learning and readjusting over time.

Appendix I – Case study D – References

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4 van Vollenhoven RF, Fleischmann RM, Furst DE, Lacey S, Lehane PB. Longterm Safety of Rituximab: Final Report of the Rheumatoid Arthritis Global Clinical Trial Program over 11 Years. The Journal of rheumatology 2015;42 (10):1761-6. https://doi.org/10.3899/jrheum.150051 (PDF accessed 8 September 2024).

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E. Varenicline (Chantix) and serious neuropsychiatric events

This case study illustrates the employment of innovative elements in clinical study design to confirm or refute signals in post-marketing settings as to contribute to the BRA. It highlights the:

- Challenges of evaluating and integrating data from multiple sources, including but not limited to post-marketing data, clinical studies, observational data and non-clinical evidence;
- Need for innovative study designs and tools to rigorously test the signals generated by spontaneous post-marketing reports;
- Importance of stakeholder involvement (key opinion leaders, health care professionals, and patients) into the decision-making process.

TOPIC	SUMMARY INFORMATION
Purpose/ Objective of the case study example	This case study illustrates the employment of innovative elements in clinical study design to confirm or refute signals in a post-marketing setting as to contribute to a BRA.
Indication/ Disease treated	Varenicline (Chantix) is a nicotinic receptor partial agonist indicated for use as an aid to smoking cessation treatment.
Benefits	The significant worldwide burden of illness imposed by smoking, and the reduction in that burden achieved by quitting, are both well-documented, placing smoking cessation among the most valuable of public health measures. Cigarette smoking is a risk factor for six of the eight leading causes of death, including heart disease, stroke, lung disease, tuberculosis, and lung cancer. Varenicline has shown consistent efficacy across studies of generally healthy adult smokers in different geographical regions and in smokers with co-morbidities such as cardiovascular disease and COPD.
Known risks	During the pre-marketing development, over 4500 subjects were exposed to varenicline, with over 450 treated for at least 24 weeks and approximately 100 for a year. Most study participants were treated for 12 weeks or less. In the placebo-controlled, pre-marketing studies, the most common AEs associated with varenicline (>5% and twice the rate seen in placebo-treated patients) were nausea, abnormal (vivid, unusual, or strange) dreams, constipation, flatulence, and vomiting.

TOPIC	SUMMARY INFORMATION
Background	A post-marketing safety signal of serious Neuropsychiatric Symptoms (NPS) AEs emerged shortly after approval. The safety signal was based on an increased spontaneous reporting rate of serious NPS AEs, which was apparently stimulated by high-profile media coverage of a musician who was taking varenicline and fatally shot a neighbour following a dispute with his partner. In the absence of large, population-based observational studies that analysed the NPS safety of varenicline, the available clinical data were not adequate to confirm or rule out an association, and it was acknowledged that an analysis of spontaneous post-marketing reports would not be sufficient to assess the association, given the limitations of spontaneous reporting being generally utilised as a hypothesis-generation tool, rather than a hypothesis-testing tool. The Regulatory Authorities (e.g. US FDA, EU EMA) initiated evaluation procedures and the varenicline labels (e.g. US, EU) were conservatively updated to alert the prescribers and patients to the potential risk of such events occurring.
Benefit-risk assessment method	A large clinical study with novel elements aiming to overcome the inherent limitations of the post-marketing data (e.g. reporting bias, lack of a standardised endpoint, the inability to establish incidence rates, lack of a control group, etc.) and to improve collection of NPS AEs was conducted to rigorously test the signal. The EAGLES was a randomised, double-blind, triple-dummy, placebo- and active-controlled study, with four treatment arms: varenicline, bupropion, Nicotine Replacement Therapy (NRT), and placebo to compare the risk of clinically significant NPS events, and to determine whether individuals with prior history of psychiatric disorders are at greater risk for development of clinically significant neuropsychiatric events compared to individuals without such history, while using varenicline as an aid to smoking cessation.[1] The EAGLES study design included novel design elements and procedures to help ensure robust and thorough collection of NPS data, such as: ▶ The Neuropsychiatric Event Interview (NAEI), a novel instrument developed specifically for this study, to be used as a semi-structured interview to systematically solicit patients to report the presence and severity of NPS events of interest through a series of targeted questions, used along the common validated psychiatric rating scales (C-SSRS, HADS, CGI-I) and required mental health assessments; ▶ A composite neuropsychiatric AE endpoint, developed specifically for the study, to allow for increased sensitivity in detecting treatment and/or cohort differences in the rates of NPS events. The endpoint was composed of 16 components, representing distinct psychiatric constructs selected to cover the spectrum of events reported in post-marketing cases. The study was complemented by additional analyses from other RCTs, observational studies, and non-clinical investigations, taking into account varenicline's mechanism of action and non-clinical profile, in determining causality for this type of AE. The results were discussed in a public Advisory Committee Meeting[2] that allowed stakeholders (experts, health care providers, and patient representatives) to present data, information and views.

TOPIC	SUMMARY INFORMATION
Assessment results	The EAGLES study initiated in 2011 and enrolled 8144 subjects at 140 investigative centres in 16 countries. The EAGLES study did not support an increased risk of serious NPS AEs with varenicline treatment compared to a placebo, or compared with a NRT patch, regardless of a subject's psychiatric history. The study outcomes also showed that serious NPS AEs occur in subjects attempting to quit smoking regardless of smoking cessation treatment. With respect to efficacy, EAGLES confirmed varenicline as the most effective monotherapy treatment option currently available for smokers who want to quit. Overall, the totality of scientific evidence from the signal investigation – meta-analysis of RCTs, large observational studies and EAGLES outcomes – did not support an increased risk of serious NPS AEs with varenicline treatment compared to treatment with a placebo or NRT patch (available OTC). The feedback from the majority of stakeholders (health care professionals and patients) provided during the US Advisory Committee meeting public session also emphasised the public health value of smoking cessation with varenicline.
Conclusion	The collective data indicated that the potential risk of serious NPS AEs with varenicline use was substantially lower than previously suspected. Overemphasis of risks can lead to reduced utilisation, and therefore impact public health benefit. The varenicline US label was updated to remove the language describing the serious mental health side effects from the Boxed Warning, and the results from the EAGLES clinical trial were incorporated in the warnings section of the label, and similar changes were implemented in other countries and regions, e.g. EU.[3]

Appendix I – Case study E – References

1 Anthenelli RM, Benowitz NL, West R, St Aubin L, McRae T, Lawrence D, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. Lancet 2016;387:2507-20. https://doi.org/10.1097/jcp.0000000000001015 (PDF accessed 8 September 2024).

2 The United States Food and Drug Administration. 2016 Meeting Materials, Psychopharmacologic Drugs Advisory Committee. 2018. (Website accessed 8 September 2024).

3 European Medicines Agency (EMA). Procedural steps taken and scientific information after the authorisation. 2023. (PDF accessed 8 September 2024).

APPENDIX II.
EXAMPLE OF A COMPANY BENEFIT RISK ASSESSMENT DOCUMENT

The following is an example Benefit risk assessment document (BRAD) based on the FDA Benefit-risk framework.[1] This is intended to be an example template that each company is welcome to modify as appropriate for its needs.

CONFIDENTIAL
[DRAFT# OR FINAL] [DD MONTH YYYY]

STRUCTURED ASSESSMENT OF BENEFIT RISK

[INVESTIGATIONAL/TRADE DRUG NAME]

[INDICATION]

Note: General technical document instructions inserted here (eg, navigation through document, referencing process)

Identity of (Investigational) Medicinal Product:	
Indication(s):	
Effective Date:	
Version Number:	
Replaces Version / Date:	
Rationale for the update	

(This document is an internal guide for assessment of structured benefit-risk framework during the product lifecycle and is not intended to be a legal or regulatory document. *Further legal wording to be inserted around confidentiality, as per company procedures.)*

1 [INVESTIGATIONAL/TRADE DRUG NAME] [INDICATION]

EXECUTIVE SUMMARY

This is the Benefit-Risk Assessment Document (BRAD) for [Investigational/Trade Name] prepared in anticipation of <insert status ofproduct lifecycle, eg, "IND/CTA submission", "entering P2/POC", "start of P3", "filing for NDA/MAA", "PBRER with data lock ofdd mm yyyy", etc.>.

[Investigational/Trade Name] is a [describe the therapeutic class] that is being administered [insert route(s) ofadministration] in clinical studies as [Dose and Formulation] for the treatment of [Indication]. [Describe mechanism of action, if known]

Table 1-1. Benefit-Risk Summary and Assessment

[Insert Structured Benefit-Risk Framework selected by company/team. In the current instance, the SBRF selected aligns with the US FDA SBRF]

Benefit-Risk Summary and Assessment		
Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk and Risk Management		

Table 1-2. Effects Table

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of Evidence	References
Favourable Effects						
Unfavourable Effects						

[Follow with **Table of Contents** *and* L**ist of Abbreviations]**

1. MODULE I – ANALYSIS OF CONDITION

1.1. Indication

1.2. Medical Condition or Disease

1.2.1. Summary of Medical Condition or Disease

1.2.2. Medical Condition or Disease

2. MODULE II – CURRENT TREATMENT OPTIONS

2.1. Therapeutic Options

2.1.1. Summary of Therapeutic Options

2.1.2. Therapeutic Options

2.2. Medical Need

2.2.1. Summary of Medical Need

2.2.2. Medical Need

2.3. Key Characteristics of the Product(s)

2.3.1. Summary of Key Characteristics of the Product(s)

2.3.2. Key Characteristics of the Product(s)

3. MODULE III – BENEFIT

3.1. Key Benefits

3.1.1. Summary of Key Benefits

3.1.2. Key Benefits

Table 3-1. Table of Ke Benefits

Key Benefit	Optimizing Benefits

Table 3-2. EMA Effects Table, Benefit Part

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of Evidence	References
Favourable Effects						

4. MODULE III – RISK AND RISK MANAGEMENT

4.1. Key Risks

4.1.1. Summary of Key Risks

4.1.2. Key Risks

Table 4-1. Table of Key Risks

Risk	Key? (Yes/No)	Additional Risk Information	Comments

Table 4-2. EMA Effects Table, Risk Part

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of Evidence	References

4.2. Risk Management Needs

4.2.1. Summary of Risk Management Needs

4.2.2. Risk Management Needs for Key Risks

Table 4-3 Summary of Risk Management Activities for Key Risks

Risks	Key? (Yes/No)	Additional Risk Information	Nonclinical data	Clinical data	Action Plans for Risk Evaluation	Action Plans for Patient Risk Minimization

Table 4-4. Description of Routine Risk Minimisation Measures by Identified/Potential Risk

Identified/Potential Risk	Routine Risk Minimisation Activities

Table 4-5. Additional Risk Minimisation Measures/Risk Evaluation and Mitigation Strategies

Additional Risk	Risk Minimisation Measure/Risk Evaluation and Mitigation Strategies

5. ANNEX

Annex 1. Summary of Risk Management Activities for Key Risks during Drug Development

Annex 2. Summary Table of Uncertainties

Table 5-1. Summary Table of Uncertainties

Uncertainty (Disease, Treatment options, Benefit, Risk, etc.)	Action Plan	Milestone	Outcome and Action

Uncertainty (Disease, Treatment options, Benefit, Risk, etc.)	Action Plan	Milestone	Outcome and Action

Annex 3. Local or Regional Considerations

Table 5-2. Regional Considerations for <insert region/country

Benefit-Risk Summary and Assessment		
Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk		
Risk Management		

Table 5-3. Regional Considerations for <insert region/country

Benefit-Risk Summary and Assessment		
Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk		
Risk Management		

Annex 4. Summary of Changes to the BRAD Over Time

Version	Internal Approval Date	Rationale for Update	Changes	Impacted Documents or FARs

Version	Internal Approval Date	Rationale for Update	Changes	Impacted Documents or FARs

6. REFERENCES (IF APPLICABLE)

7. EXAMPLES & RESOURCES FOR INTERNAL USE

7.1. Link to FDA Benefit Risk 2021 draft guidance

- Benefit-Risk Assessment for New Drug and Biological Products Guidance for Industry

7.2. Link to ICH M4E(R2) 2016

- Revision of M4E guideline on enhancing the format and structure of benefit-risk information in ICH
  - The Benefits and Risks Conclusion is Section 2.5.6

Appendix II – Reference

1 The United States Food and Drug Administration (FDA). Benefit-Risk Assessment for New Drugs and Biological Products. 2023. (Website accessed 8 September 2024).

APPENDIX III.
CIOMS WG XII STATEMENT

COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES

ESTABLISHED UNDER THE AUSPICES OF THE WORLD HEALTH ORGANIZATION AND UNESCO

CIOMS

CONSEIL DES ORGANISATIONS INTERNATIONALES DES SCIENCES MEDICALES

FONDE SOUS LES AUSPICES DE L'ORGANISATION MONDIALE DE LA SANTE ET DE L'UNESCO

3 June 2020

Medicines assessment during public health emergencies needs good science, best practices and proper communication

Statement[1] of Council for International Organizations of Medical Sciences (CIOMS) International Expert Working Group[2]

Following the essential principles of evidence-based medicine and regulatory decision-making remain key also in times of public health emergencies. As has been the case with the COVID-19 pandemic, such emergencies can develop rapidly, and much-needed, robust, scientific data may not be immediately available to close the knowledge gaps. Pressures to make decisions without proper evidence have the potential to overcome sound scientific judgement and lead to unjustifiable conclusions, as well as the use of unproven therapies that may be ineffective or harmful, and have a further negative impact on public health.

One of the most complex, scientific activities during public health emergencies is to determine whether a candidate medicine intended to prevent or treat the disease is effective, and establish whether its expected benefits outweigh its potential risks to patients. This assessment is based on all available evidence about the medication and the surrounding situation including: the severity of the disease; how well patients' medical needs are addressed by alternative, available therapies; the uncertainty around how data from clinical trials or testing environments extrapolate to real-life situations; and whether specific risk management measures need to be applied to mitigate known and/or potential risks. In the case of a public health emergency, such information is often not readily available in sufficient quantity or quality to adequately support evidence-based decision-making, and the urgency of the decision context magnifies the potential consequences of action or inaction.

When decision-making in the face of high uncertainty cannot be avoided, increased focus on monitoring the safety and effectiveness of such new therapies once they are approved for use in the public domain is critical. Considerations for this expanded surveillance role should include appropriate, evidence-generating or adverse reaction monitoring strategies such as: phase IV clinical trial studies; observational studies; manufacturer-run patient registries and/or patient support programmes; patient focus groups and implementing proactive adverse reaction monitoring strategies. The monitoring of "repurposed" medicines will also be necessary under the different uses made in the pandemic, since their efficacy/effectiveness remain to be confirmed and their safety profile may well be different in a different indication. In addition, the acceptability of potential harms may be different than in other indications.

The contemporary pharmaceutical development systems benefit from the collaborative efforts of multiple stakeholders including regulators, industry, academia, patients, health-care providers and health insurers, all of whom contribute to increasing knowledge about benefit/risk relationships and the consideration of the uncertainties. When facing a public health crisis, we urge all concerned parties to maintain solid, scientific, and evidence-based principles and best practices for conducting the proper benefit/risk assessment of potential new prevention or therapy options. Among others, potential confounders and possible bias should be considered when assessing available data. All parties should uphold full transparency of the decision-making process, with a high degree of focus on the relevance of the therapy decision for the patients being treated during the emergency.

In the midst of an emergent health crisis, stakeholders should follow best practices for communication and provide information that is timely, accurate, credible, understandable, actionable, consistent, and empathetic. Poor communication, such as a lack of information; unexplained changes in key messages; or failure to communicate uncertainties can undermine credibility and disrupt risk mitigation efforts.

Members of the various CIOMS Working Groups are working to define and advance measures and approaches to improve the development and benefit/risk assessment of new therapies and enhance public health. We wish to applaud the efforts of the health-care and scientific communities, including practitioners, regulators and patients, who have come together to fight COVID-19 and hope that the CIOMS Working Groups' outcomes can also be helpful in addressing the product-related challenges and future decision-making during public health emergencies.

[1] Disclaimer. The views and opinions expressed in the statement above are consolidated views of the participants of the CIOMS Working Group and should not be attributed to any individual expert in those or any organization with which these individuals are employed or affiliated.

[2] CIOMS Working Group WG XII: Benefit-Risk Balance for Medicinal Products – Update of CIOMS IV. More about the Working Group and the List of its members.

APPENDIX IV.
CIOMS WORKING GROUP MEMBERSHIP AND MEETINGS

The CIOMS Working Group XII on *Benefit-risk balance for medicinal products* included the following groups of stakeholders: academics and pharmacovigilance, pharmaceutical companies, regulatory authorities, and World Health Organization.

Academics and pharmacovigilance		
Name	**Company/Organisation**	**Country**
Evans, Scott	Milken Institute School of Public Health, George Washington University	USA
Evans, Stephen	London School of Hygiene & Tropical Medicine	United Kingdom
Yue, Qun-Ying	Uppsala Monitoring Centre	Sweden

Pharmaceutical companies		
Name	**Company/Organisation**	**Country**
Caubel, Patrick	Pfizer	USA
Da Silva-Tillmann, Barbara	AbbVie	USA
Geary, Stewart	Eisai	Japan
Ianos, Claudia	Pfizer	USA
Kaplan, Karen	MSD	USA
Laljee, Hussein	Gilead	United Kingdom
Mt-Isa, Shahrul	MSD	Switzerland
Oladipo, Anthony	AbbVie	USA
Plouffe, Leo	Gilead	USA
Quartey, George	Roche	USA
Renz, Cheryl	Formerly AbbVie	USA
Strauss, Carmit	Takeda	USA
Tcherny-Lessenot, Stéphanie	Sanofi	France
Verdugo, Maria	AbbVie	USA
Vulcu, Sebastian	Boehringer-Ingelheim	Germany
Zhang, Xi	Gilead	USA

Regulatory authorities		
Name	**Company/Organisation**	**Country**
Asami, Ezaki	Pharmaceuticals and Medical Devices Agency (PMDA)	Japan
Corrêa de Matos, Guacira	Brazilian Health Regulatory Agency (ANVISA)	Brazil
Glagolev, Sergei*	Federal Service for Surveillance in Healthcare (Roszdravnadzor)	Russian Federation
Hogan, Vicky	Health Canada	Canada
Ikuma, Mutsuhiro	Pharmaceuticals and Medical Devices Agency (PMDA)	Japan
Kawarazaki, Shuichi	Pharmaceuticals and Medical Devices Agency (PMDA)	Japan
Khosrovani, Sara	Medicines Evaluation Board (MEB)	The Netherlands
Kuga Wataru	Pharmaceuticals and Medical Devices Agency (PMDA)	Japan
Mari, Kihara	Pharmaceuticals and Medical Devices Agency (PMDA)	Japan
Noriaki, Kitami	Pharmaceuticals and Medical Devices Agency (PMDA)	Japan
Salmonson, Tomas	Consilium Salmonson and Hemmings, formerly Chair at Committee for Medicinal Products for Human Use (CHMP)	Sweden
Storre, Stephanie	Swissmedic	Switzerland
Straus, Sabine	Medicines Evaluation Board (MEB)	The Netherlands
Thirstrup, Steffen	European Medicines Agency (EMA) / University of Copenhagen / Copenhagen Centre of Regulatory Science	Denmark
Tsukuda, Mariko	Pharmaceuticals and Medical Devices Agency (PMDA)	Japan
Williams, Julie	Medicines and Healthcare products Regulatory Agency (MHRA)	United Kingdom

World Health Organization (WHO)		
Name	**Company/Organisation**	**Country**
Eun Mi, Kim	WHO	Switzerland
Goto, Takahiro	WHO	Switzerland
Gwaza, Luther	WHO	Switzerland
Pal, Shanthi	WHO	Switzerland
Takanashi, Fumihito	WHO	Switzerland

CIOMS		
Name	**Company/Organisation**	**Country**
Hill, Sanna	CIOMS	Switzerland
Le Louët, Hervé	CIOMS	Switzerland
Rägo, Lembit	CIOMS	Switzerland
Tsintis, Panos	CIOMS Adviser	United Kingdom

*Participated only in the 1st meeting on 17-18 September 2019.

The Working Group XII met 12 times from 2019 to 2023. Most of the meetings took place virtually except for the first meeting, which was held in-person in Geneva, Switzerland. The meetings took place as follows:

1. 17-18 September 2019
2. 29-30 April 2020
3. 8 September 2020
4. 2-3 March 2021
5. 18 June 2021
6. 21 September 2021
7. 11 April 2022
8. 14 September 2022
9. 26 January 2023
10. 23 May 2023
11. 12 October 2023
12. 20 November 2023

The CIOMS Working Group XII Editorial Team met 15 times from September 2023 to October 2024.

APPENDIX V.
LIST OF PUBLIC CONSULTATION COMMENTATORS

Name	Company/Organisation	Country/region
Bherwani, Anand	GE Healthcare	USA
Chong, Susan	Amgen	USA
Colopy, Michael	UCB	Belgium
Desai, Ankur	Amgen	USA
Frey, Patrick	Amgen	USA
Gonzalez, Danny	Gilead Sciences	USA
Grüger, Thomas	Federal Institute for Drugs and Medical Devices (BfArM)	Germany
Hauber, Brett	Pfizer	USA
Hibberd, Mark	GE Healthcare	USA
Ho, Jeffrey	Perigent	United Kingdom
Kamath, Padmaja	Global Self-Care Federation	Switzerland
Kumar Buddha, Siva	Pharmacovigilance Consultant and SME	India
Members of the association	German Pharmaceutical Industry Association	Germany
Members of the group	European Federation of Statisticians in the Pharmaceutical Industry (EFSPI)/PSI, Benefit-Risk Special Interest Group (BRSIG)	Europe
Norton, Jonathan	Takeda	USA
Pharmacovigilance Working Group	European Clinical Research Organisation (CRO) Federation (EUCROF)	Germany
Representative	AstraZeneca	USA
Representative	Bristol Myers Squibb	USA
Representative	Roche	Switzerland
Roessink, Burkhard	GE Healthcare	USA
Seifert, Karin	Federal Institute for Drugs and Medical Devices (BfArM)	Germany
Sun, Stephen	PharmaLex	USA
Thakur, Rohit	Novo Nordisk A/S	India
Tremmel, Lothar	CSL Behring	USA

This report provides insights into the methods used to evaluate the benefit-risk (BR) balance of a medicinal product. A favourable BR profile must be established for all medicinal products prior to marketing. This balance must be reassessed periodically in the post-marketing setting when new information regarding the benefits and risks, or the landscape of their application, becomes available. This report builds on the foundations of the CIOMS Working Group IV report published in 1998, and entitled: *Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals*; and expands to BR management throughout a product's lifecycle using structured approaches and updated methodologies.

This report reflects the consensus opinion of the CIOMS Working Group XII members, including experts in BR assessment drawn from academia, industry, and regulatory organisations. It was finalised after considering comments received during a public consultation.

The report is intended for medicinal product developers, regulatory authorities, and key stakeholders including academic and government researchers, healthcare professionals, and patients/consumers – all those interested in how the balance between the benefits and risks associated with a medicinal product is established and managed.

Benefit-risk balance for medicinal products. Report of the CIOMS Working Group XII. Geneva: Council for International Organizations of Medical Sciences (CIOMS), 2025.

This publication is freely available on the CIOMS website.

CIOMS publications may be obtained through the publications emodule at https://cioms.ch/publications/. CIOMS, P.O. Box 2100, CH1211 Geneva 2, Switzerland, www.cioms.ch, email: info@cioms.ch.

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