Benefit-risk balance for medicinal products

CIOMS Working Group report
Draft, 12 June 2023

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Please note that the layout will be improved in the final version, and best efforts will be made to correct remaining typographical and/or grammatical errors, as well those pertaining to references.

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Suggested citation: Benefit-Risk Balance for Medicinal Products.

CIOMS Working Group report. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2023.

DOI number tbc

This publication is freely available on the CIOMS website at:
tbc

Acknowledgements

(to follow)

Table of contents

List of tables, figures and boxes

List of boxes

List of figures

List of tables

Abbreviations

ADR	Adverse Drug Reaction
AML	Acute myelocytic leukaemia
AR	Absolute risk
ARLG	Antibacterial Resistance Leadership Group
AF	Atrial fibrillation
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
CBER	Center for Biologics Evaluation and Research (of the US FDA)
CCDS	Company Core Data Sheet
CDC	Centers for Disease Control & 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 Intervals
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus disease 2019 (the illness caused by severe acute respiratory syndrome coronavirus 2 – SARS-CoV-2)
CIRS	Centre for Innovation in Regulatory Science
CMR	Centre Medical Research
CMO	Chief Medical Officer
CRE	Carbapenem-resistant Enterobacteriaceae
CTA	Clinical Trial Application
CTTI	Clinical Trials Transformation Initiative
DMC	Data Monitoring Committee
DCDS	Development Core Data Sheet
DCE	Discrete choice experiments
DCIS	Ductal carcinoma in situ
DDI	Drug-drug interactions
DDFS	Distant disease-free survival
DFS	Disease-free survival

DMC	Data Monitoring Committee
DOOR	Desirability of outcome ranking
DRMP	Developmental risk management plan
DSUR	Development safety update report
ECG	Electrocardiogram
ED	Emergency department
EFSPI	European Federation of Statisticians in the Pharmaceutical Industry
EGFR	Epidermal growth factor receptor
EPF	European Patients' Forum
ER	Oestrogen receptor
EU	European Union
EUPATI	European Patients Academy on Therapeutic Innovation
FAERS	Food and Drug Administration Adverse Event Reporting System
EMA	European Medicines Agency
EVDAS	EudraVigilance date analysis system
GBCA	Gadolinium-based contrast agents
Gd	Gadolinium
GE	Gastroenteritis
HCP	Health care professional
HTA	Health Technology Assessments
IB	Investigator's brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSR	Individual Case Safety Report
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
NH	Null hypothesis
IND	Investigational New Drug
ITT	Intention-to-treat
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
JADER	Japanese Adverse Drug Event Report Database
KBRS	Key Benefit-Risk Summary

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)
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NDA	New Drug Application
NIS	National Immunization Survey
NOAC	Novel oral anticoagulant
NOAEL	No Observed Adverse Effect Level
NVAF	Nonvalvular atrial fibrillation
OAC	Oral anticoagulant
PBRER	Periodic Benefit-risk Evaluation Report
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
PrOACT-URL	Problems, Objectives, Alternatives, Consequences, Trade-offs, Uncertainties, Risk attitudes/risk tolerance, Linked decisions
PSI BRA SIG	Statisticians in the Pharmaceutical Industry Benefit-risk assessment Special interest group
PCT	Pragmatic clinical trial
QD	Quaque die [one per day]
QoL	Quality of life
QSPI BRWG	Quantitative Sciences in Pharmaceutical Industry Benefit-Risk Working Group
RCT	randomised controlled trial

REMS	Risk evaluation and mitigation strategy
RMM	Risk minimisation measures
RMF	Risk Management File
RMP	Risk Management Plan
RT	Rotavirus
RTGE	Rotavirus-associated gastroenteritis
RV	Rotavirus vaccine
RWD	Real-world data
RWE	Real-world evidence
SBRF	Structured benefit-risk framework
SAE	Serious adverse event
SAG	Scientific advisory group
SAP	Statistical analysis plan
SIG	special interest group
SMQ	Standardised MedDRA Query
SMT	Safety management team
TEAE	Treatment emergent adverse event
TTDR	Time to distant recurrence
UK	United Kingdom of Great Britain and Northern Ireland
UMBRA	Unified Methodologies for Benefit-Risk Assessment
UN	United Nations
URT	Uncertainty reduction theory
US	United States of America
US FDA	US Food and Drug Administration
VAC4EU	Vaccine monitoring Collaboration for Europe
WHO	World Health Organization

Foreword

We must establish a benefit-risk (BR) balance for all medicinal products – such as drugs, biologics and devices – prior to their marketing, and reassess this balance periodically in the post-marketing setting when new information arises regarding the benefits and risks, or the landscape of their application. This report provides insights into the current thinking and methods used to evaluate the BR balance of a medicinal product, and it provides an update to the report of the CIOMS Working Group IV, published in 1998, entitled BR Balance for Marketed Drugs: Evaluating Safety Signals.

The report emphasises the use of structured framework as a core for every BR assessment (BRA), and additional quantitative analysis to support structured BRA for certain complex problems. This report presents new, key concepts for consideration when thinking about benefits and risks, including the need to take a lifecycle approach. This involves assessing a product's BR balance from early development, reassessing when new information becomes available through the regulatory process, ongoing monitoring, and use in healthcare 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 in all aspects of the assessment and risk management process. The report describes the importance of selecting an appropriate assessment method, which includes input from patients who have direct experience with a medicinal product and of the need to follow a standardised and/or structured approach when assessing and reassessing the BR relationship 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 industry, regulatory organisations, and academia. It is anticipated that this document will provide important insights on the topic to a variety of different stakeholders including product developers, regulatory authorities, academic researchers and patients, who have personal experience with the products or are interested in how the balance between the benefits and risks associated with a medicinal product is established.

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 harms is identified during the lifecycle of a medicinal product. Examples from case studies are used to illustrate pragmatic approaches to assessing /reassessing BR in a variety of different circumstances. This report touches briefly on the decision making needed in taking appropriate actions to manage newly identified risks. However, more detailed sources of information on this topic are 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 discusses the BR landscape and provides information on the up-to-date context surrounding BRA of medicinal products and discusses newer BR methods and how to assess them to determine their fitness for use. The chapter also provides some 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 contribution of patients to assessing benefits and risks. The importance of seeking out and including the patients' voice in the overall assessment of benefit-risk is emphasised in this chapter. For further insight into the important way patients engage in all aspects of medicine development, regulation and product 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 BR methodology considerations and includes a discussion on the fundamental principles in assessing BR. Two new points of emphasis include: (1) a transition from BR evaluation as a post-hoc exercise to proactively incorporating BR considerations into clinical trial design using a structured approach, and (2) a pragmatic patient-centric approach to BRA to ensure proper reflection and evaluation of the benefits and harms as experienced by patients. Methods and current thinking on how to attain these goals are described. Key points to consider in addressing uncertainties are presented as are various approaches to visualisation of BRA and the importance of employing a multidisciplinary team, including patient perspectives, when assessing BR.

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, 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.

This report provides practical guidance on the conduct of high quality, balanced and comprehensive evaluation of benefits and risks to inform decision making, thereby helping all stakeholders to work together to meet patients' needs in the best possible way.

From the CIOMS Working Group XII

December, 2023, Geneva, Switzerland

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 methods to be used across the medicines lifecycle. We introduce new concepts and discuss how they relate to the BR assessment (BRA) of medicinal products.

New concepts in BR landscape presented in this report

- Start 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, 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 and conduct in contrast to a post-hoc analysis exercise;
- Assimilate pragmatic patient-centric BR methods;
- Include the patient perspective in the assessment of benefits and risks;
- Standardise approaches to evaluate the BR balance of medicines;
- Develop and continuously update appropriate documentation of the BRA during the product lifecycle.

Components of a SBRF

We aim to introduce the components of a SBRF, the lifecycle approach of BR and the role of the patient in the SBRF and the additional quantitative analysis 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 benefits and the 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 profile for the product is favourable or unfavourable.

We describe 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 and late development stage, to post-marketing/ on market stage.

We describe the importance of incorporating patient 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, selection of “key” benefits and “key” risks, and development of risk minimisation measures.

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

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

BR methodology

Here, we focus 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. For example, we make clear recommendations around membership of the team assembled to conduct the assessment.

We cover the considerations about the assessment of the BR methodologies, the role of study designs and predefined or post-hoc analysis. We also introduce innovative methods related to the patient-level BRA and the role of pragmatic or large simple trials. Then, we provide guidance on how to gain insights from patients, how to address uncertainties and how to visualise the BRA. Finally, we detail which functions are expected to be part to a multidisciplinary BRA team.

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

BR methods for special situations

Situations where there is an important lack of information on benefits and harms, and uncertainty over the magnitude of benefits and harms, creates 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 product, special populations such as rare diseases and paediatric, and advanced therapy medicinal products.

Conclusion

This report describes a number of recent new concepts in 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 harms. 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 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)[1] since the publication of CIOMS Working Group IV report published 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 advice on approaches, processes, and methods for conducting a BRA.

The report has four chapters. The first 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 two presents an overview of approaches to BRA, including examples from case studies to illustrate basic principles of BRA. Chapter three covers specific considerations for methods used in the BRA process. Chapter 4 tailors Chapters 2 and 3 for selected special situations. The report concludes with a series of appendices, including a glossary and case examples. For more details on how best to use this book, please refer to section 1.7 on How to use this book.

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 at the time of licensing, nor can it maintain its approval should new information significantly shift the BR balance post-approval. The previous considerations established by the CIOMS Working Group IV report published in 1998 focused on the post-approval phase of a medicines' lifecycle, but it is relevant to extend this to cover the pre-approval phase.

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, health insurers, 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 patients' role in decision making.

1.2 New products and new data sources

Pharmaceuticals have over the past 20 years developed from being small molecules and a few, simple biologicals (proteins or peptides) to also include complex biologicals (e.g. 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 drugs bring promise to influence the disease rather than only symptomatic relief and in

[1] The **benefit-risk assessment** is a process for evaluating the key benefits and key risks of a medicinal product, and determining whether the key benefits outweigh the key risks based on the weighing of these key benefits and key risks.
Source: Proposed by CIOMS Working Group XII, modified from ICH Harmonised Guideline. Revision of M4E Guideline on Enhancing the Format and Structure of Benefit-risk Information in ICH Efficacy M4E(R2). Current Step 4 Version.

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, we have seen an increase in the number of pharmaceuticals targeting rare or ultra-rare conditions where the ability to perform randomised clinical 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 experience data, for example, patient-reported outcomes 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, often, methodological challenges with these endpoints.

The above-described scientific developments, which are in many ways welcomed, are frequently inherently linked to the fact there remain important 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-approval 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 alignment of decision-making considerations between regulatory agencies and payers and health technology assessment bodies when a decision is based on data from post-approval clinical practice, for example real-world data (RWD).

Last, we would once again point to the fact that transparency in these BR approaches is of utmost importance as it allows other stakeholders, such as patients, to make informed decisions about their use of medical products.

1.3 New BR methods

In the last two decades there has been a shift in the approach to evaluating the BR profiles 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 are also 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, on the other hand, may also 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 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).

Several SBRFs have been proposed.[1,2,3,4] For example, the US 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.[6] 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.[7] The Unified Methodologies for Benefit-Risk Assessment (UMBRA) follows the same principles and contains all the key features of the other frameworks.[8] 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 may be supported/complemented with 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. A EMA methodology report suggested using quantitative approaches such as Multicriteria Decision Analysis (MCDA)[9] 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 benefit and risk at the patient level to help identify subgroups of patients who may experience greater benefits without associated increase in risks.

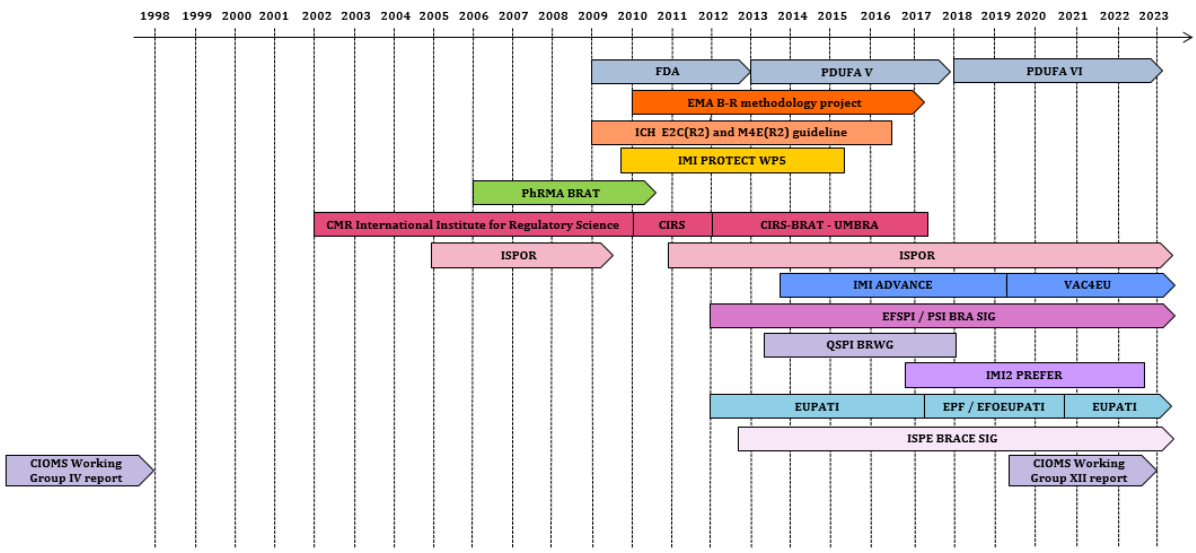
Therefore, a SBRF may be complemented and supported by quantitative BRA methods that include but are not limited to:[10] (i) methods for evaluating benefits and risks at each patient level to provide important insight on the interaction of benefits and risks across subsets and over time (ii) methods 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 BR 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 elsewhere instead hyperlinks are provided for more information.

Figure 1: Timeline of global BR 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.[11]



Abbreviations for Figure 1

BRAT	Benefit-Risk Action Team
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
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 both regulatory authorities and pharmaceutical industry. The ICH has formulated guidelines covering the format and content of BRA pre-approval (ICH M4E R2) and post-approval (ICH E2C-R2).

In the M4E R2 guideline, ICH provides guidance focussing on the BRA of the medicinal product in the proposed indication(s) by the Applicant 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 applicants 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 perspectives;
- severity of disease and how expected benefit 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, such as registries or restricted distribution systems.

There are many approaches available for conducting the 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 adequate. An applicant 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 method, the applicant 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[12] and the US FDA[13] have published reports and guidance[14] on 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"[15].

Post-approval 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 continue 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 the authorities.

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 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 profile, as appropriate.

1.4.1 Innovative Medicines Initiative (IMI): 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 European Medicines Agency (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 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 five years.

In line with its mandate, PROTECT undertook to examine the limitations of the current methods used in pharmacovigilance and pharmacoepidemiology 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 BR methods into scientific assessment of medicines with a particular emphasis on graphical methods to display BR profiles and enable subsequent communication of these benefits and risks.

For further information on the five work packages defined in this project and their results please visit http://www.imi-protect.eu/.

1.5 Assessing BR 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 audience. 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.

Three major stakeholder groups drive the overall process: patients, health care systems (including physicians and payers) and healthcare 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 the inherent uncertainty of any life situation. 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 product throughout its 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.

In this overall context, it is important to acknowledge and remember that specific BR methodologies may be chosen depending on different treatment modalities or the primary purpose of the assessment. Such is the case for 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 socio-economic environment including the field of Health Technology Assessments. The context for the individual patient is further influenced by their life circumstances, including the cultural context and the access to health care.

1.6 Purpose statement

This update of the CIOMS Working Group IV report puts forward a lifecycle-based approach to BRA of pharmaceuticals 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, including patient-level integration and assessment of benefits and risks when possible. Assessments should involve multidisciplinary teams and should be informed by the perspectives of key stakeholders.

1.7 How to use this report

Chapter 2 describes a structured, descriptive approach to BRA. This approach focuses on the key components of BRA, the role of patient input, and the role of additional quantitative BR analysis. This approach is fully consistent with regulatory guidance on BRA, such as guidance from ICH on the content of Module 2.5.6 or the PBRER. This approach can be applied at any point in the medicinal product development lifecycle and updated as new information is gathered, new decision points arise, or judgements and priorities change. Also included are implementation recommendations, including planning for the use of the approach. The methods and principles in this chapter can and should be used for all development programs, as well as for the post-approval program.

Chapter 3 provides additional methods that can supplement the BRA process and approach described in Chapter 2. Use these methods when there are, or there is anticipation of, additional BR questions and uncertainties that cannot be fully addressed by the structured, descriptive approach. Methods are provided with the BR question or uncertainty they address. Methods for economic assessment are not included.

Chapter 4 tailors Chapters 2 and 3 for selected special situations. Use this chapter if applicable.

The terminology in the field continues to evolve. We encourage readers to refer to the *CIOMS Cumulative Glossary, with a focus on Pharmacovigilance (Version 2.1)*, which contains terms and definitions from past CIOMS reports, and the *Glossary of ICH terms and definitions* published by CIOMS. Where definitions used in this report differ from those given in these named references, other established definitions and references have been provided, as well as de novo definitions from CIOMS Working Group XII where necessary.

Annexes include case examples and the statement issued by the CIOMS Working Group XII during the Coronavirus disease (COVID-19) pandemic.

References

[1] *Coplan PM, Noel RA, Levitan BS, Ferguson J, Mussen F. Development of a framework for enhancing the transparency, reproducibility and communication of the benefit-risk balance of medicines. Clinical Pharmacology and Therapeutics. 2011;89(2):312-315. https://doi.org/10.1038/clpt.2010.291*

[2] *Phillips LD, Fasolo B, Zafiropoulos N, Beyer A. Benefit–risk Methodology Project Work Package 2 Report: applicability of current tools and processes for regulatory benefit–risk assessment. European Medicines Agency. 2011. (PDF accessed 20 April 2023).*

[3] *The United States Food and Drug Administration (FDA). Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making. Draft PDUFA V Implementation Plan - February 2013. 2013. (PDF accessed 20 April 2023).*

[4] *Walker S, McAuslane N, Liberti L, Leong J, Salek S. A universal framework for the benefit-risk assessment of medicines: is this the way forward?. Therapeutic Innovation & Regulatory Science. 2015;49:17-25. https://doi.org/10.1177/2168479014547421*

[5] *The United States Food and Drug Administration (FDA). Benefit-Risk Assessment in Drug Regulatory Decision-Making 2018: Draft PDUFA VI Implementation Plan (FY 2018-2022). 2018. (PDF accessed 20 April 2023).*

[6] *Phillips LD, Fasolo B, Zafiropoulos N, Beyer A. Benefit–risk Methodology Project Work Package 2 Report: applicability of current tools and processes for regulatory benefit–risk assessment. European Medicines Agency. 2011. (PDF accessed 20 April 2023).*

[7] *Coplan PM, Noel RA, Levitan BS, Ferguson J, Mussen F. Development of a framework for enhancing the transparency, reproducibility and communication of the benefit-risk balance of medicines. Clinical Pharmacology and Therapeutics. 2011;89(2):312-315. https://doi.org/10.1038/clpt.2010.291*

[8] *Walker S, McAuslane N, Liberti L, Leong J, Salek S. A universal framework for the benefit-risk assessment of medicines: is this the way forward?.Therapeutic Innovation & Regulatory Science. 2015;49:17-25. https://doi.org/10.1177/2168479014547421*

[9] *Angelis A, Kanavos P. Multiple criteria decision analysis (MCDA) for evaluating new medicines in health technology assessment and beyond: the advance value framework. Social Science & Medicine. 2017;1;188:137-156. https://doi.org/10.1016/j.socscimed.2017.06.024*

[10] *Quartey G, Ke C, Chuang-Stein C, He W, Jiang Q. Overview of Benefit-Risk Evaluation Methods: A spectrum from qualitative to quantitative. Eds. Qi Jiang and Weili He. In Benefit-Risk Assessment Methods in Medicinal Product Development: Bridging Qualitative and Quantitative Assessments. CRC Press Taylor & Francis Group; 2016.*

[11] *Statisticians in the Pharmaceutical Industry (PSI). Resources. (Website accessed 2 May 2023).*

[12] *European Medicines Agency (EMA). Benefit-Risk Methodology Project, Work Package 4 Report: Benefit Risk Tools and Processes. 2012. (PDF accessed 20 April 2023).*

[13] *The United States Food and Drug Administration (FDA). Benefit-risk Assessment in Drug Regulatory Decision-Making 2018: Draft PDUFA VI Implementation Plan (FY 2018-2022). (PDF accessed 20 April 2023).*

[14] *The United States Food and Drug Administration (FDA). Benefit-Risk Assessment for New Drugs and Biological Products. 2021. (PDF accessed 20 April 2023).*

[15] *The United States Food and Drug Administration (FDA). Benefit-Risk Assessment for New Drugs and Biological Products. 2021. (PDF accessed 20 April 2023).*

Chapter 2: Structured BR 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 complicated and surprisingly short history[16] 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."[17] 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 SBRF

A SBRF provides a structured and 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 also provides a standardised yet flexible approach for incorporating study outcomes and preference weights in BRA as well as strategies for communicating the rationales for BR decisions.[2] 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 SBRF

The ultimate purpose of 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 Licensure Application (BLAs) reviews and both CDER and CBER have incorporated the BR summary table in clinical review templates. Because the framework is explicit about the dimensions being assessed and the evidence considered, it helps to focus review on the evidence or uncertainties that have contributed to the final BR conclusions. It also helps to provide valuable feedback to applicants even in cases where the conclusion of a review does not support product approval by pointing to the evidence and agency's rationale, which led to the regulatory decision. In addition, pharmaceutical companies use BRA to assess and determine the company's BR position and strategy and to inform "go or no go" decision in their drug development programs. 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 groups and the

[2] A **structured benefit-risk framework (SBRF)** provides a structured and 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 also provides a standardised yet flexible approach for incorporating study outcomes and preference weights in BRA as well as strategies for communicating the rationales for BR decisions.
Source: Proposed by CIOMS Working Group XII

public. Finally, use of a SBRF may enhance consistency of regulatory decision from regulatory agencies.

2.1.3 Examples of SBRF

A few SBRFs are in the public domain. Each has its unique perspective and focus. Some of the well-known frameworks are summarised in this section.

The BRAT framework

The BRAT (Benefit-Risk Action Team) framework[18] includes a six-step process, as shown below, with goals for both better BR decision making and communicating.

1. Defining the decision context involves specifying the therapeutic context, comparator to use of the product, time horizon for exposure and 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[19]:

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 is published in the current draft guidance.[20] 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 to manage risks or reduce uncertainties.

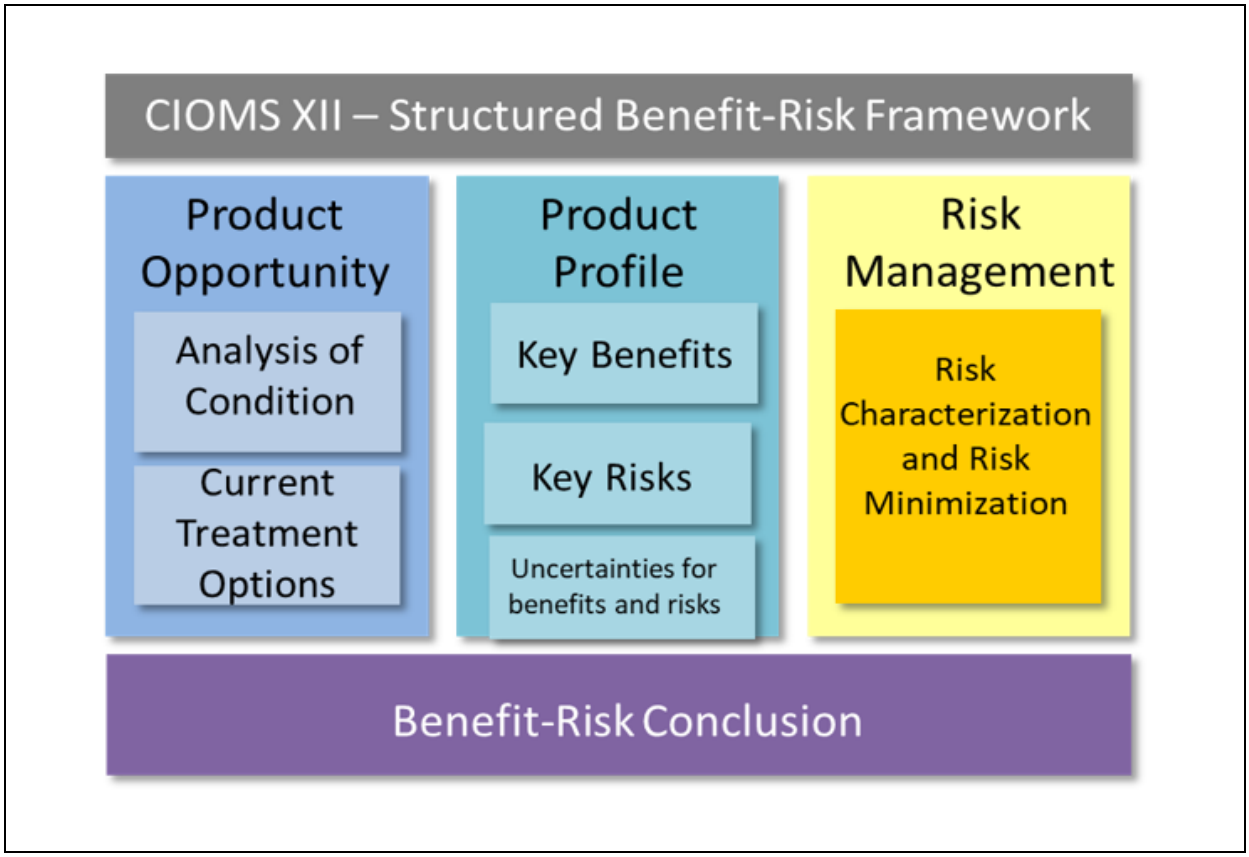
Some of the frameworks such as BRAT and PrOACT–URL describe a set of processes and tools for selecting, organising, summarising, and interpreting data that is relevant to the BR decisions. The others such as US FDA framework mainly focus on the dimensions of considerations in BRA. The commonalities of these frameworks are to determine whether the benefits of a medicinal product outweigh the risks based on the totality of the evidence, which include therapeutic context, benefit and risk evidence, uncertainty, weigh 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 can play an important role in SBRF and how additional quantitative analysis can support SBRF and assist the BRA for complex problems.

2.2 Components of a SBRF

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) can be developed at earlier stages of drug development and updated continuously throughout the product lifecycle. Each component of the SBRF and corresponding documentation in the BRAD will be reviewed.

Figure 2: Components of a SBRF – perspective of CIOMS Working Group XII

Source: Modified from ICH M4E (R2), EMA PROACT-URL, and other BR frameworks[21,22]



2.2.1 Product opportunity - therapeutic context

It is essential that any evaluation of benefits and risks of a medicinal product considers the therapeutic context which consists of the disease or patient condition the drug is intended to treat, the population intended to be treated, and the benefits and risks of currently available therapies,

since therapeutic context varies a great deal depending on the target of the medical 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, for example:

- **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 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 of onset (i.e. malignancy).
- **Mortality and Severity** – Patients suffering from very severe diseases (i.e. those that are life-threatening) may tolerate more risk.[23] An example is the relaunch of thalidomide to treat multiple myeloma, where use during pregnancy is known to cause severe side effects to the foetus including malformation of the limbs.[24]The safety profile of thalidomide may be acceptable in patients with malignant tumour, but not for patients with less severe conditions.
- **Quality of life** – Impact on QoL of the medical product should be described. For example, medical products which improve QoL but only have a small effect on improving prognosis may still be beneficial for patients in late-stage cancer who may have limited treatment options.
- **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. treatment for COVID-19 global pandemic).

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 risks, and the intended population (i.e. to-be-indicated population). These management options 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 limitations of current treatments to treat the intended population, this should be noted.

An understanding of the 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 by the BRA should fill an unmet need for the patient population with the disease 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 have failed prior biologic therapies. 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 have failed prior biologic therapies.

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.

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 (Figure 3, below). 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 BRMT) should be formed to discuss the key benefits and risks and developed a commonly agreed value tree. Below are key points to consider when determining the key benefits and risks:

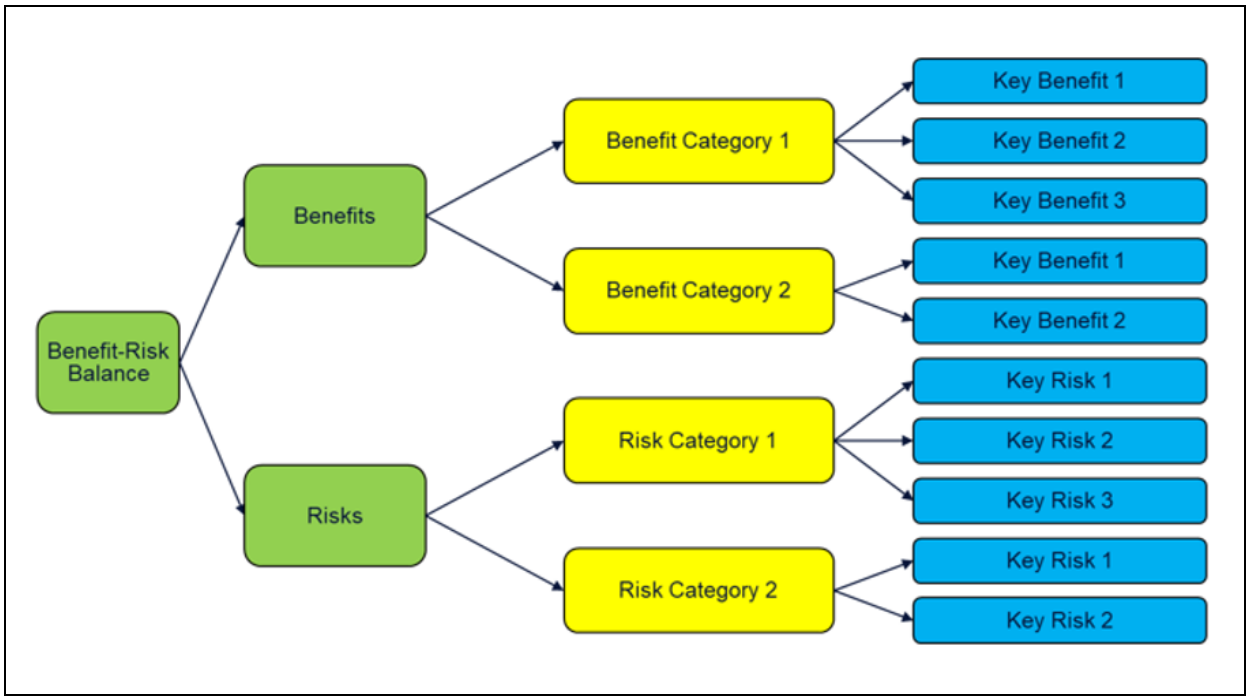
- A key benefit is one which demonstrates efficacy required for approval of a product in a specific indication. It may also highlight aspects of efficacy which may be unique for a product, and which can provide support for how the product fulfils an unmet need.[3,25]
- A key benefit will usually include the key primary endpoints used to establish efficacy of a product for a specific indication.
- Additionally, key benefits can also include benefits from among the secondary endpoints which are considered clinically meaningful and commonly used in clinical practice. These and may also be benefits which are included in product labelling since they are relevant to prescribers.
- A key benefit may also include those benefits considered relevant to a specific sub-population (e.g. paediatrics patients)
- A key benefit may also be those benefits considered relevant to patients, since these may differ from clinical trial endpoints considered by regulators or prescribers and may need to be captured differently in a BRA.
- A key risk is one that is required to contextualise the benefits of a product in a specific indication.[4,25] When assessing a key risk the team should discuss the severity and frequency of the risk as well as the duration. A key risk should usually include a risk that requires additional risk minimisation measures and will include the important identified risks in the Risk Management Plan (RMP) per GVP Module V, Revision 2 since these are considered associated with the product and should be considered in the BRA. The risks that are well understood and could be well managed may not be considered as key risks in the BRA.
- Other risks which may be included as part of the key risks may be those included in the RMP as the important potential risks; while not all of them may be included.
- BRMT may consider risks which are of regulatory importance or risks which may have great impact on BR due to severity of resulting adverse clinical outcomes.

[3] **Key benefits** are favourable effects generally assessed by primary and other clinically important endpoints across the studies in a development program.
Source: ICH Harmonised Guideline. Revision of M4E Guideline on Enhancing the Format and Structure of Benefit-risk Information in ICH Efficacy M4E(R2). Current Step 4 Version.
[4] **Key risks** are unfavourable effects that are important from a clinical and/or public health perspective in terms of their frequency and/or severity.
Source: ICH Harmonised Guideline. Revision of M4E Guideline on Enhancing the Format and Structure of Benefit-risk Information in ICH Efficacy M4E(R2). Current Step 4 Version.

- The value tree[5,26] is crucial to defining what aspects of efficacy and safety 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.

Figure 3: Example of a BR 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)[27]



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 (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 from the clinical study(ies) to provide evidence for each key benefit. This discussion may take time since many clinical development programs include multiple endpoints which may assess varying aspects of the same benefit. The team would need to align on which endpoint to use for the BRA. Typically, this may be a primary endpoint or key secondary endpoint, so these may be where the BRMT starts when they align on the key benefits. Possible reasons to include certain factors as key benefits include that:

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

In the BRAD, documenting a rationale for why each specific key benefit has been selected may be helpful. The rationale may include why the benefit is important for clinical evaluation of 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

[5] **Tree diagrams** in benefit-risk assessments are called value trees. Value trees are a visual, hierarchical depiction of key ideas, values, or concepts used in decision, through an explicit visual map of the attributes or criteria of decisions that are of value to the decision-makers. The value tree is a particularly useful tool because it requires decision-makers to clarify which benefits and risks are pivotal to the benefit-risk balance, and its visual nature greatly enhances communication.
Source: PROTECT, the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium.

dermatitis, itching is a primary symptom reported by over 90% of patients with moderate to severe atopic dermatitis.[28,29,30] 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 can 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, usually study data demonstrating the effectiveness of the product, is then provided. When multiple clinical 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.[31] 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 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 optimising appropriate use for that subpopulation is needed as part of the BRA.

- **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 other therapies such as biologic therapies for an immunologic disease and has been shown to be an inadequate responder to biologics (bio-IR), it may be helpful to show that the product is 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 BRA), but tables providing efficacy data should also be considered to be included in 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 BRA).

Clinical importance and key evidence for the risks

Similar to the key benefits, each key risk 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 risk determined to be an important identified risk for the product and included in the RMP since there is sufficient evidence to establish a causal association between the medicinal product and the risk. These risks will usually be key risks. Please see the Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2) of 28 March 2017.[32]

- 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 concern for 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 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 for 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 having a serious infection on morbidity and mortality could be described.
- **Example 2** - for a product used to treat acute myelocytic 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 key risks above, the key evidence include clinical study data to characterise 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 BRA). When multiple clinical studies are part of the clinical program, integrated data are used. Early discussion with health 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[33] and/or similar approaches used to identify cases for evaluation of the key risk as was done for the clinical summary of safety should be used. If post-marketing data is 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 for a 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 BRA), 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	Product Dose X Week 52 N=XX XX PY	Product Dose Y Week 52 N=XX XX PY
Serious infections	N(%)	N(%)	N(%)	Exposure adjusted rates	Exposure adjusted rates
Major Adverse Cardiovascular Event (MACE)	N(%)	N(%)	N(%)	Exposure adjusted rates	Exposure adjusted rates

Focus of BRA when multiple doses have been evaluated in clinical trials

Clinical development programs may assess multiple doses of a product either to select a single dose for approval or if multiple doses may be required for treatment of the disease under evaluation. If this occurs, then the key evidence section of BRAD should include data from each dose unless it has been determined that a particular dose will not be considered for approval. In the scenario where a dose which was part of the clinical development program is not going to be proposed for approval, it is generally helpful to provide this rationale prior to the BRA since this will allow focus of the BR on the to-be-proposed dose in the targeted population.

Visualisation of key evidence in a BRAD

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 BRA). 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 visualisations are heat maps, waterfall plots and tornado plots.

The BR narrative

In addition to the components of SBRF described above, a concise but adequately detailed summary narrative of the BRA should be included in BRAD. The elements in accordance with SBRF introduced in earlier sections of BRAD should be further related and elaborated in the narrative.

- For instance, for a medicinal product being assessed for rheumatoid arthritis, the early section of the BRAD about the analysis of condition may describe patients with rheumatoid arthritis as having a high frequency of fatigue which interrupts their daily life and decreases their QoL.
- For the unmet need in treatment of rheumatoid arthritis, the need for a treatment, which is effective at lowering fatigue more than the current standard of care may be discussed.
- As a result, one of the key benefits may be reduction in fatigue and a second key benefit may be improvement in QoL.
- Both these key benefits would then be included in the conclusion section of the BRAD.
- Similarly, if a risk is well recognised for a medicinal product class, but the product has a lower frequency and severity of the risk, then this may be introduced in the treatment options section, then further discussed for the product as part of key risk section, and then elaborated on in the conclusions of the BRAD.

For more information about the BRAD, see section 3.6.5 on Company Benefit-Risk Assessment Document (BRAD).

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, which are typically discussed in a BRAD. (For more a comprehensive list of sources of uncertainty see section 3.4 on Methodological considerations for addressing uncertainties in BRA).

The types of uncertainties to consider when preparing a BRAD are described in Table 2. A more comprehensive list of uncertainties to be considered in BRA is included in Table 15 - examples or sources of uncertainties that could be considered in the SBRF.

Table 2: Sources of uncertainty typically included in a BRAD

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 comparator	Relevance of the comparator drug in the treatment landscape when the clinical program has completed.
Duration of exposure (e.g. duration of study versus intended use)	For diseases which require long-term treatment, are there limitations to the relatively short duration of the clinical program?
Studied (enrolled) patient population (as representative of the target population)	Are there exclusion criteria which limit generalisability of the clinical program results?
Subgroups not studied or studied in limited numbers of patients (consider susceptibility to benefits/risks)	Are there 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 benefits	Impacts generalisability to real-world population.
Patient monitoring during the clinical program may differ from clinical practice	May impact detection and timing of detection of an adverse event 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 and issues that could affect interpretation of results	Methods not typically used may need to be explained or limitations outlined.
Deviations from guidelines or scientific advice	May need to speak to this if this impacts applicability of the results.

2.2.3 Risk management

Risk management is an important component of the SBRF for a product. Ensuring there are clear measures in place to effectively manage the risks associated with a product are deemed necessary to supporting a positive BR balance. This also needs to be in the context of an approach that looks to collect and evaluate emerging safety data throughout the product's lifecycle with the aim of utilising that data to optimise the safe and effective use of a product throughout its lifecycle. For further information on the lifecycle approach (see section 2.3 on Lifecycle approach to BRA within this chapter). The rationale for the approach to the risk management along with the plans for further data collection are detailed in the RMP for the product, however, a high-level description may be appropriate to be included in a BRAD to demonstrate that this has been considered in the context of the product's overall BRA. (See figure 2 on Components of a SBRF framework.)

Risk characterisation

Any decision about the balance of benefits and risks of a medicine is based on the information that is 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 at the time of decision. 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 pharmacovigilance planning.

The idea of pharmacovigilance planning was first proposed by Waller and Evans in 2003[34] and this thinking also influenced the ICH E2E guidance[35] and the concepts of a safety specification and the pharmacovigilance plan.

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 BRA 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 address the recognised uncertainties or identify 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. The safety specification should be derived from the product profile and the key benefits and key risks that have

been identified. 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 reactions 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.

Any BRAD should describe the proposals for further pharmacovigilance activities to characterise and quantify the key risks and identify new adverse reactions (the pharmacovigilance plan). The need for and nature of the planned pharmacovigilance activities should be driven by the safety specification along with the clinical importance of the risks and any uncertainties that exist with regards to these risks. As described in the section on Clinical importance and key evidence for the benefits within this chapter, the clinical importance of the risks of a medicinal product is influenced by the medical seriousness of that risk, the frequency, predictability, preventability and reversibility, and also the potential impact on public health.

For each key risk, the pharmacovigilance plan that is described in the RMP should include a description of the:

- Safety issue;
- Objective of the proposed action(s);
- Action(s) proposed;
- Rationale for the proposed action(s);
- Monitoring for the safety issue;
- Milestones for evaluation and reporting.

It is recognised that through the pharmacovigilance system, routine pharmacovigilance activities should be in place for all medicinal products. Detailed information on proposed pharmacovigilance activities should be included in the pharmacovigilance plan of the medicinal product's RMP.[36] The BRAD should, in particular, focus on whether there are particular risk(s) and/or gaps in knowledge where obtaining further information is key to informing the continuous balance of benefits and risks. Specifically, it should describe where and why it has been determined that pharmacovigilance activities beyond routine activities (i.e. additional pharmacovigilance activities) are required and discuss how the proposed activities have been selected.

Additional pharmacovigilance activities may include non-clinical studies, clinical trials or non-interventional studies. 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-authorisation 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 adverse event(s)/adverse drug reaction(s) along with the anticipated timelines for availability of results.

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 can be valuable to include some key information in the BRAD. 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 minimisation

Risk minimisation measures (RMMs) 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 adverse drug reaction (ADR). The CIOMS Working Group IX[37] distinguished between risk prevention (reducing the frequency of an ADR) and risk mitigation (reducing the severity of ADR 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[38] and CIOMS Working Group VI report[39] have been widely adopted but their interpretation has varied. Within Europe[40,41,42] and Japan[43], legislation requires RMPs for all newly authorised products, which include strategies for characterising and managing the medicinal product's risks over time through routine and/or additional RMMs. Other jurisdictions, such as Health Canada[44], Welfare and the Ministry of Food and Drug Safety in Korea[45], and Australia[46]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[47], known as Risk Evaluation and Mitigation Strategies (REMS) to be developed and implemented only for those products that 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/carers 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, consideration needs to be given to how the RMMs need to be revised or expanded upon in order to accommodate any newly identified risk(s).

The approach to risk management and selection of the appropriate RMMs will be driven by the important identified and important potential risks of the product and the uncertainties that exist with regards to the data to inform these risks (Missing Information). Further information on this is provided in the earlier paragraphs on Uncertainties under section 2.2.2. on Product profile and the section 3.4 on Methodological considerations for addressing uncertainties in BRA.

With the exception of those products with serious risks routine RMMs are likely to be sufficient to mitigate the risk. These are measures that can be applied to every medicinal product and relate to:

- the **product information** provided to HCPs and patients –to ensure that HCPs and patients have the necessary information in a clear and accessible format to support safe and appropriate use and to optimally inform discussions and joint decision making;
- **labelling on the immediate or outer packaging** – ensures that key information is highly visible; limited space on packaging means that such warnings should be reserved for special situations

- the **pack size**(s) – limiting the pack size can be of particular value where overdose or diversion are an important risk or where it may help support clinical testing and/or timely clinical evaluation
- the **legal status** of the product – this controls the conditions under which the medicinal product may be made available (i.e. availability on prescription only) and may also restrict where the medicinal product can be administered (e.g. hospital) or by whom it may be prescribed (e.g. specialist).

For products with serious risks, where we need to consider the magnitude of the risk, such as the impact on public health, and where there exists the potential for prevention, it may lead to a decision that additional RMMs are needed to manage the risk. In the United States this would involve a REMS. The likely additional burden to the healthcare delivery system and patient/carers means that such measures should be employed only when necessary to support safe and effective use. Any proposed additional RMMs should have a clear objective, be appropriately justified and focus on the most important, preventable risks.

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 healthcare system. This is especially important when additional RMMs are being contemplated and aspects to consider in relation to these areas is 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 used in routine clinical practice and the healthcare setting. Introducing RMMs involves interactions between all these factors, therefore, it may be possible that certain measures may apply to one indication, population or healthcare setting but not others.

Table 3: Key areas and points to consider in determining need or approach to 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 utility of the product (i.e. 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 with stakeholders ○ Clinical trials – do these data inform on the impact of restrictions to indication, dose, duration of treatment ○ Published literature ○ Human Factors studies (qualitative or quantitative) ○ Previous experience with similar measures
Stakeholder needs	• Which stakeholders may need additional support; • Type and extent of support required: ○ appropriate patient selection ○ training to mitigate risk ○ verification of patient monitoring
Feasibility	• Potential impact on healthcare 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 – may result in less appropriate prescribing options • Sustainability over time – designs based on behavioural change models (e.g. the PRE-CEDE-PROCEED model) are likely to be more effective

An important aspect to consider and discuss is whether and how the proposed RMMs will impact on the efficacy and effectiveness of the product. In particular, where the proposed risk minimisation will result in a restriction to the use of the product (e.g. restricted indication and/or target population, reduction of dose and/or reduction of duration of treatment) there should be a discussion of how this may potentially impact on the efficacy of the product.

The nature of the safety concern in the context of the BR balance of the product, the therapeutic need for the product, the target population and the required clinical actions for risk minimisation are factors to be considered when selecting risk minimisation tools and developing an implementation strategy to accomplish the desired public health outcome. 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 Healthcare 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 *HCPs* (e.g. HCP guide, Prescriber checklist, Demonstration kit)	• 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?

Patients and/or carers (e.g. Patient/carer guide, Risk awareness /acknowledgement forms, Patient diaries, Patient cards	• 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 healthcare systems • Need for materials to be periodically updated and reissued. • 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 healthcare systems or specialists, or availability of clinical testing) • May need to be adapted to local healthcare settings • Unintended consequences – may discourage use and result in diversion to less appropriate prescribing options or patient discontinuation

When proposing the implementation of additional RMMs other factors also be included, such as setting and timing or frequency of intervention, the target audience, distribution plan for educational materials. 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.

Impact of RMMs on health care / patient decisions

RMMs should always be proportionate to the applicable risks. Consequently, it is important to consider how the proposed measures may impact on healthcare delivery and patient access.[48,49] For example, where clinical monitoring is proposed, consider whether the nature and the periodicity of the proposed monitoring is consistent with or can reasonably be accommodated into existing clinical practice. Where this is not the case it will be essential to understand the views of stakeholders about the additional burden that will be imposed and whether this is proportionate to risk and in turn how this informs the overall balance of benefits and risks.

Measures that are overly burdensome may impact on the adherence by HCPs and/or patients. Additionally, the proposed measures should not result in unnecessary treatment interruption or delays, particularly if the medicinal product is used in the treatment of serious or life-threatening conditions.

In this respect, it is necessary to understand whether the proposed measures are acceptable to the end users, whether they can be accommodated into existing clinical practice and also to identify any potential barriers to patients' access and consider how these may be minimised. Ideally, this should be factored into the design stage and here engagement with key stakeholders in developing the RMMs is advisable and can be beneficial. This could take the form of interviews with stakeholders or use of focus groups to identify burdens and ways to reduce them.

Where possible, information should be provided that demonstrates that the additional burden on the healthcare system or effects on patient access have been considered and describe the attempts that have been made to minimise the potential burden. Pilot testing of the measures with the intended population could be conducted but this will depend on the nature of the safety concern and the urgency with which RMMs need to be introduced. Where pilot testing is conducted the results should be presented and a discussion provided as to how they support the final proposed measures.

Where RMMs are intended to apply globally or in a number of different countries, it will also be important to consider whether there is a need to allow flexibility with regards to some elements of the risk minimisation in order that they can accommodate local differences in clinical practice.

There should be careful selection of the metrics, data sources, analytical tools and methodologies that will be used to assess the impact on patient access and burden on the healthcare system as a result of the implementation of the proposed RMMs. Whilst much of the detail of this will be included in the study protocol and/or RMP, as appropriate, it may be valuable to include high-level information within the BRA on the proposed methods, data sources and metrics.

Effectiveness of risk management

Effectiveness evaluation of risk minimisation interventions.

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/carers it is essential that consideration is given to what data may be available or further activities needed, 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[50,51,52], and submit information on effectiveness of these measures, as part of a submission (BRA) in the context of the RMP or an update to the RMP.

The need for risk management 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.[53]

To assess the effectiveness of the risk management and monitoring approach, in accordance with regulatory guidance (EMA[54], US FDA[55])[56], 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 healthcare setting that have undergone any required training).

2. Knowledge – stakeholder (e.g. patient/caregiver, prescriber, pharmacist) understanding of 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 adverse reaction). 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 having been prescribed the 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 should discuss why particular metrics and data sources have been selected and any limitations and resulting uncertainties should be described.

The possible limitations of the available data mean that no single metric, data source or methodology is likely to be sufficient to fully assess effectiveness of the RMMs. Several metrics, data sources and methodologies should be considered. Furthermore, multiple complementary data sources are likely to provide more complete information (both qualitative and quantitative) about the impact of the measures. However, some data sources may be used in assessing several identified metrics (e.g. drug utilisation studies can inform on changes in prescribing behaviour as well as unintended consequences).

As risk minimisation is an iterative process there should also be clear plans for when and how the findings from the agreed activities and results of studies will be factored into the ongoing monitoring of the product and continued evaluation of the balance of benefits and risks. There may be a need to evaluate the effectiveness of risk minimisation at several time points. If so, consideration should be given to how this will be achieved and the appropriate periodicity. Ideally the periodicity should allow for timely evaluation including determining whether any corrective action is needed.[57] Consequently, the initial evaluation should occur relatively soon (e.g. within 12-18 months) after the RMMs/programme were first introduced. For later time points it may be preferable that these coincide with a suitable regulatory procedure (e.g. the renewal of a MA or any planned periodic evaluation of the REMS or in the context of a PBRER).

It is also important to explore whether it is possible to specify performance thresholds for determining the effectiveness of the RMMs. Alongside any proposed thresholds there should be a discussion of the potential limitations of these thresholds and consideration as to whether suitable alternative approaches can be employed (e.g. comparison of the reporting rate of an event from data obtained from a drug registry with a background rate of that event in a similar patient population from a suitable database).

Once the findings are available these need to be evaluated to determine whether there is a need to revise or refine the current RMMs and consequently make changes to the product's RMP and/or REMS. Where there are clear data available from multiple timepoints that support the persistence of the effectiveness of the measures or demonstrate that the measures have become integrated into routine clinical practice then this could potentially be used as a basis for evaluating the continued need for the additional RMMs.

2.2.4 BRA conclusion – the overall assessment summary

This section discusses the points to consider when concluding the BRA on a medicinal product in a proposed indication. Here are some principles.

- The significance of the disease/condition, the unmet medical need, and the product's place in the treatment armamentarium.
- The reasoning and judgment used in assessing and weighing the key benefits and key risks, within the specific therapeutic context.
- 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 way to mitigate risk or limit use in this population.
- Explain how any uncertainties impact the assessment.
- How the expected key benefits influence the acceptability/trade-off of the key risks.
- How the benefit(s) and/or risk(s) differentiate the product from other important alternative therapies.
- Any available information on the patient perspective.

- 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.

Finally, include a statement acknowledging whether the overall BR profile for the product is favourable or unfavourable.

BR trade-offs

The trade-off between a specific risk versus achieving a certain degree of efficacy is complex. It should consider 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 the section 2.4 on Role of the patient in SBRF for a discussion on patient preference studies (PPSs) and how they can inform the BRA.

In summary, a SBRF includes multiple components which consider the disease to be treated, the unmet need that the medicinal product fills, key benefits and risks, risk management, and finally the overall benefit and risk conclusion. All of these should be documented in the BRAD and accompanied by tables and graphics which help to clarify the BR narrative.

2.3 Lifecycle approach to BRA

A SBRF provides a structured and systematic BRA approach through the lifecycle of the drug. 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, 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 drug discovery process 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 MA.

Because each step forward in this process requires substantial additional resources and time, 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 of the start of clinical trials or submission to a regulatory authority for authorisation. 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 consider 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 Development Safety Update Report (DSUR) described by ICH E2D. 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 to decide whether or not the BR profile 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 drug 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 and pharmacology and other non-clinical studies necessary to allow the first use in human subjects. 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 preclinical stage of development.[58] 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 preclinical 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 Investigators Brochure which informs the study protocols and Informed Consent Form (ICF) documents which 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 2 clinical trials)

The incorporation of pharmacovigilance activities and BRA is required throughout the entire lifecycle of a product.

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 Phase 1 and 2, activities that include risk management planning and safety milestone assessments as early as 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 drug development.

Prior to the start of Phase 1, 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 signals for first-in-human studies. Agencies can provide feedback about the clinical trial protocol and study design including identification, collection, analysing, monitoring, documentation, and mitigation of potential risks in in clinical trial.

In Phase 1 studies, usually conducted in healthy volunteers, 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), 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, 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 may be a critical point for BR planning based on available information about treatment effect and 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 regulatory agency about the available information, BR planning and Phase 3 trials design and regulatory agencies may provide 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 best practices in collection and use of 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 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 documentation of such activities in early stages of 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 investigator's brochures (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, it is recommended that pharmaceutical companies will integrate all available data and conduct a comprehensive BRA following a SBRF as it is useful for designing pivotal trial protocols and essential for the marketing application.

Using a structured approach to the BRA will assist companies in preparing a 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 BRAD summarising the BRA. The BRAD in late development is comprehensive and includes all clinical data within the different assessment sections.

During late development, the BRAD is used as a standard document which is developed and updated by pharmaceutical companies through the lifecycle of the drug as well as by regulators per defined triggers post approval. The BRAD uses a structured and systematic approach in accordance with SBRF for identifying, evaluating, and communicating the considerations which factor into a BRA.

During the development phases of the medicinal product (Phase 1, 2 and 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 Phase 3, pivotal randomised controlled clinical trial data are available which provide a complete overview of the product BR profile during development. 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 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 end points 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 team will then further describe in the BRAD the types of risk minimisation measures 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 SBRF 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 Company Core Data Sheet and will guide 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 meetings, early BR discussion, Pharmacovigilance Risk Assessment Committee (PRAC), 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 provide 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 BRA).

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 provide guidance on additional risk minimisation measures that should be introduced during launch time when applicable.

Regulatory agencies review Marketing authorisation applications (MAAs), NDAs and BLAs submitted by sponsors (applicants). Considering the therapeutic context, the totality of evidence on the key benefits and 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 adverse events, 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 (therapeutic context, benefits, risks and BR trade-off) of the SBRF. Therapeutic context plays an important role in 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. 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 drug 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, 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.

When cases of adverse drug reactions that are both serious and unexpected are reported from Individual Case Safety Reports (ICSRs), a MAH must promptly report to regulatory authorities in accordance with local regulations and discuss the need to improve the BR balance through risk

minimisation activities. In addition to ICSRs, any safety information from other observations such as solicited sources (e.g. post-authorisation 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 WHO Uppsala Monitoring Centre and regulatory authorities that analyse the spontaneous reporting system for adverse drug reactions 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). Evidence of lack of efficacy should not usually be expedited but should be discussed in the relevant periodic safety update report (PBRER).

Key deliverables are RMP (EU, Japan), REMS (US) and PBRER

RMPs include information such as a drug's safety profile, pharmacovigilance plans, risk minimisation activities, risk evaluation and mitigation strategies are continually modified and updated throughout the lifecycle of a drug 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 an 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. 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.

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 approval indication) of 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, MAH assess the need for changes of the product information such as labels and CCDS, and propose changes as appropriate to regulatory authorities. In addition, a MAH may discuss with regulatory authorities the necessity of the 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 becomes available post-approval. Post-market evidence can come from a diverse set of sources, such as post-marketing studies, adverse event 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 adverse events 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 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 profile of the marketed drug under the current

requirements for approval. Examples of regulatory decisions that may be informed by such assessments include addition, modification and, rarely, marketing withdrawal.

2.4 Role of the patient in SBRF

2.4.1 Importance of incorporating patient perspective

Patients are the ultimate end users of medicines and consequently not only do they experience the benefits but they are also exposed to the harms. It is, therefore, vital and increasingly expected that their views, along with those of their carers, where appropriate, are collected. 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 risk minimisation measures. To best support success involving patients should happen as early as possible and ensure that patients and their needs are at the heart of medicines development and involved throughout the product lifecycle. The CIOMS Working Group XI has recently published guidance that includes pragmatic Points to Consider for patient involvement and recommendations regarding patient involvement throughout the product lifecycle.[59]

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.[60,61,62,63]

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.[64]

A number of initiatives and projects are in place and some of these have developed 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 Innovative Medicines Initiative (IMI) project to produce recommendations to guide industry, regulatory authorities and Health Technology Assessments (HTA) / reimbursement bodies on how and when to include patient preference information.[65,66]
- IMI-PARADIGM – cross industry partnership that aims to promote greater patient engagement in the development of innovative therapies.[67]
- 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.[68,69,70]
- Clinical Trials Transformation Initiative (CTTI) - focusing on ensuring patients are included as equal partners in the drug development process.[71]

- 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.[72]
- 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.[73]
- MHRA - has developed a patient involvement strategy to better engage and involve the public 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.[74]
- 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.[75]

2.4.2 Patient input to inform components of SBRF

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 will help 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;
- 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 focused treatment burden: preferred treatment attributes and levels, as well as trade-offs among attributes and levels;
- 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 resulting in more meaningful outcome measures[76], which should positively impact the recruitment to and retention of patients within the trials.[77] 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 US[78] UK[79] and Japan.[80]

Involving patients at the trial design stage and during protocol development can 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.[81]. 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 patient-reported outcomes (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).[82] Their involvement can help with the development of information and questions that are easily understood by patients but also cognizant of their needs, which can aid the correct interpretation and communication of study results.[83]

With some clinical trial designs (doubly randomised preference trials), the effect of preferences on clinical outcomes can be analysed.[84,85] Involvement of patients may also help define subgroups with different BR trade-offs.[86,87,88]

Using patient preference for the identification and selection of a product's key benefits and key risks, BR 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 committee members 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 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 the 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.[89,90,91]

Engaging with patients to understand their views and incorporating those views into decision making is of particular valuable 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;[92]
2. there is considerable uncertainty or variability in the available evidence;
3. 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.[93]

The development of RMMs

The role of patients and the public should not end once the decision-making process has concluded. Indeed, they have an equally valuable role to play in critical aspects around risk minimisation and risk communication.

The views of patients can inform some critical aspects relating to the proposed RMMs (either print or digital), including whether the proposed measures are considered acceptable and feasible (e.g. accessible, level of comprehension and readability). All measures should meet appropriate health literacy standards for patients. It is desirable that proposed measures undergo user testing (i.e. usability) to assess layout design, understanding and comprehension of the risk messages and patient's behaviours that minimise the serious risks. This approach will aid their optimal design, improve actionable messages, and help support implementation. Where the urgency of the need to introduce risk minimisation allows, there may be scope to consider pilot testing of the proposed measures, which may aid their optimal design and help support implementation. Furthermore, where similar RMMs exist for another product then it may be beneficial to understand what the current patient experience is with these RMMs and in turn consider how this influences the development of the proposed measures.

Where the RMMs focus on provision of information and /or training on the safe use of the product, patient and/or carer views can be beneficial with regards to:

- the most critical and actionable messages to convey;
- tailoring the materials to best meet the needs of patients/carers;
- how BR information should be presented (content and tone);
- how effective the measures are in terms of conveying risk information and/or educating about how to use the product safely and appropriately;
- the best vehicles and routes to ensure that the messages are received and understood by the target audience.

Once RMMs have been introduced in order to optimise safe use and support a favourable BR balance, it is essential (and in some jurisdictions can be a requirement of legislation) to ensure that the introduced measures have been effectively implemented and are achieving the desired/intended outcome. Patient representatives, groups and charities have an important role to play in this respect and can be helpful with regards to the conduct of studies and/or surveys to

measures/monitor/explore the effectiveness of risk minimisation. For example, in the UK, three charities (Epilepsy Action, Epilepsy Society and Young Epilepsy) have worked together to conduct surveys of women and girls with epilepsy who took valproate as a medicine and their patients and carers.[94] These surveys were conducted in 2017 and 2019/2020 and followed regulatory action at European level[95,96] to strengthen risk minimisation measures with regards to the use of valproate in women and girls due to the risk of malformations and developmental problems in babies who were exposed to valproate in the womb. The surveys sought to explore the awareness of the risk minimisation measures, including the valproate Pregnancy Prevention Programme, and provision of educational materials to patients and have informed regulatory decision making and/or implementation of risk minimisation measures.

Patient involvement at each stage of the product lifecycle will help to ensure that the evidence generated to inform the ongoing BRA is aligned with the needs and priorities of patients. Additionally, it will best support decision making that is cognizant of patients' views and experiences and the implementation of feasible and acceptable measures to optimise safe and effective use in routine clinical use.

2.5 Additional quantitative analysis

Additional quantitative analysis for BR conceptually refers to any advanced quantitative analysis beyond the basic descriptive analyses typically conducted to determine the efficacy and safety of drugs, such as statistical analysis of clinical trial data.[6] To name a few, the additional quantitative analysis could be modelling and Monte Carlo Simulation to estimate the benefit and risk of vaccine, 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. These quantitative analyses are an optional component of a BRA within the structured framework; it may not be needed for most cases but may definitely be needed for some cases.

2.5.1 When is additional quantitative analysis needed?

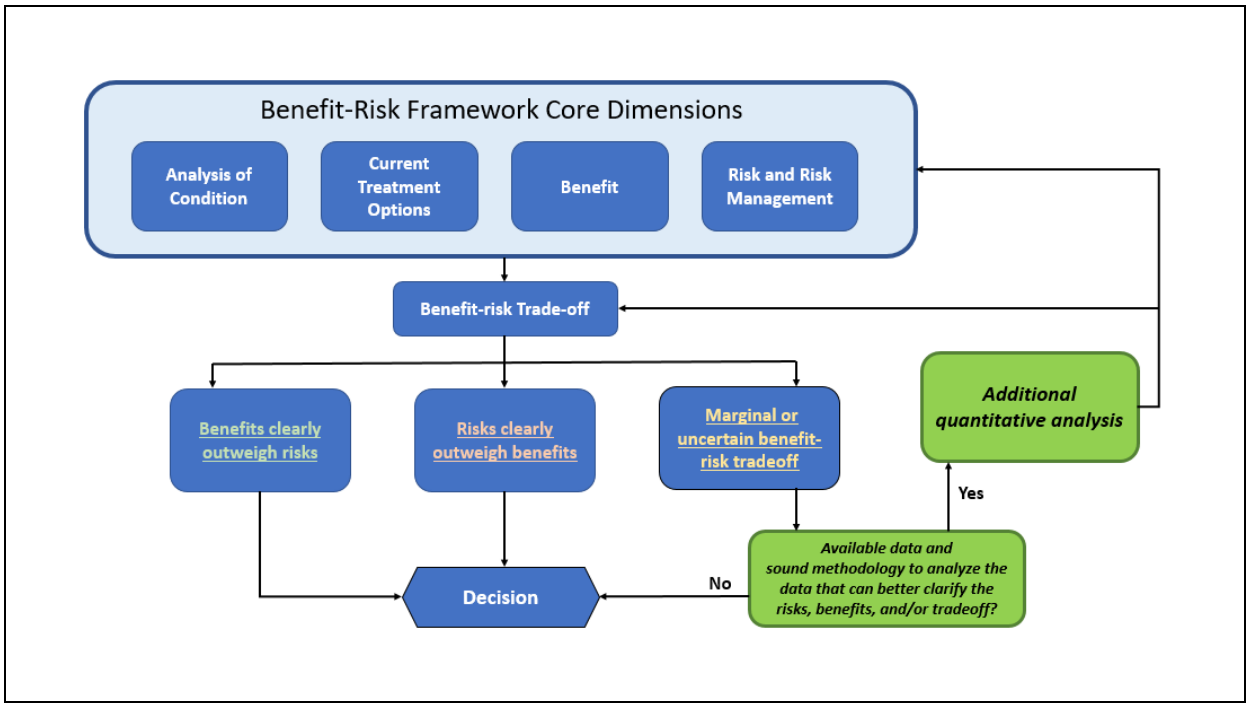
All BRAs follow a SBRF and begin by analysing the core dimensions' evidence and uncertainties, with the core dimensions including analysis of the condition, current treatment options, benefit, and risk and risk management. A decision is then made based on the BR trade-off as described in the figure below. 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 these cases, additional quantitative analysis may have added value in reducing the uncertainties and understanding the impact of remaining uncertainties in benefits, risks, or BR trade-off.

[6] **Additional quantitative analysis** for BR conceptually refers to any advanced quantitative analysis beyond the basic descriptive analyses typically conducted to determine the efficacy and safety of drugs, 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 benefit and risk of vaccine, 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. These quantitative analyses are an optional component of a BRA within the structured framework; it may not be needed for most cases but may definitely be needed for some cases.
Source: Proposed by CIOMS Working Group XII

Figure 4: Decision tree for additional quantitative analysis in BRA for medical products

Source: CIOMS Working Group XII



2.5.2 Purpose of additional quantitative analysis

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 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 risks, evidence related to the key benefits and risks, uncertainty of the evidences and their impact on the BR, 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.

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

These uncertainties may include but are not limited to:

- the condition when the natural history of disease is not well known;
- the extent of remaining medical needs with the current treatment options;
- expected benefit of a new drug for which only surrogate endpoints were measured;
- quantification of expected risks when sample size in trials was limited;
- extrapolating the results of clinical trials to real-world setting post market;
- trade-off between the clinical benefits and severe adverse effect of the treatment.

The additional quantitative analysis can be designed to address critical questions related to the BR decision. Examples of such questions could be what the expected benefits of the drug post-market are, what are the expected risks are in the real population, how the knowledge gaps could impact BR balance or whether the benefits outweigh the risks for specific patient groups.

Quantitative analysis may 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 health care providers and 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, 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 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.

2.5.3 A wide range of methodologies and tools to address different problems and purposes

Different types of additional quantitative analyses can be used, the most frequent ones as well as their main purpose are described with more details in Chapter 3 (see Chapter 3 on BR methodology considerations).

2.5.4 Analyses conducted at different stages of lifecycle depending on the study question

Analyses conducted at different stages of the product lifecycle depends on the objectives of the drug 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 that 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 BRA). For example, evaluation of patients' preferences using measurement methods in early drug development may help identify the patient needs and the benefit endpoints that are important to the patients; while MCDA may be helpful when there is a difficult trade-off decision for a drug with clear clinical benefit but severe adverse effects.

2.5.5 Analyses conducted with sound methodologies and fit for purpose data quality

The appropriate methods for additional quantitative analyses are determined on a case-by-case basis in term of whether the methodology is scientifically sound to address the specific challenges and questions as well as whether the quality of the available data are fit for the purpose. For example, integration of benefits and risks requires valid measures of endpoints for all the relevant product attributes, extrapolation and simulation require reliable scientific evidence to validate model assumptions. Moreover, when needed, multiple methodologies can be used in synchronisation.

2.5.6 Important requirements for additional quantitative analysis

There are major requirements to consider when implementing additional quantitative analyses to ensure they will be relevant.

Transparency

All these additional quantitative analyses require high transparency on the methods used including model inputs, assumptions and limitations. Model inputs and assumptions and sources of data need to be presented as well as the rationale of selection. Limitations of the methods need to be presented and discussed.

Scientific rigor in methods

The appropriate methods used have to be applied with a predefined analysis plan and to be based on high-quality data.

Cross-functional team

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

2.5.7 Integration of additional quantitative analysis in the overall evidence

The results of any additional quantitative analysis performed to address specific challenges are to be merged with the rest of the evidence as these methods may aid the decision making and contribute to the overall BRA.

In the end, the decision is a judgement call and should be made based on the total evidence including additional results from quantitative analysis within the context of the SBRF.

References

[16] *Juhaeri J. Benefit–risk evaluation: the past, present and future. Therapeutic Advances in Drug Safety. 2019;10:1-10. https://doi:10.117/2042098619871180*

[17] *Benefit-risk balance for marketed drugs: evaluating safety signals. CIOMS Working Group IV report. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 1998. (PDF accessed 20 April 2023).*

[18] *Coplan PM, Noel RA, Levitan BS, Ferguson J, Mussen F. Development of a framework for enhancing the transparency, reproducibility and communication of the benefit-risk balance of medicines. Clinical Pharmacology & Therapeutics. 2011;89:312-315. https://doi.org/10.1038/clpt.2010.291*

[19] *Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT Benefit-Risk). PrOACT-URL. (Website accessed 20 April 2023).*

[20] *The United States Food and Drug Administration (FDA). Benefit-Risk Assessment for New Drug and Biological Products Guidance for Industry. Draft Guidance. 2021. (PDF accessed 20 April 2023).*

[21] *The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH M4E (R2): Revised guideline on Common Technical Document –Efficacy. (PDF accessed 20 April 2023).*

[22] *Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT Benefit-Risk). PrOACT-URL. (Website accessed 20 April 2023).*

[23] *The United States Food and Drug Administration (FDA). Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications. Guidance for Industry and Food and Drug Administration Staff. (PDF accessed 20 April 2023).*

[24] *Kumar A. Risk and benefit analysis of medicines. Journal of International Medical Research. 2020;48(1):0300060518771424. https://doi.org/10.1177/0300060518771424*

[25] *ICH Harmonised Guideline. Revision of M4E Guideline on Enhancing the Format and Structure of Benefit-risk Information in ICH Efficacy M4E(R2). Current Step 4 Version. (PDF consulted 29 May 2023)*

[26] *PROTECT, the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (Website accessed 25 May 2023)*

[27] *Coplan PM, Noel RA, Levitan BS, Ferguson J, Mussen F, Development of a Framework for Enhancing the Transparency, Reproducibility and Communication of the Benefit–Risk Balance of Medicines. Clinical Pharmacology & Therapeutics (2011) 89 2, 312–315. doi:10.1038/clpt.2010.291*

[28] *Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpron EL et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. Journal of the American Academy of Dermatology. 2014;70(2):338-351. https://doi.org/10.1016/j.jaad.2013.10.010*

[29] *Dawn A, Papoiu AD, Chan YH, Rapp SR, Rassette N, Yosipovitch G. Itch characteristics in atopic dermatitis: results of a web-based questionnaire. British Journal of Dermatology. 2009;160(3):642-644. https://doi.org/10.1111/j.1365-2133.2008.08941.x*

[30] *Yew YW, Thyssen JP, Silverberg JI. A systematic review and meta-analysis of the regional and age-related differences in atopic dermatitis clinical characteristics. Journal of the American Academy of Dermatology. 2019;80(2):390-401. https://doi.org/10.1016/j.jaad.2018.09.035*

[31] *The United States Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH M4E(R2): The CTD — Efficacy Guidance for Industry. 2017. (PDF accessed 20 April 2023).*

[32] *Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2) of 28 March 2017 EMA/838713/2011 Rev 2* (Website accessed 25 May 2023)*

[33] *The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Medical Dictionary for Regulatory Activities (MedDRA). Introductory Guide for Standardised MedDRA Queries (SMQs) Version 24.1. 2021. (PDF accessed 20 April 2023).*

[34] *Waller PC, Evans SJ. A model for the future conduct of pharmacovigilance. Pharmacoepidemiology and Drug Safety. 2003;12(1):17-29. https://doi.org/10.1002/pds.773*

[35] *European Medicines Agency (EMA). ICH E2E Pharmacovigilance planning (Pvp) - Scientific guideline. 2005. (PDF accessed 20 April 2023).*

[36] *Practical Approaches to Risk Minimisation for Medicinal Products. CIOMS Working Group IX report. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2014. (PDF accessed 20 April 2023).*

[37] *Practical Approaches to Risk Minimisation for Medicinal Products. CIOMS Working Group IX report. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2014. (PDF accessed 20 April 2023).*

[38] *European Medicines Agency (EMA). ICH E2E Pharmacovigilance planning (Pvp) - Scientific guideline. 2005. (PDF accessed 20 April 2023).*

[39] *Management of Safety Information from Clinical Trials. CIOMS Working Group VI report. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2005. (PDF accessed 20 April 2023).*

[40] *The European Parliament and the Council of the European Union. European Commission. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. 2020. (Website accessed 20 April 2023).*

[41] *The Human Medicines Regulations 2012 (HMR). UK Statutory Instrument. 2012 No. 1916. (Website accessed 20 April 2023).*

[42] *European Medicines Agency (EMA). Heads of Medicines Agencies (HMA). Guideline on good pharmacovigilance practices (GVP) -– Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2). 2017. (Website accessed 20 April 2023).*

[43] *Pharmaceuticals and Medical Devices Agency (PMDA). Risk Management Plan templates, instructions and publication. PSEHB/PED notification No. 0318-2, PSEHB/PSD Notification No. 0318-1. March 18, 2022. (PDF accessed 5 June 2023).*

[44] *Government of Canada. Health Canada. Guidance Document for Industry: Submission of Risk Management Plans and Follow-up Commitments. 2015. (PDF accessed 20 April 2023).*

[45] *Korea Ministry of Food and Drug Safety (MFDS). Regulation for Pharmaceutical Approvals, Notifications and Reviews. Ministry of Food and Drug Safety Notification No. 2021-38. Partially Amended and Enforced on April 30, 2021. (Website accessed 2 May 2023).*

[46] *Australian Government. Department of Health. Therapeutic Goods Administration. Risk management plans for medicines and biologicals Australian requirements and recommendations V3.3. 2019. (PDF accessed 2 May 2023).*

47 The United States Food and Drug Administration (FDA). Public Law 110-85. Food and Drug Administration Amendments Act (FDAAA) of 2007. Title IX, Subtitle A, Section 505-1. Enhanced Authorities Regarding Postmarket Safety of Drugs, Risk Evaluation and Mitigation Strategies. 2007. (PDF accessed 20 April 2023).

[48] *Prieto L, Spooner A, Hidalgo-Simon A, Rubino A, Kurz X, Arlett P. Evaluation of the effectiveness of risk minimization measures. Pharmacoepidemiology and Drug Safety. 2012;22;21(8):896-899. https://doi.org/10.1002/pds.3305*

[49] *Mazzaglia G, Straus SM, Arlett P, da Silva D, Janssen H, Raine J, Alteri E. Study design and evaluation of risk minimization measures: a review of studies submitted to the European medicines agency for cardiovascular, endocrinology, and metabolic drugs. Drug Safety. 2018;41:191-202. https://doi.org/10.1007/s40264-017-0604-4*

[50] *The United States Food and Drug Administration. Public Law 110-85. Food and Drug Administration Amendments Act (FDAAA) of 2007. Title IX, Subtitle A, Section 505-1. Enhanced Authorities Regarding Postmarket Safety of Drugs, Risk Evaluation and Mitigation Strategies. 2007. (PDF accessed 20 April 2023).*

[51] *Government of Canada. Health Canada. Guidance for industry – Submission of targeted risk management plans and follow-up commitments for prescription opioid-containing products. 2018. (Website accessed 20 April 2023).*

[52] European Medicines Agency (EMA). Heads of Medicines Agencies (HMA). Guideline on Good Pharmacovigilance Practices (GVP). Module XIV Risk Minimisation Measures: Selection of Tools and Effectiveness Indicators (Rev 2). 2017. (PDF accessed 20 April 2023).

[53] Management of Safety Information from Clinical Trials. CIOMS Working Group VI report. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2005. (PDF accessed 20 April 2023).

[54] European Medicines Agency (EMA). Heads of Medicines Agencies (HMA). Guideline on Good Pharmacovigilance Practices (GVP). Module XIV Risk Minimisation Measures: Selection of Tools and Effectiveness Indicators (Rev 2). 2017. (PDF accessed 20 April 2023).

[55] The United States Food and Drug Administration (FDA). REMS Assessment: Planning and Reporting. Guidance for Industry. 2019. (PDF accessed 20 April 2023).

[56] Prieto L, Spooner A, Hidalgo-Simon A, Rubino A, Kurz X, Arlett P. Evaluation of the effectiveness of risk minimization measures. Pharmacoepidemiology and Drug Safety. 2012;22;21(8):896-899. https://doi.org/10.1002/pds.3305

[57] Mazzaglia G, Straus SM, Arlett P, da Silva D, Janssen H, Raine J, Alteri E. Study design and evaluation of risk minimization measures: a review of studies submitted to the European Medicines Agency for cardiovascular, endocrinology, and metabolic drugs. Drug Safety. 2018;41:191-202. https://doi.org/10.1007/s40264-017-0604-4

[58] Dowden H, Munro J. Trends in clinical success rates and therapeutic focus. Nature Reviews Drug Discovery. 2019;1;18(7):495-496. https://doi.org/10.1038/d41573-019-00074-z

[59] Patient involvement in the development, regulation and safe use of medicines. CIOMS Working Group report. Draft for comment, 24 February 2022. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2022. (PDF accessed 20 April 2023).

[60] The United Stated Food and Drug Administration (FDA). Learn about FDA Patient Engagement. 2021. (Website accessed 20 April 2023).

[61] European Medicines Agency (EMA). Revised Framework for Interaction Between the European Medicines Agency Patients Consumers Their Organisations. EMA/637573/2014. 2014. (PDF accessed 20 April 2023).

[62] Medicines and Healthcare Products Regulatory Agency. Patient Involvement Strategy 2021-2025. Opportunities for patients and the public to be involved in the work of the MHRA. (Website accessed 20 April 2023).

[63] Government of Canada. Health Canada and the Public Health Agency of Canada – Guidelines on Public Engagement. 2019. (Website accessed 20 April 2023).

[64] Kürzinger ML, Douarin L, Uzun I, El-Haddad C, Hurst W, Juhaeri J, et al. Structured benefit–risk evaluation for medicinal products: review of quantitative benefit–risk assessment findings in the literature. Therapeutic Advances in Drug Safety. 2020;11;1-12. https://doi:10.1177/2042098620976951

[65] Innovative Medicines Initiative (IMI) PREFER. About PREFER. Including the patient perspective. 2016. (Website accessed 20 April 2023).

[66] de Bekker-Grob EW, Berlin C, Levitan B, Raza K, Christoforidi K, Cleemput I, et al. Giving patients' preferences a voice in medical treatment life cycle: the PREFER public–private project. The Patient-Patient-Centered Outcomes Research. 2017;10:263-266. https://doi.org/10.1007/s40271-017-0222-3

[67] Innovative Medicines Initiative (IMI) Patients Active in research and Dialogues dor an Improved Generation of Medicines (PARADIGM). PARADIGM Patient Engagement Toolbox. (Website accessed 20 April 2023).

[68] Warner K, See W, Haerry D, Klingmann I, Hunter A, May M. EUPATI guidance for patient involvement in medicines research and development (R&D); guidance for pharmaceutical industry-led medicines R&D. Frontiers in Medicine. 2018;9;5:270. https://doi:10.3389/fmed.2018.00270

[69] Haerry D, Landgraf C, Warner K, Hunter A, Klingmann I, May M, et al. EUPATI and patients in medicines research and development: guidance for patient involvement in regulatory processes. Frontiers in Medicine. 2018;17;5:230. https://doi:10.3389/fmed.2018.00230

[70] Klingmann I, Heckenberg A, Warner K, Haerry D, Hunter A, May M, et al. EUPATI and patients in medicinesresearch and development: guidance for patient involvement in ethical review of clinical trials. Frontiers in Medicine. 2018;7;5:251. https://doi.org/10.3389/fmed.2018.00251

[71] Clinical Trials Transformation Initiative. CTTI Recommendations: Patient Group Engagement. 2015. (PDF accessed 20 April 2023).

[72] The United States Food and Drug Administration (FDA). The FDA Patient-Focused Drug Development. Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making. (Website accessed 20 April 2023).

[73] Mühlbacher AC, Juhnke C, Beyer AR, Garner S. Patient-focused benefit-risk analysis to inform regulatory decisions: the European Union perspective. Value in Health. 2016;1;19(6):734-740. https://doi.org/10.1016/j.jval.2016.04.006.

[74] Medicines and Healthcare Products Regulatory Agency. Patient Involvement Strategy 2021-2025. Opportunities for patients and the public to be involved in the work of the MHRA. (Website accessed 20 April 2023).

[75] *Pharmaceuticals and Medical Devices Agency (PMDA). Patient Centricity WG. (Website accessed 20 April 2023).*

[76] *Patient Focused Medicines Development (PFMD). Mission and strategy. (Website accessed 20 April 2023).*

[77] *de Wit M, Abma T, Koelewijn-van Loon M, Collins S, Kirwan J. Involving patient research partners has a significant impact on outcomes research: a responsive evaluation of the international OMERACT conferences. BMJ Open. 2013;1;3(5):e002241. https://doi:10.1136/bmjopen-2012-002241*

[78] *Ennis L, Wykes T. Impact of patient involvement in mental health research: longitudinal study. The British Journal of Psychiatry. 2013;203(5):381-386. https://doi:10.1192/bjp/bp112.119818*

[79] *The United States Food and Drug Administration (FDA). Food and Drug Administration Safety and Innovation Act (FDASIA). 2012. (Website accessed 20 April 2023).*

[80] *Pharmaceuticals and Medical Devices Agency (PMDA). Patient Centricity WG. (Website accessed 20 April 2023).*

[81] *The Medicines for Human Use (Clinical Trials). Amendment, EU Exit, Regulations. 2019. (Website accessed 20 April 2023).*

[82] *Geissler J, Ryll B, di Priolo SL, Uhlenhopp M. Improving patient involvement in medicines research and development: a practical roadmap. Therapeutic Innovation & Regulatory Science. 2017;51(5):612-619. https://doi10.1177/2168479017706405*

[83] *Chaudhuri SE, Ho MP, Irony T, Sheldon M, Lo AW. Patient-centered clinical trials. Drug Discovery Today. 2018;1;23(2):395-401. https://doi.org/10.1016/j.drudis.2017.09.016*

[84] *Lim SS, Kivitz AJ, McKinnell D, Pierson ME, O'Brien FS. Simulating clinical trial visits yields patient insights into study design and recruitment. Patient Preference and Adherence. 2017;31:1295-1307. https://doi:10.2147/PPA.S137416*

[85] *Franco MR, Ferreira ML, Ferreira PH, Maher CG, Pinto RZ, Cherkin DC. Methodological limitations prevent definitive conclusions on the effects of patients' preferences in randomized clinical trials evaluating musculoskeletal conditions. Journal of Clinical Epidemiology. 2013;1;66(6):586-598. https://doi.org/10.1016/j.jclinepi.2012.12.012*

[86] *Marcus SM, Stuart EA, Wang P, Shadish WR, Steiner PM. Estimating the causal effect of randomization versus treatment preference in a doubly randomized preference trial. Psychological Methods. 2012;17(2):244. https://doi.org/10.1037/a0028031*

[87] *Medical Device Innovation Consortium (MDIC). Patient centered benefit-risk project report: a framework for incorporating information on patient preferences regarding benefit and risk into regulatory assessments of new medical technology: Medical Device Innovation Consortium. 2015. (PDF accessed 20 April 2023).*

[88] *Biotechnology Innovation Organization (BIO). Key considerations for developing & integrating patient perspectives in drug development: examination of the Duchenne case study: Biotechnology Innovation Organization and Parent Project Muscular Dystrophy. 2016. (PDF accessed 20 April 2023).*

[89] *Ho M, Saha A, McCleary KK, Levitan B, Christopher S, Zandlo K, et al. A Framework for incorporating patient preferences regarding benefits and risks into regulatory assessment of medical technologies. Value in Health. 2016;19(6):746–750. https://doi.org/10.1016/j.jval.2016.02.019*

[90] *Ho MP, Gonzalez JM, Lerner HP, Neuland CY, Whang JM, McMurry-Heath M, Brett Hauber A, Irony T. Incorporating patient-preference evidence into regulatory decision making. Surgical Endoscopy. 2015;29:2984-2993. https://doi.org/10.1007/s00464-014-4044-2*

[91] *Morel T, Aymé S, Cassiman D, Simoens S, Morgan M, Vandebroek M. Quantifying benefit-risk preferences for new medicines in rare disease patients and caregivers. Orphanet Journal of Rare Diseases. 2016;11(1):1-2. https://doi.org/10.1186/s13023-016-0444-9*

[92] *Tegenge MA, Moncur MM, Sokolic R, Forshee RA, Irony T. Advancing the science of patient input throughout the regulatory decision-making process. Learning Health Systems. 2017;1(3):e10032. https://doi.org/10.1002/lrh2.10032*

[93] *Bernabe RD, van Thiel GJ, van Delden J. Patient representatives' contributions to the benefit–risk assessment tasks of the European Medicines Agency scientific committees. British Journal of Clinical Pharmacology. 2014;78(6):1248-1256. https://doi.org/10.1111/bcp.12456*

[94] *British Epilepsy Association. Results of our Valproate survey. (Website accessed 20 April 2023).*

[95] *European Medicines Agency (EMA). Valproate and Related Substances. 2014. (Website accessed 20 April 2023).*

[96] *European Medicines Agency (EMA). Valproate and Related Substances. 2018. (Website accessed 20 April 2023).*

Chapter 3: BR methodology considerations

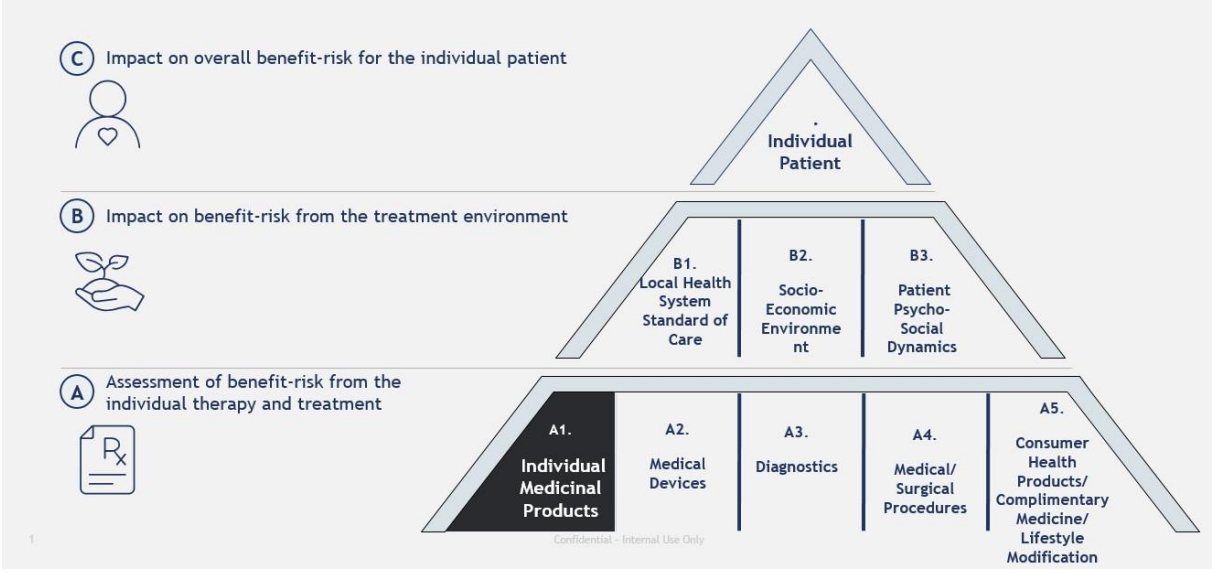
The chapter will focus specifically on methods used in the BRA process. While this includes presentation of statistical methods, we also wanted to provide pragmatic recommendations around the conduct of BR related activities. For example, we provide clear recommendations around membership of certain teams. At the same time, we appreciate the complexity and scope of methods used in the field of BRA. 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.

3.1 Applying BR methodologies across the many dimensions of patient care: different scopes and purposes

Chapter 1 highlighted the respective context of BRAs from the approval of individual medicinal product to the last step being the interaction between the patient and their health care provider. These incorporate three key dimensions: the patient, the health care and the integrated health system. Chapter 2 focused on the BR considerations for individual medicinal product. We will briefly describe here how the methods to assess BR vary greatly depending on the focus of the assessment. For example, the assessment of medical devices uses a different framework. Similarly, the approach for Health Technology Assessments is distinct. Essentially, for each of the components outlined in Figure 5, different methodologies to evaluate BR have been applied and are evolving over time. We will briefly review some of the approaches for each category to highlight the variety of BRA methodologies at play. 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.

Figure 5: Key components of overall BRAs and decision making

Source: CIOMS Working Group XII



3.1.1 Individual medicinal products (A1)

Specific methodological considerations regarding the BRA of individual medicinal product will be the primary focus of this chapter. Many of these methods are equally relevant to the BRA relevant to

other components of Figure 5. However, there are currently acknowledged differences. It is important to understand these.

For one, the BRA for any medicinal product needs to consider the standard-of-care and available treatments in the country/region. Some of these may be other medicinal products (A1), but they also include medical devices (A2), medical and surgical interventions (A4), as well as other elements of healthcare, such as consumer health products and lifestyle modifications (A5). The characteristics (e.g. sensitivity and specificity) and reliability (e.g. inter-laboratory reproducibility) of diagnostic methodologies (A3) are also a critical component of the assessment.

Importantly, the BRA processes applied beyond medicinal products are also evolving rapidly. It is therefore important to understand the current situation for these as well as the likely evolution of the methods for these specific areas. A summary of some of these considerations follows.

3.1.2 Medical devices (A2)

Medical devices (A2) are rapidly evolving in number, scope and complexity. This is being driven by technological advances including 3D printing and artificial intelligence. Regulatory authorities have long played a key role in the oversight of medical devices and it is important to understand the interface with medicinal products. 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.[97] A key component of this complex topic relates to the potential release of particulate metal materials causing local tissue reaction or systemic effects. For example, cobalt is a component of these implants, and has been the focus of much research in the field. These devices continue to be in clinical use is most countries but are subject to on-going clinical monitoring.[98,99,100,101]

Another example relates to one subset of breast implants, and the potential link to anaplastic large cell lymphoma.[102,103] A third example is provided by the use vaginal mesh products in the management of pelvic organ prolapse.[104] These two examples, a small sample of those in the field of medical devices, highlight the complexity of the topics, the interface with the HCPs, medical societies and difference across countries and regions.

The US FDA defines a medical device as: “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.”[105]

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

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 5.

Table 5: ISO 14971 Standard Risk Management Process

Source:[106]

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 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. 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 end-users outside the business, to the internal facing functions of product supply, manufacturing, quality, regulatory, commercial, and safety who contribute to the medical device product Risk Management team. Together these differing perspectives and experiences yield a total risk management lifecycle: design, develop, 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 boxes.

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 BR analysis for a medical device looks at the results of the risk analysis, risk evaluation, 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 residual risks are acceptable. The contrast is seen as this assessment is engineered into the device by design and continues throughout the lifecycle post authorisation.

Device BRA = risk analysis + risk evaluation

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.

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, device risk management is a holistic lifecycle

process that is continuous. That said, the device developer must regularly review all incoming field data, complaints and other material feeding into the risk management process to ensure the product's BR remains favourable under normal, intended use.

There are several instances where it is critical to understand the assessment of benefit- risk for devices in parallel to that for 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 device (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); this is frequently referred to as a drug device combination product and is becoming an increasing area of interest and scrutiny for regulatory agencies.

3.1.3 Diagnostic methodologies (A3)

Fundamental to any disease state is the ability to make an accurate diagnosis. In this context, diagnostic methodologies (A3) are an important consideration in the BRA of any medicinal product. The appropriate BR profile of a medicinal product is highly linked to the level of certainty around the diagnosis and/or prognosis of the target disease state.

The clinical examination and evaluation continue to be a crucial part of disease diagnosis, which impacts directly on the choice of therapy and medicinal product. The variability in the clinical acumen of practitioners, and the insights into the patients are thus an essential underlying component of the overall BR profile of any therapeutic intervention. Many examples can be highlighted; we will detail two of these.

The diagnosis and management of arterial hypertension is heavily dependent on the clinical examination. Yet, it is well documented that blood measurement can be highly variable, depending on the method used and the context in which the blood pressure is assessed.[107] These considerations are highly relevant in conducting controlled clinical studies, extrapolating results to real-world circumstances, and determining the BR of medicinal products for hypertension.

Major depressive disorder (MDD) is a condition with a high index of morbidity and mortality. The initial clinical suspicion is highly dependent on the clinician's acumen and suspicion. This can optimally be followed by administering established structured clinical assessments, each with variable degree of sensitivity and specificity.[108] Pivotal clinical studies incorporate robust assessment for MDD. Unfortunately, the every-day clinical situation may not follow such rigorous diagnostic protocols, and this must be considered in determining the overall BR for antidepressants.

It is important to acknowledge that several diagnostic methodologies involve the use of a medicinal product (e.g. drug-enhanced magnetic resonance imaging (MRI)), which then drives a specific medicinal product BRA relative to the diagnostic procedure itself. A classic example of this relates to MRI contrast agents, as outlined here.

Gadolinium-based contrast agents (GBCAs) were approved in 1988 for use in MRI. Since then, they have been used in more than 600 million patients worldwide and have demonstrated an excellent safety profile with a very low rate of mostly mild and transient adverse events. All commercially available GBCAs are molecularly composed of gadolinium (Gd+3) bound to a chelating ligand. GBCAs are categorised as linear versus macrocyclic, based on the molecular structure of the ligand, and as nonionic versus ionic, based on whether they are charged in solution. As a rule of thumb, macrocyclic agents are more stable than linear, and ionic agents are more stable than nonionic. While free Gd+3 is highly toxic, chelation makes a GBCA safe for intravenous injection while maintaining the paramagnetic properties of the gadolinium (Gd) for MRI.[109,110]

Nephrogenic systemic fibrosis

In 2006, 18 years after the 1st GBCA (Magnevist®, Bayer) was introduced, an Austrian researcher[111,112] postulated that GBCAs could be the trigger for a new fibrosing disorder (Nephrogenic Systemic Fibrosis, NSF) in patients with dialysis-dependent chronic kidney disease (CKD). NSF was first designated as a new clinical entity in 2000, when researchers discovered several cases dating back to 1997.[113]

NSF is primarily manifested by thickening and hardening of the skin and subcutaneous tissues, sometimes leading to painful joint contractures and immobility, but studies have shown that some patients experienced fibrosis of deeper structures, including muscle, fascia, lungs, and heart.[114,115,116] Bayer's own non-clinical research showed that the least stable GBCA (Omniscan®) was capable of inducing NSF-like skin lesions in rats.

Following an Article 31 Referral Procedure in Europe in November 2008 and an FDA Advisory Committee in the US, risk minimisation measures were put into place. These included Dear Health Care Professional Letters, labelling changes (including a black box warning in the US), requirements to list the brand and dose of GBCA received by patients in their medical records, adoption of a targeted questionnaire to follow up on potential NSF cases, periodic reports on the topic to health authorities, and the initiation of a clinical study to evaluate the possibility of long-term retention of Gd in bone and skin. All of these post-marketing requirements have been completed. The study of Gd in bone and skin was not able to determine that there were any clinical effects of Gd in bone and could not make any risk differentiation among the GBCAs. Clinician awareness of NSF, adoption of restrictive policies regarding use and dosing of GBCAs in patients with advanced kidney disease, and the increasing use of more stable GBCAs led to a dramatic reduction in NSF cases after 2007. The disease today has been virtually eliminated.

Concerns about Gadolinium presence in the brain and other organs

In 2014, researchers in Japan[117] and Italy[118], noted that increased signal intensity could be observed on the unenhanced scans of patients who had received multiple doses of primarily linear GBCAs, such as Magnevist and Omniscan. These studies prompted intensive investigations by Bayer and health authorities worldwide. Studies showed that when a GBCA is administered, traces of the administered Gd may remain in the body, including the brain, for various periods of time. No adverse clinical effects of retained Gd have been confirmed to date in patients with normal renal function; however, some patients attribute a wide range of persistent symptoms to GBCA administration.[119,120]

Following an Article 31 Referral Procedure in Europe in March 2017 and an FDA Advisory Committee in the US, as well as evaluations by other authorities including Health Canada, the European Health Authority suspended the MAs of multi-purpose linear GBCAs on a precautionary basis, while acknowledging that no harm to patients had been confirmed. Additionally, various risk minimisation measures were introduced to mitigate any possible clinical effects of the retained Gd. These included Dear Health Care Professional letters, labelling changes, enhanced pharmacovigilance including introduction of a targeted questionnaire to follow up on cases of Gd presence and cases of persistent symptoms. Bayer performs an interval and cumulative analysis of this topic in annual PBRERs. Additional non-clinical studies in neonatal and juvenile mice (completed) and non-human primates (ongoing) were undertaken to further investigate any potential risk of Gd presence in the body. No adverse effects of Gd presence were observed in the completed mice studies. Additionally, Bayer and other developers of GBCAs are participating in a clinical study, named Odyssey, with long term (five year) follow-up to further investigate the safety of GBCAs.

While the presence of Gd in the skin has been associated with NSF in patients with severe kidney disease, to date there has been no scientific evidence that Gd presence in the brain or elsewhere has been responsible for clinical adverse effects in patients with normal renal function.

The field of companion diagnostics is rapidly evolving. One of the first example was the use of trastuzumab for breast cancer, and the assay for HER2 overexpression.[121] Another example is the development and ultimate approval of pembrolizumab coupled with the immunotherapy biomarker assay, measuring PD-L1.[122,123] Assessing these predictive markers is a very complex domain which requires in-depth evaluation.[124,125] Failure to appropriately assess the patient for the presence or absence of these markers is critical in the overall BRA. It could result in withholding a likely effective therapy for the appropriate patient (i.e. false negative test), or expose the patient to a non-indicated treatment (i.e. false positive test). The field is expanding to other therapeutic areas, introducing equal complexity to areas where the BR balance may be narrower.[126] Labelling for medicinal products highlights the interdependencies between these complex diagnostic modalities in the indication for the specific product.

Artificial intelligence (AI) also contributes to the area of diagnostics. There are numerous examples where enhanced diagnostic methodologies are improving the accuracy of diagnosis and potentially identifying populations more or less likely to respond to therapeutic modalities, including anatomical sites as diverse as the skin and the macula.[127,128] The field of cardiology is rapidly providing examples of patients using wearable technology and AI algorithms to analyse the data, highlighting both opportunities and challenges around this evolution.[129] AI is also expanding the possibilities around pharmacogenomics in selecting optimal populations for use of a specific medicinal products in the context of the overall BR.[130]

Other diagnostic procedures involve specific risks (e.g. myocardial infarction (MI) during cardiac stress test procedure), which also needs to be weighed against the benefit of the information gained from the test.[131] Specifics around these BRAs will not be detailed further here.

Overall, most diagnostic tests involve minimal risks and as such, the BR for each test is more related to the quality and reliability elements of the test, measurements such as sensitivity and specificity. Detailed methodologies exist to assess these dimensions, and in most countries, there are one or more regulatory bodies that approve the original (or subsequent major updates) version of a test, including the US FDA or EMA, as appropriate. Recently, a specific framework has been proposed relative to the BRA for diagnostics (BED-FRAME).[132] In addition, in most countries, professional societies or agencies oversee the quality elements of such testing to ensure that adding laboratory level these tests perform as originally designed (e.g. American College of Pathology). The overall evaluation from these professional bodies is an important element to consider in the BRA of medicinal products that depend on the diagnostic methodologies. Significant fluctuations in the sensitivity and specificity of tests, either inherent to the technology or because of challenges in laboratory-to-laboratory variability, may introduce a significant level of uncertainty around the clinical performance of a medicinal product for a given condition.

A rapidly evolving field is the so-called wearable diagnostic devices (e.g. wrist watch) as well as smartphone-based technologies, often coupled with artificial intelligence algorithms. These can assess a broad range of conditions, including heart rhythm, blood glucose, skin conditions and fundoscopy.[133,134,135] This is a relatively new area, compared to more established methods, where the specific parameters of quality and reliability are being defined. It should be expected, however, that there will be a rapid and broad expansion of such methods for a wide range of medical conditions, and the performance characteristics for these technologies will become an important element in the BRA of medicinal products in the management of the respective medical condition.

3.1.4 Medical and surgical interventions (A4)

For a wide range of medical conditions, medical or surgical interventions (A4) are widely used as treatment options and must be considered in the overall BRA of a medicinal product. A major challenge in considering these different therapeutic modalities is the framework that is used to assess the BR profile.

Usually, clinical interventions are not subject to any formal approval by a national health authority. They may, or may not be supported by local payer and reimbursement agencies, but this is highly variable. 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. Multiple studies have established the wide range of care across countries for a wide range of medical conditions including rheumatoid arthritis, hypertension and Parkinson's disease.[136,137,138]

Some procedures have been subject to detailed and rigorous studies. An example are the comparative studies of coronary artery bypass graft surgeries (CABG) compared to transcutaneous stenting procedures.[139,140] In addition to these studies, other parallel evaluations have highlighted that the BR of the interventions 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 surgeon and medical centre.[141,142]

Another example is the assessment of different surgical approaches for the management of prostate cancer. This provides an example of how evaluations and assessment 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.[143] Despite such early assessments, the novel methods continued to gain in popularity amongst urologic surgeons.[144] 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.[145,146,147]

The interface between pharmaceutical therapy and surgery presents a high level of complexity when there is clear recognition that surgical technique and patient level characteristics (e.g. quality of tissue) itself influences the overall outcome. A clear example of this is the BRA of anti-thrombotic agents used in the context of surgical cardiac revascularisation.[148,149] 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 patients undergoing surgery, and treatment duration.

Medical and surgical procedures may be important considerations in the therapeutic alternatives to medicinal products. The process to assess the BR balance of these relies on a range of different frameworks. Ultimately this leads to greater uncertainty in comparing efficacy and safety of such procedures compared to a medicinal product. Local medical practice in the overall efficacy of such procedures is also much more likely than for medicinal products. These are all important considerations to evaluate while conducting a BRA for a medicinal product.

3.1.5 Consumer health products, complementary medicine and lifestyle modifications (A5)

As highlighted in Chapter 1, this is a broad area of products which ultimately play a role in the treatment of many patients. We will focus first on the broad category of complementary and alternative medicine (CAM), which effectively includes most consumer health products.

The importance and relevance of CAM in patient management is highly relevant. Studies show a wide range of use in the general population but in some instances nearing 70%, differing by countries and individual characteristics.[150] These numbers become even more relevant when looking at specific populations that are already being treated with a number of complex medications, such as cancer patients, where CAM can be used by the majority of patients to mitigate some of the side effects of treatments, but may also introduce potential for DDI.[151]

The US National Institutes of Health has outlined a framework to consider complementary health approaches. These fall under the following categories, including examples:

- Nutritional – e.g. special diets, dietary supplements, herbs, probiotics, and microbial-based therapies;
- Psychological – e.g. meditation, hypnosis, music therapies, and relaxation therapies;
- Physical – e.g. acupuncture, and massage spinal manipulation;
- Combinations such as psychological and physical or nutritional – e.g. yoga, tai chi, dance therapies, some forms of art therapy, and mindful eating.

Many national and international efforts are under way to assess the efficacy and safety of all these approaches in the overall therapeutic armamentarium. In most countries, these interventions are not regulated under the national health authority. They may be subject to regulation by other national authorities (e.g. agriculture) or certifying bodies (e.g. medical licensure for acupuncturists).

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. Wearable technology is also rapidly expanding to these lifestyle interventions and contributing further to the evolving science in this area.

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 treatment of obesity.

In summary the use of CAM tends to be widespread. In many instances, these are used along with medicinal products and should be considered when performing a comprehensive BRA of an individual medicinal product. This includes potential for DDIs as well as modulation of the overall benefit- risk profile in instances where CAM are used to potentially mitigate adverse events.

3.1.6 Local health system standard-of-care (B1)

Within each community so-called standard-of-care (B1) 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 the political state or provincial driven system) within each country.

Guidelines from national and international professional medical societies provide further input to medical professionals around 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 and latitude in their practices. As highlighted in Chapter 1, 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 standard of care is generally defined in a broad manner, with highly variable systematic or framework driven analysis. Nonetheless, ultimately this is most frequently what informs the interaction between the patient and the health care provider in BR discussions. We view this area as a great opportunity for future improvements.

3.1.7 Socio-economic environment (B2)

Patients and HCPs live in communities where the social and economic environment ultimately play a determinant role in the access and quality of care provided (B2). This is widely acknowledged in

terms of health care disparities seen across the world. These challenges can be seen within a country, as illustrated in the US elderly population relative to racial disparities.[152] They may be seen across international borders, potentially related to access to health care, as demonstrated in a study of a technologically complex procedure such as lung transplant.[153] They are consistently confirmed through global studies on the burden of illness such as cancer and chronic obstructive pulmonary disease.[154,155]

As highlighted in Chapter 1, the advent of increasingly complex medicinal products has 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 to evaluate 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 defined by the Pan American Health Organization / World Health Organization:

> *"Health Technology Assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technology. It should include medical, social, ethical, and economic dimensions, and its main purpose is to inform decision-making in the health area. These assessments look at benefits and efficacy, clinical and technical safety, and cost-effectiveness. Informed decision-making comprises issues surrounding coverage and reimbursement, pricing decisions, clinical guidelines and protocols, and lastly, medical device regulation. The main purpose of HTA is to inform a policy decision making in health care, and thus improve the uptake of cost-effective new technologies and prevent the uptake of technologies that are of doubtful value for the health system."*

HTA is used to define which benefits to include while carrying out evidence-based assessments. New technologies are usually costlier than older ones and contribute to rising health expenditures. In this context, the HTA process ensures that new technology is not added until it is proven to be effective. Meanwhile, older technology is not removed from the health package until it is shown to be ineffective or not cost-effective. HTA is also concerned with quality, and the role of new technologies to improve health outcomes.

The methodologies used to conduct HTAs are varied, but they overlap in many instances with that for BRA of medicinal products.[156] Two important differences 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.[157] 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.[158]

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.[159,160]

For this complex topic, the USA provides a clear example of challenges linked to HTA assessments. The majority of patients access care through private healthcare 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 healthcare. 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 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 great influence the HTA area in the US is the Institute for Clinical and Economic Review.[161,162,163] Authors have highlighted discrepancies between the HTAs conducted by ICER and other HTA researchers and the opportunities for further evolution.[164,165,166] Ultimately the recommendations from such group determine whether or not an individual patient in the US has reimbursed access to a medicinal product, regardless of the approval status of such drug and the recommendations of the treating HCP.

The interface between regulatory approval and HTA recommendations continues to be an area of great interest and controversy.[167] At present, these continue to be considered as separate processes with overlapping considerations and methodologies, but different ultimate focus and scope. These sometimes occur serially and at other times sequentially. These considerations are likely to evolve further over time, given the overall economic context of healthcare delivery.

3.1.8 Patient psycho-social dynamics (B3)

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*).[168] 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 of study patients (B3).

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 socioeconomic standings, are all important considerations for National Health authorities as they look to assess the BR of a medication. They are equally if not more important to be considered by the HCP for the individual patient living under these circumstances.

3.1.9 Individual patient (C)

The final decision about using a medicinal product rests with the patient, based on the information provided by their HCP (C). This is the final pragmatic synthesis of all the information generated in the pyramid depicted in figure X. 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 and potential opportunities.

One important component is the time given to making such a decision. It is a reality of modern healthcare that in most instances the face-to-face time between the patient and their HCP is very limited, frequently less than 10 minutes in total. 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. 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 events linked to the COVID-19 pandemic give us pause that such a positive reality can ever exit, but we should still strive for it.[169,170]

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.[171,172,173,174,175,176,177]

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.[178,179] 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.[180]

3.2 The evolution of BRA: study designs and statistical approaches

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 profile of a medicinal product must be flexible enough to meet the expectations of most national health authorities, as outlined above. We will focus first on the a priori design of pivotal studies and the predefined statistical analysis plan (SAP). We will discuss later additional statistical approaches to conducting BRA in a post-hoc fashion, frequently enhanced by additional data sets (e.g. RWE). While these are general categories, one must acknowledge that there is always flexibility in the approach to datasets, especially when aligned between the sponsor and Health authority.

3.2.1 Classic study design and statistical approach to inform the BRA leading to registration

The vast 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 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 is linked to the medical condition under study, as well as the minimum duration of treatment and follow-up. The outcome 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 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. Increasingly, alternatives for the comparator group are becoming accepted (e.g. ICH E8 and E10 guidances). These can include historic controls, case-matched controlled, and others. 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 assessment during Phase 1 and Phase 2, the approach to the assessment of Phase 3 studies 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 randomised controlled trials. 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 subject to 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. adverse event 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 adverse event, 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 benefit and risk assessment.

3.2.2 Patient-level BRA – 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 harms of interventions, ultimately yielding the data 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.[181] 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 standard 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 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 BR analyses

Several areas offer significant opportunities for improving the BRA. These are shown in Table 6 and discussed below.

Table 6: Issues to consider in improving BRA
Source: CIOMS Working Group XII

1. Generalisability
2. Importance of ITT and the Strategy of application
3. Absolute vs relative risks
4. Evolve away from the tradition of BR as a post-hoc exercise
5. Find more pragmatic approaches and Improve 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 (e.g. entire population) in another, then BRA, which combines those two has no clear generalisability.

2- The importance of ITT 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 is not well-defined.

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 whether outcomes labelled as efficacy, safety, or BR.[182,183]

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[184], 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 saved 59 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. Ticagrelor cost 21 safety events. 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 (ARs) summaries are more appropriate when synthesising the result of multiple endpoints.

4 - Evolve away from the tradition of BR 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[185,186] as failure to pre-specify endpoints can introduce bias and creates 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 BR 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 interpretation of component outcomes. Treatment effect heterogeneity is typically evaluated based on a single efficacy or safety endpoint, and rarely evaluated based on BR. 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. 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 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.[187] 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 has clinical failure without SAEs. This is intuitive though 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.

Let's illustrate this 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 7 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 7: 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 8) of the data reveals the following, focusing on Cell M – efficacy 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 8: A more granular analysis of the data

Source: CIOMS Working Group XII

Outcome (Category)	**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 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 therefor clearly reflects how treatments compare with respect to their effect on patients.[188]

Integration of BRA 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 harms 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 9.

Table 9: Recommendations for integrating BR 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) and Dalbavancin as an Option for Treatment of S. aureus bacteremia (DOTS) 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
	Carefully 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 sub-groups 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."[189] Concepts and methodologies for data monitoring based on BR have been described and implemented.[190]
	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 result of multiple endpoints that reported on a relative risk 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 (DOOR)

The desirability of outcome ranking (DOOR)[191] 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.[192] Recent publications have developed and applied DOOR outcomes for complicated intra-abdominal infections (cIAI) based on an FDA ORISE fellowship[7], and complicated urinary tract infections (cUTI) based on a working group consisting of academic investigators, regulators and industry partners.[193,194]

A simple example of a 3-level DOOR for a life-threatening disease is in Table 10.

Table 10: A simple example of a DOOR incorporating survival status and SAEs

Source: CIOMS Working Group XII

DOOR Rank	Patient-Centric Outcome
1 (most desirable)	Survives without a SAE
2	Survives with an 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.

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 DOOR, a rank-based approach based on pairwise patient comparisons and using *partial credit* have been proposed. The recommended statistical analysis plan (SAP) for 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 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*N2 possible pairwise comparisons. When comparing a specific patient's results from one treatment group to a patient from the other treatment group, a more desirable (win), less desirable (loss), or equally desirable (tie) result will be observed. Researchers have proposed use of 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.

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 tied desirability]) in one treatment relative to another treatment, the proportion in favour of treatment,[195] and the *win ratio*,[196] i.e. the relative frequency by which one treatment has a more desirable result than another, can be calculated by tabulating the pairwise comparison results.

DOOR probability = (#wins + 0.5[#ties])/(N1*N2)

Proportion in favour of treatment (net benefit) = (#wins – #losses)/(N1*N2)

Win ratio = # wins/#losses

The DOOR probability and the proportion in favour of treatment can be viewed as absolute measures whereas the win ratio can be considered as a relative measure. Approaches for incorporating for

[7] US FDA 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.

example, stratification variables into calculations are available[197] as are methods that account for censoring.[198]

Using the rank-based approach, for example the DOOR probability is estimated along with an associated confidence interval. 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 hazard ratio), 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 BR, 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 3-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

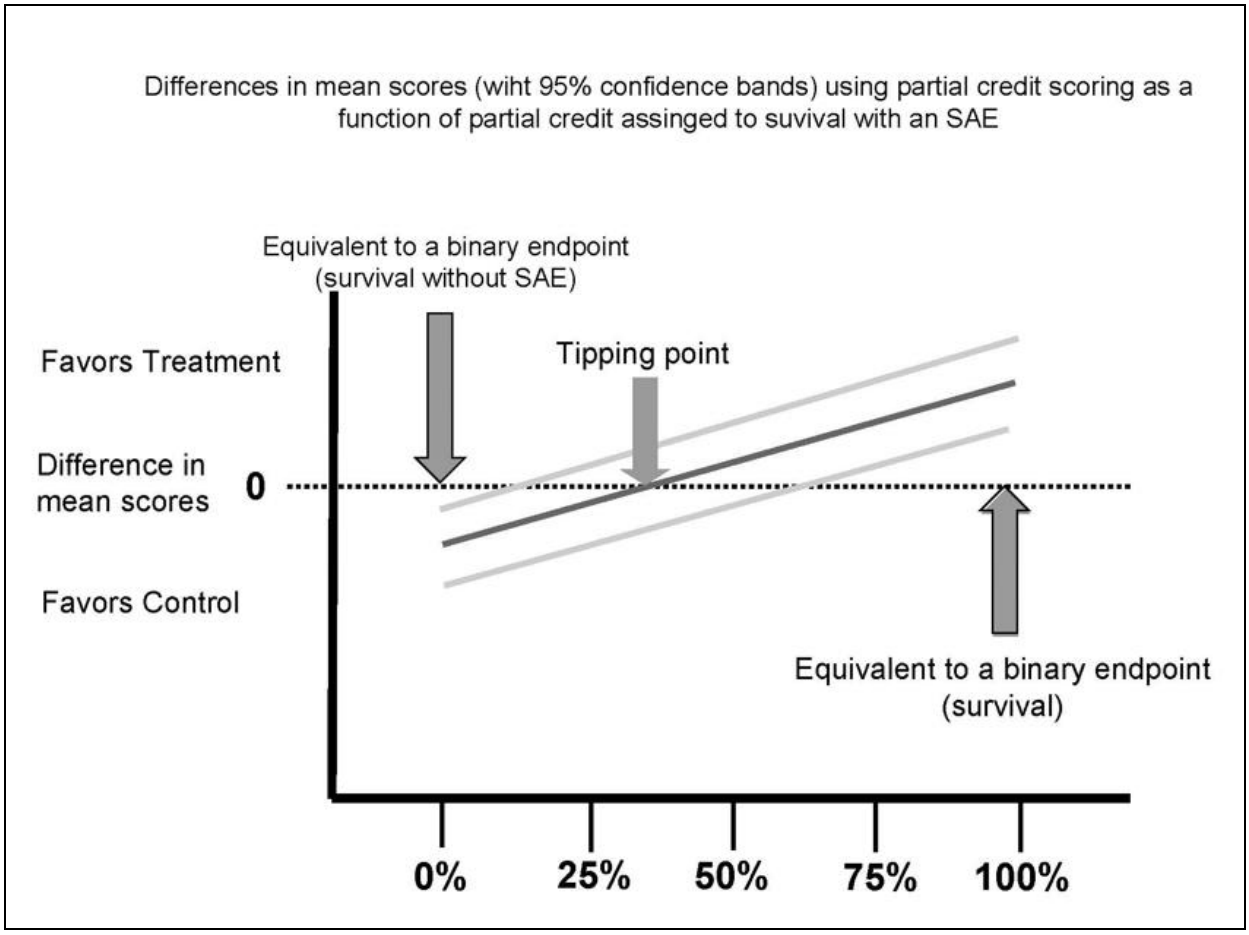
Partial credit analyses[199] can be conducted to directly address the concerns with pairwise comparison methodologies. Partial credit analyses involve grading the levels of the ordinal DOOR outcome similar to an academic test, i.e. from 0% to 100%. Consider the example of the simple 3-level DOOR in Table 10. If the patient experiences the most desirable outcome (survival without an 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 an SAE), directly accounting for the desired distance between categories. Assigning a partial credit of 100% provides full credit for surviving with an SAE. This would equate to 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 an SAE. This would equate to analysis of a binary endpoint of survival without an 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:[200]



Ordered priorities

An alternative strategy to constructing a composite outcome is through the prioritisation of individual outcomes and then utilised the rank-based methods described above. For example, suppose two outcomes are considered: survival and whether an adverse event occurred. Further, suppose that survival is prioritised over the adverse event. 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 adverse event status. The win ratio, proportion in favour of treatment, and the DOOR probability could then be estimated. Score based analyses 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 the case studies in Appendixes A and B.

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.

3.2.3 Estimands in BRA

Another statistical approach that is continuing to attract interest in the context of BRA is the concept of estimands, which are a precise description of the treatment effect to be estimated from a trial reflecting its objectives. Although the word "estimand" was suggested in 1939, and used by Tukey in 1968, it has only become part of the mainstream statistical constructs since 2010.[201] Clearly defining the scientific question of interest is crucial to have alignment among planning, design, conduct, analysis, and interpretation of clinical trials. In practice, however, the choice of scientific question may be masked partially or wholly by the analysis set and statistical analysis, leading to confusion in answering the true clinical question. Recognising the gap and 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).[202]

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) may also be helpful to bring 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 risk-benefit. 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[203] and efforts have been made to apply the estimand paradigm to analysis of adverse events.[204]

The process of articulating the question of interest is a multi-disciplinary task that requires cross-functional discussions with different stakeholders. The framework of estimand, which is proposed in ICH E9(R1), 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 use of an additional or alternative therapy. There are five strategies suggested by ICH E9(R1) 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 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 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 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 success or failure (e.g. clinical response or not), use of rescue medication could be another case of failure. Thus, a composite variable could be 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 ADR 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) 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[205], most discussions in the literature are provided around assessing efficacy from randomised clinical trials. 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 adverse events 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 BRA for a more detailed discussion about suitability of these summaries for BR). 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 hazard ratio as population-level summary (see paragraphs on Absolute vs relative risk in section 3.2.2 on Patient-level BRA – A novel paradigm through drug development and lifecycle management for a more detailed discussion about hazard ratio for BR).

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 ignore 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 the wrong treatment and had adverse events, they would be more naturally attributable to the actual treatment, rather than the randomised treatment (see section 3.2.2 on Patient-level BRA – A novel paradigm through drug development and lifecycle management for a more detailed discussion). In addition, if rescue medication was used and an adverse event happened, clinical judgement is 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[206] and varying exposures.[207]

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[208], 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 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 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.[209] Instead, a sensitivity analysis was presented that included data after 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 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 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. Further examples can be found in.[210] 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[211,212,213,214] as well as a comprehensive review.[215]

3.2.4 Pragmatic and large simple trials as opportunities to better inform BRA

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 underrepresented 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.[8] 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.[216,217,218,219,220,221,222,223,224]

The concept of the pragmatic trial emerged decades ago from the general division of randomised controlled trials 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[225] 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 over-the counter medications under routine medical care.[226]

There is a high degree of overlap between the definition of PCT and LSTs; 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.[227] Pragmatic trials are generally classified according to the 'pragmatism' of their design with multiple tools available[228,229,230] whereas the LSTs are primarily characterised by their large sample size and simple and streamlined data collection processes.[231,232,233] A trial can meet both pragmatic and LST definition, 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 investigating BRA questions and safety topics of interest, which would not be feasible to evaluate in a traditional trial due to 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. Generally conducted in post-approval setting, but may be useful in early development[234,235] or for label expansions.[236] 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.[237]

Pragmatic and large simple trials can generate RWE if they collect data from RWD sources,[238] although 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.[239]

There are ongoing efforts to understand whether randomised clinical trial results can be replicated using rigorous design and statistical methods in observational studies with RWD. Until such results 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.

[8] **A traditional clinical trial** is usually supported by a research infrastructure that is largely separate from routine clinical practice and is designed to control variability and maximise data quality.

Table 11: High-level comparison of study types

Source: CIOMS Working Group XII

	Traditional pivotal RCT	**PCT/LST**	**RWE - EHR**	**RWE – AdmDB**
Sample Size	Approx. 500-10,000*	Larger, 1000 – 10,000*	1,000 to 100,000+	1,000 to Million+
Control for Bias	Randomisation	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 EHR 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 BR methods for special situations).

3.2.5 Statistical approaches to enhance the BRA

As has been clearly outlined, there are inherent 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. All of these tools (Table 12) are of great assistance in the right context. Which of these should be used 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 12: Quantitative BRA methods

Source: CIOMS Working Group XII

(Example in Appendix if applicable) • MCDA (see Appendix II, B) • Stochastic multicriteria acceptability analysis • Monte Carlo Simulation (see Appendix II, A.2) • Metrics: number needed to treat (NNT), number needed to harm (NNH), impact numbers, and BR ratio • Estimation techniques o Probabilistic simulation model o Indirect/multiple treatment comparison o 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 assessment of benefit-risk and risk management measures. 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.[240,241]

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

Source: CIOMS Working Group XI[242]

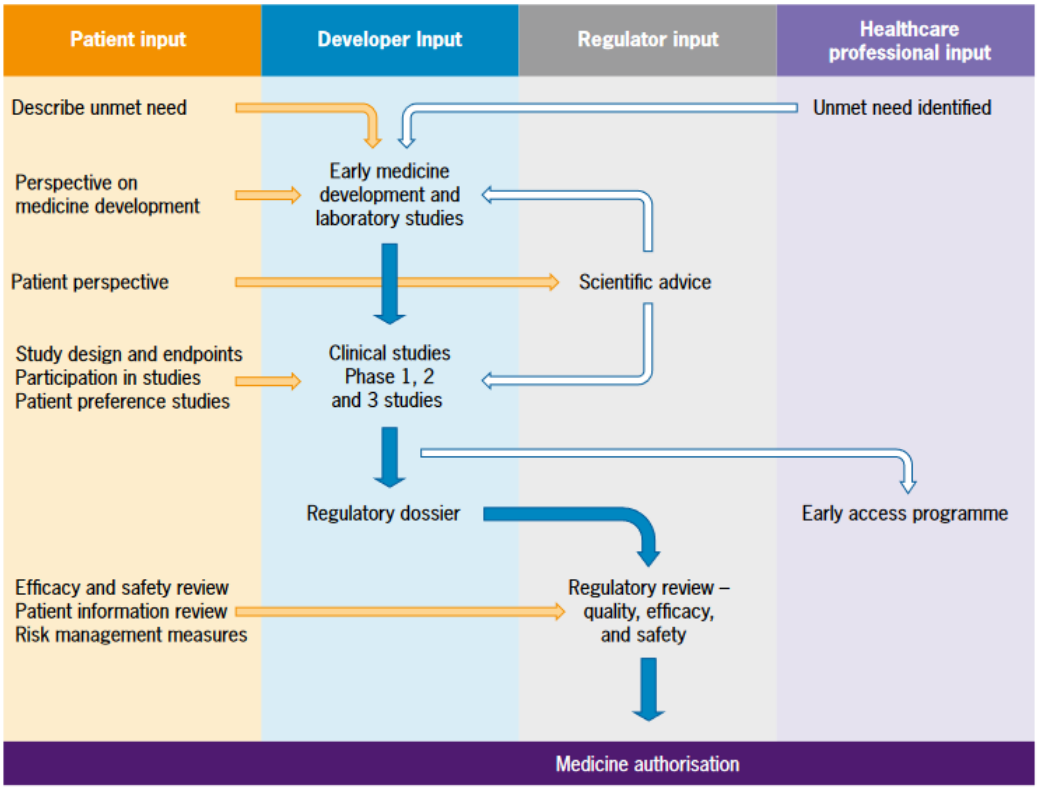
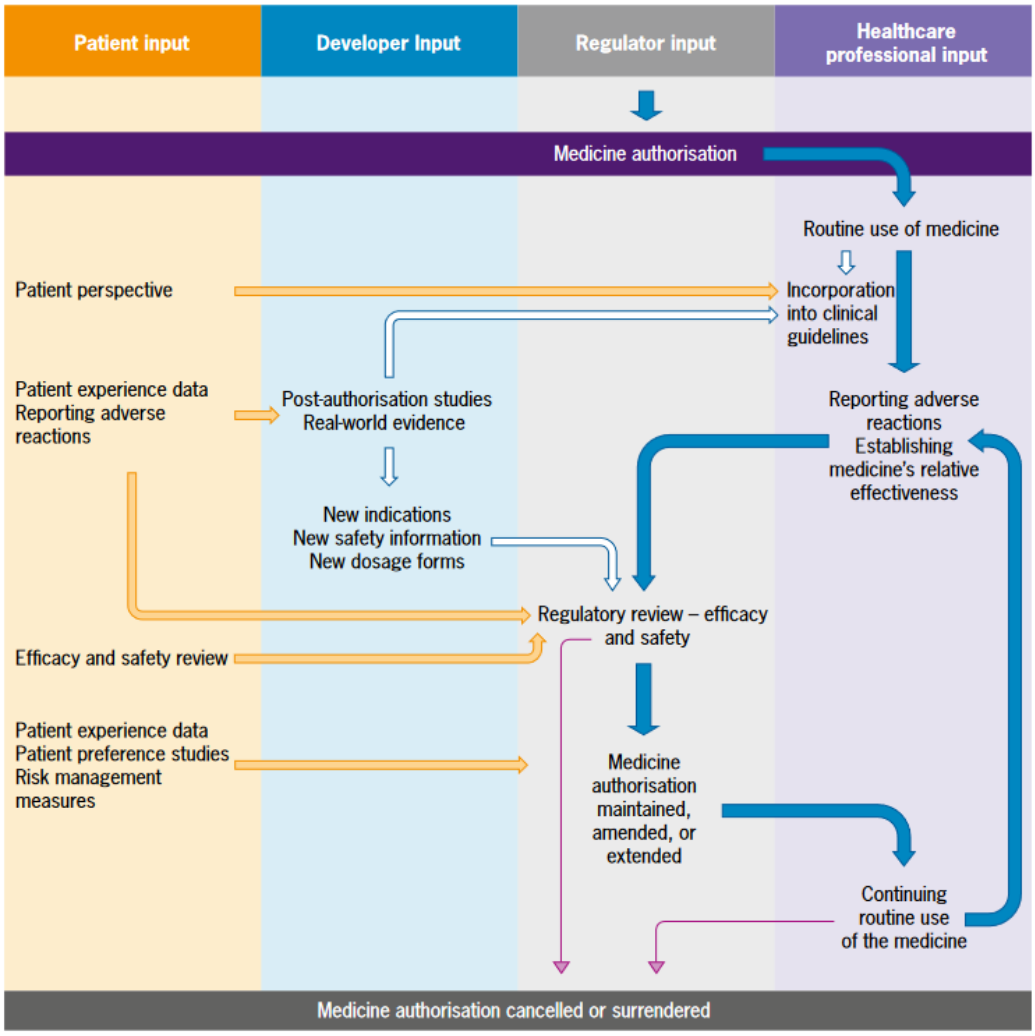


Figure 8: Patient involvement during a medicine lifecycle – post-authorisation

Source: CIOMS Working Group XI[243]



The CIOMS Working Group XI report provides a very useful framework for guiding principles, both in terms of 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. 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.[244] We present here a brief overview of different methods; 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". 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.[245] As highlighted in the CIOMS Working Group XI report,[246] "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).[247] 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.)[248] The CIOMS Working Group XI report further highlights the output from IMI-PREFER, which provides Principles for Patient Preference Studies.[249]

Box 1: Principles for Patient Preference Studies
Source: [250]

IMI-PREFER, a 5-year, multi-stakeholder initiative to provide evidence-based recommendations on how and when Patient Preference Studies (PPS) should be performed to inform medical decision making, has proposed the following principles for interacting with patients in the context of a PPS.

1. Use easy to understand, non-technical language, and include glossaries of technical terms where required.
2. Clearly and concisely describe the roles of patient research partners.
3. Undertake outreach work to involve patient research partners in community settings.
4. Enable flexibility around meeting times, including out-of-office hours.
5. Use easily accessible meeting venues (e.g. lift/ramps, locations).
6. Provide opportunities for patient research partners to contribute remotely (e.g. via email, teleconferences, video meetings).
7. Ensure meetings are structured to accommodate the needs of patient research partners (e.g. frequent breaks, refreshments, lay summaries of presentations/documents, care givers can attend).
8. Reimburse any expenses and payments for time spent.
9. Provide recaps at regular intervals of the study background and objectives, progress updates, and the impact of the patient research partner activities.
10. Allow sufficient time for the completion of involvement activities.
11. Ensure there is no requirement for patient research partners to sign or review lengthy and/or complex documents or legal agreements.
12. Ensure patient research partners have the requisite skills and knowledge to support meaningful involvement (e.g. to enable patients to contribute to aspects of data analysis or study conduct, assertiveness skills to support participation in management meetings). This may require specific training or provision of information or support.

13.	Provide training for study sponsors so they can effectively involve members of the public (e.g. communication skills, needs awareness, outreach training).

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. 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 mind more between benefits (e.g. between lowering weight or lowering blood sugar level) and between risks (e.g. between severe hypoglycaemic events or transient nausea).[251]
- The acceptability of trade-offs – how do patients weigh benefits versus risk/harm and burdens. This might include different scenario, 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.[252] At a high level, they characterise methods into: a. patient preference exploration and. 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, at times leveraging specific processes such as the Delphi method or the Dyadic interview method, to public meetings. 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 BR 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[253]:

- 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 are classified based on the use of ranking exercises to capture the order of alternatives or attributes within a presented set;
- 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 are methods based on their utilisation of comparative rating approaches, often allowing participants to express the strength of their preferences along a labelled scale.

Among the numerous preference elicitation methods[254], the most popular and more likely to address decision makers' needs are discrete choice experiments (DCE), best-worst scaling (BWS), threshold technique (TT), and swing weighting (SW). All these methods have been selected in PREFER project.

Over the past years, DCE has been increasingly used to quantify patients' preferences for health outcomes, health services, and medical treatments.[255] DCE is a utility-theoretic method that can be used for eliciting preferences for medical interventions.[256] 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 typically presented with a series of alternative hypothetical scenarios containing a number of variables or attributes (usually ≤5), each of which may have a number of variations or levels. Participants are asked to state their preferred choice between two or three competing scenarios, each of which consists of a combination of these attributes/levels.

Table 13: List of selected attributes and levels in a preference study in early rheumatoid arthritis

Source: Hazlewood et al, 2016.[257]

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 15 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 are examples of DCE choice sets presented to patients asking them to choose. The first version is in tabulated text format[258] and the second version is provided as figures to help patients better understand or visualise the different levels.[259]

Table 14: Examples of discrete choice experiment choice sets: tabulated text format

Source: Bøgelund et al, 2011.[260]

	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 3 kg weight
Nausea	Mild nausea for up to 3 months	No nausea
Additional payments	200 DKK per month	500 DKK per month

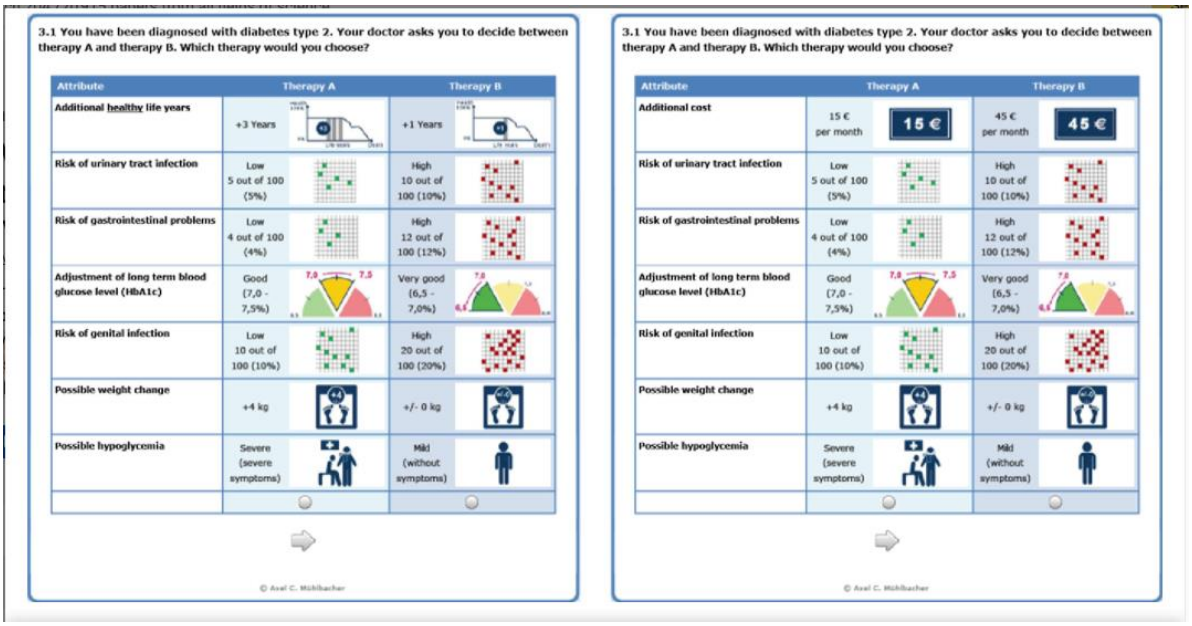
What treatment would you prefer?

○ 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.[261]



As a result, when patients have answered all the possible scenarios, preferences are revealed 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.

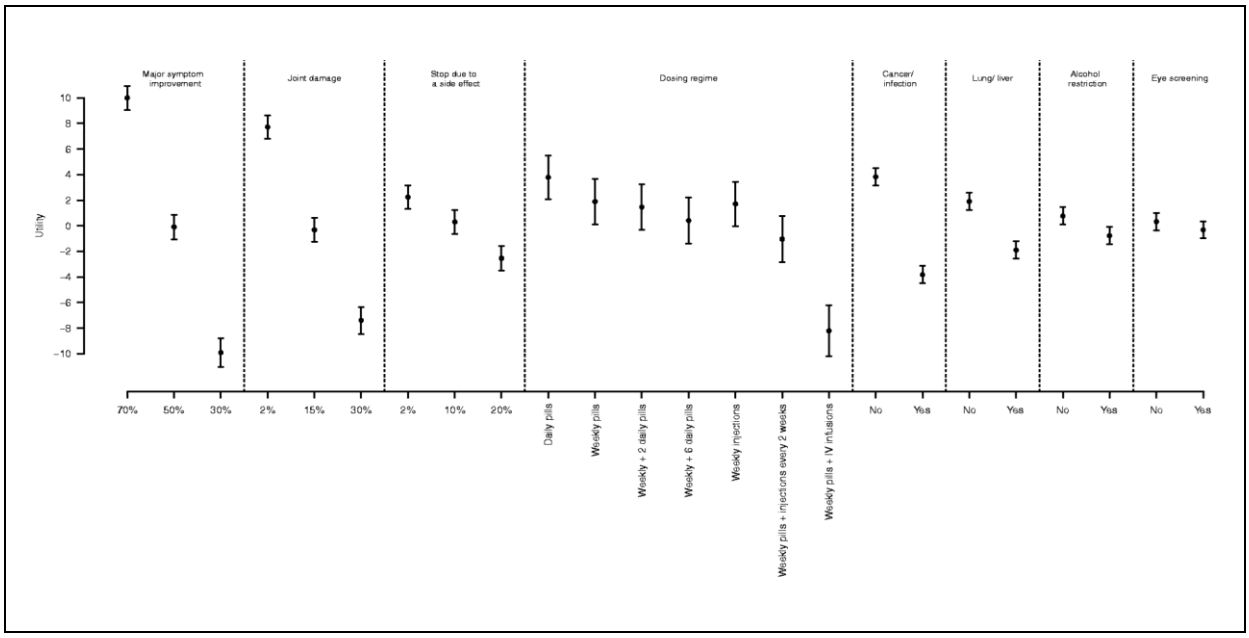
These measures can thus be used to estimate:

- 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 below provides 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 valued more (highest utility score) higher chance of a major symptom improvement by six months and lowest risk of developing serious joint damage by 10 years.[262]

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

Source: Hazlewood et al, 2016.[263]



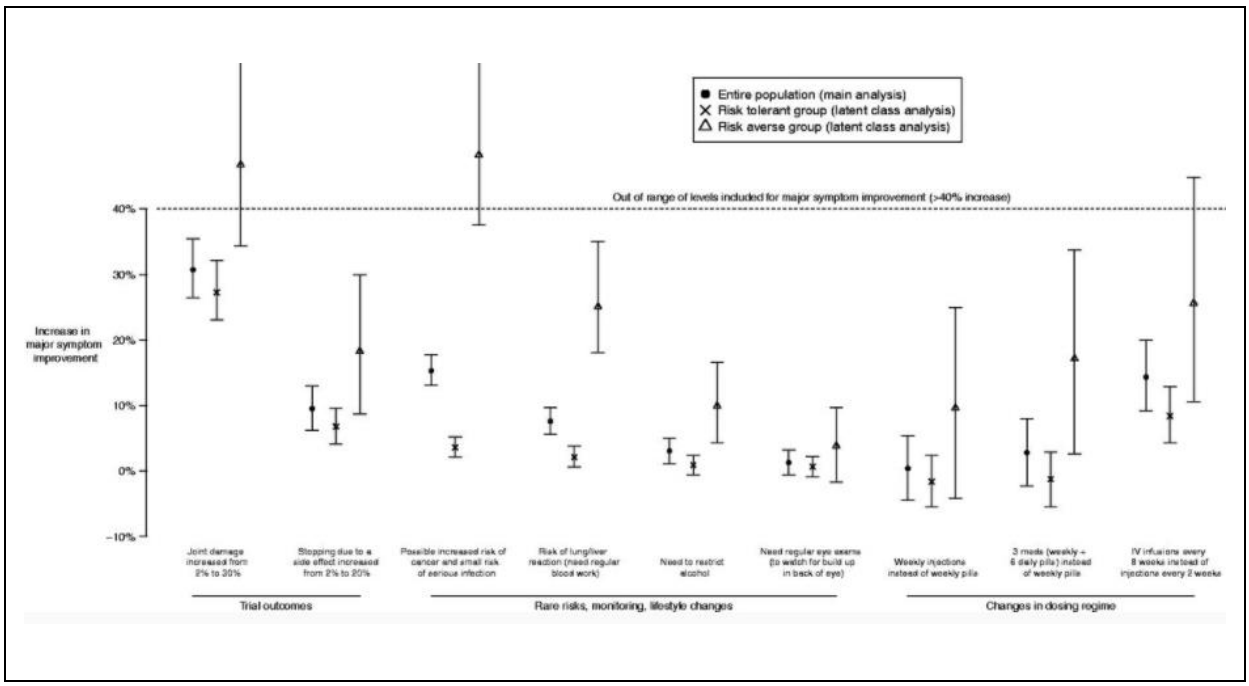
Utilities [mean (95% CI)] are scaled from −10 to + 10, with +10 indicating strong preference for the attribute level and −10 indicating strong aversion.

The figure below provides information on the minimum level of treatment benefit patients would require to accept undesirable features of treatment. Results are expressed as the marginal rate of substitution 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 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.[264]

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

Source: Hazlewood et al, 2016.[265]



Results (marginal rate of substitution) are presented as the absolute percentage increase [median (95% CI)] in the chance of major symptom improvement required for patients to accept 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,[266] in a study of relevant stakeholders, highlighted that nearly all the 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 then having to blindly extrapolate from studies conducted in other geographic or socio-cultural contexts.

3.4 Methodological considerations for addressing uncertainties in BRA

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.[267]

There are various sources of uncertainty to be considered in drug BRA – statistical uncertainty, whether the right endpoints were used, applicability of clinical trial data to real-world use, conduct and quality of the trials, implications of missing data, etc. and their importance depends on the extent to which they would affect the BR decisions. 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.[268,269]

Key sources of uncertainty in BRA

- **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 drug 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 adverse events 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.

3.4.1 Statistical approaches to 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.

Confidence intervals (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 hazard ratio, 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 is 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.[270] 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 includes 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.[271,272,273]

3.4.2 Probabilistic approaches using machine learning

The rapidly evolving big data analytics, machine learning and artificial intelligence systems provide significant potential in global health and pharmaceutical development. Machine learning is widely used to analyse big and complex datasets to uncover the hidden patterns and reach conclusive insights. Based on the observed data, machine learning systems form the basis for modelling, and then enable decision making.

Uncertainties in the data make the decision-making process difficult, thus studying and quantifying uncertainties in the data and model help to enhance the confidence in the results obtained by different methods. Data uncertainty arises from sources such as measurement noise, transmission noise, and missing values.[274] Uncertainty is fundamental to modelling, since any sensible model will be uncertain when predicting unobserved data.[275] Probabilistic approaches are now emerging as a framework for modelling uncertainty in artificial intelligence and machine learning. Probabilistic approaches to modelling, using probability theory, express all forms of uncertainty in form of probability distributions to represent all the uncertain unobserved quantities in a model (including structural, parametric and noise-related) and how they relate to the data, and to provide the basis for inferring the unobserved quantities given the observed data.[276] In moving forward, improved precision of machine learning algorithms to quantify and model uncertainty in big data will be of great use in enabling decision making in BR.

Ultimately, intelligence relies on understanding and acting in an imperfectly sensed and uncertain world.[277]

3.4.3 Uncertainty consideration in the SBRF

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 15 below provides a non-exhaustive list of examples or sources of uncertainties that could be considered in the SBRF.

Table 15: Examples or source of uncertainties that could be considered in the SBRF

Source: Adapted from Mutanga et al, 2023.[278]

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 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 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 adverse event reversibility; • Uncertainties in the ability to predict, monitor for, and/or prevent the adverse event; • Limited exposure duration; • Uncertainty of adverse events 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.	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, viral home test use), Drug adherence on the potential consequences (including adverse events 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
BR 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 BR

3.4.4 Strategies to address uncertainties of BR 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,[279] 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 profile.

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 cost of safety restrictions or absolute contraindications, and may be justified in situations when the uncertainty regarding the magnitude and consequences of the risk do not justify further evaluation in human trials to elucidate the risk uncertainty, or whilst characterisation of such risks is underway.

There are many examples of uncertainty reduction measures in form of *decisions* in BRA that are routinely applied, such as could be exclusion of women of childbearing potential in early studies when 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.[280] 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), their impact 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 profile (e.g. dosage and administration, warnings and precautions, etc.).

Valuation - Valuation of BR profile, taking into account objective information regarding benefit and risks, as well as stakeholders' values and preferences (patients, health care providers, public authorities), is an important tool to guide uncertainty reduction strategies. The fair valuation of 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[281]. Han, Klein, and Arora developed a conceptual taxonomy of uncertainty which sought to capture the various nuances and variations of uncertainties in health in a more systematic and comprehensive manner. The authors define uncertainty along three main dimensions: *source*, *issue*, and *locus*.

Source

Source refers to the underlying cause of uncertainty, which is further divided into:

- *probability* (also commonly referred to as risk), arises from the randomness or indeterminacy of the future.
- *ambiguity*, arises from limitations in the reliability, credibility, or adequacy of probability (risk) information. Ambiguity can be thought of as uncertainty that arises from limitations in the existing knowledge base about a particular topic.
- *complexity*, arises from features of available information that make it difficult to comprehend, such as multiple possible causes or outcomes.

Issue

The second dimension, issue, refers to the context in which uncertainty occurs, for example, scientific, practical, or personal. Scientific uncertainty includes those related to diagnoses, prognoses, causes of disease, and treatment options. Practical uncertainties are system-centred and encompass a lack of knowledge about healthcare structures and processes. Personal uncertainties refer to the impact of health decisions on future wellbeing, QoL, or relationships.

Locus

The last dimension in the taxonomy is locus, which describes where uncertainty resides – uncertainty can exist in patients or providers or can be a shared experience.[282, 283,284]

Determining how to understand patient sources of uncertainty, how to proactively manage and then communicate complex, uncertain, and potentially conflicting health information is therefore of critical importance.

Perceiving ambiguity in health information—that is, uncertainty elicited from believing information lacks credibility, reliability, or adequacy—is typically associated with pessimistic appraisals (e.g. high perceived risk) and behavioural avoidance.[285] 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.[286]

Past research has identified several distinct responses to ambiguity, which can be broadly classified as cognitive, affective, and behavioural. Cognitive manifestations of ambiguity aversion include heightened perceptions of the risk of the intervention at hand, diminished perceptions of the efficacy

of the intervention, and reduced confidence or trust in the intervention. Affective manifestations include heightened worry or fear about the intervention. Behavioural manifestations include avoidance of decision making and diminished uptake of the intervention.[287] One key feature of ambiguity is that it can be partially resolved by gathering information about how outcomes unfold. As ambiguous probabilities are repeatedly sampled and more information becomes available, the decision space becomes more akin to outcomes with known probabilities, since the underlying probability distributions have been learned.[288]

Patient' appraisals of illness uncertainty as dangerous or beneficial influences his or her 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 are very limited. Over the long term, these strategies are ineffective to manage the uncertainty because they do not provide solutions and could result in decreased QoL and wellbeing.[289]

Another factor to consider is the patient's intolerance to uncertainty, defined as "an individual's dispositional incapacity to endure the aversive response triggered by the perceived absence of salient, key, or sufficient information, and sustained by the associated perception of uncertainty". Intolerance of uncertainty is a dispositional characteristic resulting from negative beliefs about uncertainty and its implications, the core of which is appears to be fear of the unknown, wherein the possibility of a negative event occurring is considered threatening irrespective of the probability of its occurrence.[290] Patients with high intolerance to uncertainty interpret ambiguous information in a more threatening, negative, manner, often referred to as an interpretation bias,[291] and thus affect decision making.

3.4.6 An uncertainty reduction theory framework for uncertainty reduction strategies

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 such as recruiting processes, computer-mediated communication, online commerce, or organisational behaviour.[292,293,] Hence, URT is not only limited to the interaction of individuals but is also useful in other settings.

Individuals reduce uncertainties by 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.

For passive and active strategies, individuals rely on accessible and valuable information. Therefore, transparency, "the perceived quality of intentionally shared information from a sender", is an enabler for information-seeking strategies. Transparency is best understood as a multidimensional construct consisting of 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 for individuals (e.g. because the information is cryptic and only consists of the 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.[294] 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 case of specific signs and symptoms, direction to discuss with HCP).

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.

Social influence and trust are also two important enablers for uncertainty reduction. Trust was shown to reduce uncertainties and risks in different settings, and it is defined as “a psychological state comprising the intention to accept vulnerability based upon positive expectations of the intentions or behaviours of another”. However, initial trust may change, either as strengthened or weakened, based on specific experiences encountered.[295] Trust in government to be transparent and follow appropriate approval processes was found to be an important factor in driving vaccination intentions.[296]

3.5 Approaches to visualisation of BRA

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

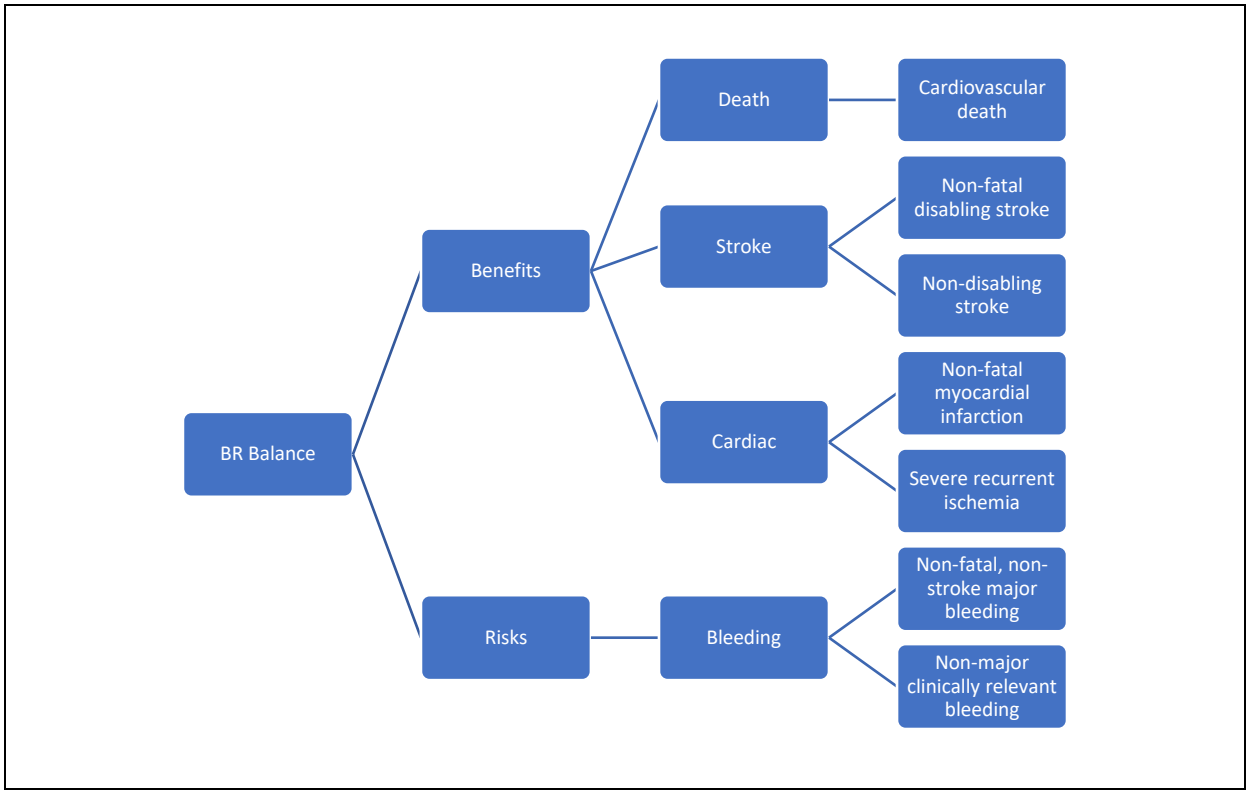
3.5.1 Attribute Tree (Value Tree)

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 multi-disciplinary 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 the study. 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[297]



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 16 provides an example of an effects table, aligned with the attribute tree in Figure 12.

Table 16: Effects Table for the attribute tree in Figure 12 (modified from Levitan B and Cross J)

Source: CIOMS Working Group XII, based on the original work by Levitan B and Cross J[298]

	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)
Nonfatal disabling stroke	44	66	-22	(-43, -1)
Nondisabling stroke	70	63	7	(-32, 46)
Nonfatal MI	450	644	-194	(-311, -77)
Severe recurrent ischemia	586	620	-34	(-137, 69)
Nonfatal, nonstroke major bleeding	155	51	104	(66,142)

Nonmajor clinically relevant bleeding	1960	1011	949	(801, 1097)

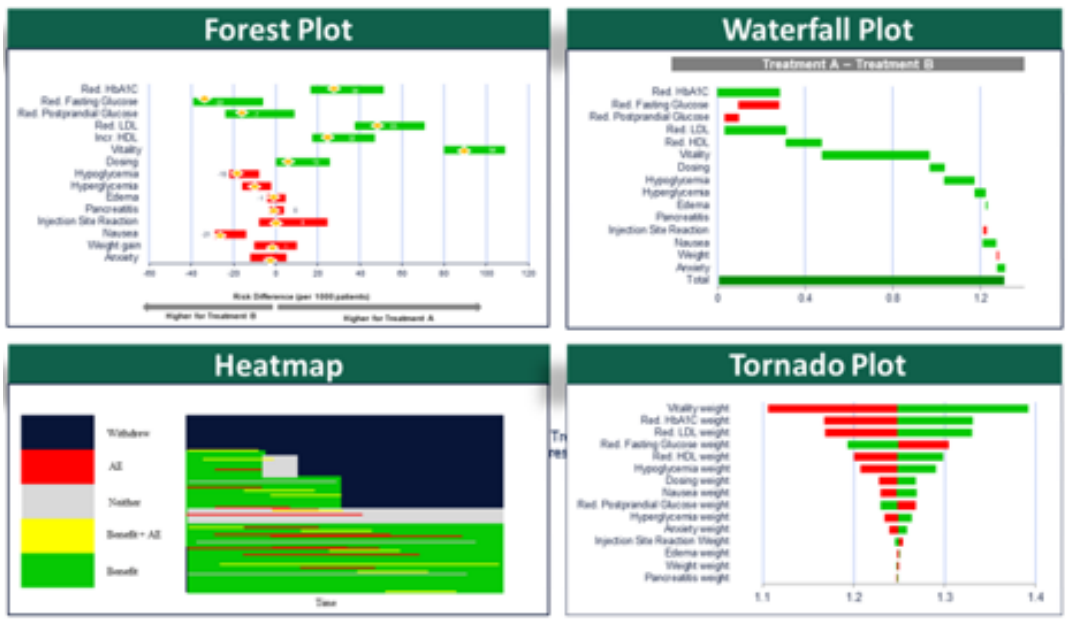
3.5.3 Graphical display tools – visual displays

Visual displays to effectively communicate results continue to evolve and offer a broad range of options, with their respective strengths and limitations.[299] The PROTECT Benefit-Risk group provided an in-depth analysis of visual representations to convey the results of BRAs of medicinal products.[300] They provided clear recommendations around addressing considerations for the audience targeted as well as the type of information being conveyed. From an audience perspective, this includes potential shifts in target audience over time, the specific message to be conveyed to this particular audience, their knowledge base and the risk of misunderstanding the information conveyed.

There are a number of visualisation methods that are very effective in communicating BR, as shown in Figure 13 below. We do not attempt to present a comprehensive summary here, but we focus first on some of the more common tools.

Figure 13: Examples of BR visuals

Source: [301]



A BR forest plot is frequently used, other types of visualisations may be used if they may better contextualise the data.[302] In the example of the BR forest plot, the endpoints used in the forest plot are based on the value tree. In addition, the text summarising clinical importance and key evidence should summarise the endpoints used in the BR forest plot, however, the text of the BRA may include additional key evidence which are not included in the BR forest plot. Determination of which endpoints are included in the BR 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. As an example, key evidence for resolution of pruritus in moderate to severe atopic dermatitis may include reduction in worst pruritus at a specific timeframe (i.e. Week 16) which is defined by the primary endpoint or key secondary endpoint of the clinical study(ies). The cross-functional team, however, may want to also mention that this reduction starts even earlier than at the defined timeframe for the endpoint (i.e. Early onset of effect at Day 2 or 3). This early onset of effect can be mentioned in

the text under key evidence, but it may not need to be included in the BR visual, since the endpoint would be reflected by the primary or key secondary endpoint at Week 16.

Linking back to the patient-centric approach to BRA (see section 3.2.2 on Patient-level BRA – A novel paradigm through drug development and lifecycle management), we wish to highlight the usefulness of the Heat Map approach. This tool has the potential to display each individual patient in a study in a limited graphical space. Specific outcomes at the patient-level can thus be represented. For example, patients who achieved the pre-defined benefit threshold while experiencing no adverse event can be coded in green. Those that experience both the benefit but also an adverse event can be coded in yellow. And those that fail to show a benefit but experience an adverse outcome can be coded in red. Such display of the data can provide a rapid and relatable visual. The full colour palette is available to convey further granularity in the data (e.g. different shades of yellow adjusted for grade of adverse event). A number of clinical data systems have the ability to generate these data representation and we therefore expect further use of this visualisation technique in the field of BR.

3.6 The multidisciplinary BRMT

As stated at the beginning of this chapter, we wish to cover aspects beyond the statistical or technical elements of the BR methods. The elements that foster cross-functional collaboration and input are just as essential to drive a state-of-the-art BRA. 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; 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 of the BRA and decision

Responsible party and decision-making models may vary in pharmaceutical companies. In most companies, 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 not limited to, non-clinical and clinical study data, ICSRs, epidemiology study results, post-marketing study or solicited program data, literature, product quality reports, regulatory agency request and assessment, 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 committee, commonly called safety management team (SMT). However, if a safety signal/issue requires immediate decision from senior management, it can be directly brought to the highest level of committee.

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, regulatory affairs. SMT is led by 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 investigator's brochure (IB) update. If escalation is required, the team submits its recommendation to the highest level of committee for final decision.

The highest level of the committee makes the final decision for products across all therapeutic areas and consists of department heads. The committee is chaired by the Chief Medical Officer (CMO) or co-chaired by CMO and head of safety department. The committee reviews safety signals/issues that may impact the BRA of a product, may require immediate notification to regulatory agency,

investigators, health care providers, and patients, may require urgent safety measures or suspending or stopping of clinical trials outside of protocol defined stopping criteria or changing conduct of the clinical development, or may require 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 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 efficacy and safety of a product. A study team analyses study efficacy and safety data. A product team assesses BR based on all relevant information including efficacy and safety data from clinical trial, non-clinical data, treatment landscape, and emerging data from the same drug class, and makes decision 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 recommendation of go, no go, or modification of a clinical development program to the highest level of committee. The highest level of committee led by CMO makes final decision on product clinical development program based on the BR profile of the product and company portfolio and strategy.

3.6.2 Cross-functional BR management team.

Pharmaceutical company:

Typically, this team includes representatives from safety pharmacovigilance, clinical development, regulatory, medical affairs, epidemiology, statistics, health-economics and outcomes research commercial and legal. The team may also include a project manager to facilitate meeting conduct and documentation of the discussion and decisions.

Pharmaceutical companies generally have at least two cross-functional teams to evaluate safety information: one is a multidisciplinary SMT – See CIOMS Working Group VI report[303]) and one is a senior leadership team.

The core members of SMT may include a representative from each of functional areas that play key roles in the product development including safety pharmacovigilance, clinical development, regulatory affairs. Representatives from other functional areas could be a regular or ad hoc member depending on company culture, stage of a product in its lifecycle, and the specific safety issues under discussion, e.g. statistician, epidemiologist, clinical pharmacologist, toxicologist, chemist, representatives from biomarker, labelling group, medical affairs, and legal.

Product lead

Product lead is responsible for designing and conducting the product development program, BRA of the product (including the BRAD), and submission for regulatory approval. Oftentimes, the product lead is a global product physician in the clinical development department.

Safety physician and pharmacovigilance scientist

Safety physician and pharmacovigilance scientist have the responsibility for identifying and evaluating risks relating to the product and working with the team to develop risk mitigation plans. Safety physician and pharmacovigilance scientist also ensure regulatory pharmacovigilance requirements are met and safety information is appropriately included in the company core safety datasheet and investigator brochure.

Regulatory affairs representative

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

Clinical pharmacologist

Clinical pharmacologist is responsible for designing and conducting studies evaluating drug pharmacokinetic (PK) and pharmacodynamic (PD), assessing drug-drug interaction, and providing dosing recommendation. Clinical pharmacologist's in-depth knowledge in mechanism of action, PK PD, and potential drug-drug interaction is critical to SMT in risk evaluation

Senior leadership team

The senior leadership team includes department heads (e.g. therapeutic area head, global safety head, regulatory affairs head) and is chaired by CMO or co-chaired by CMO and head of safety department. The senior leadership team makes decisions on emerging safety issues that requires immediate actions; e.g. notifying regulator of a safety finding, issuing a dear healthcare provider letter, changing development program, updating safety section of company core data sheet and/ or IB.

- Regulatory agency: EU Regulatory perspective: cross-functional team includes non-clinical, clinical, epidemiology, policy and others TBD; US FDA: regulatory project manager; clinical reviewer; chemistry, manufacturing and control (CMC) reviewer; statistician; toxicologist; epidemiologist; biologist, and others.

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.

Team leader

Team leader is in charge of management of the BRA schedule and close communication with each term members, related divisions and related organisations such as pharmaceutical companies.

Pharmacokinetics

Representative of Pharmacokinetics is charge of data assessment about drug absorption, distribution, metabolism and excretion and providing supportive information to consider the dosage and administration in package inserts.

Toxicology

Representative of toxicology is charge of data assessment about non-clinical data such as toxicity testing with animals and cells to identify the pharmacologic properties of a pharmaceutical, establish a safe initial dose level for the first human exposure and understand the toxicological profile of a pharmaceutical (e.g. identification of target organs, exposure-response relationships, and reversibility).

Chemistry, manufacturing and control (CMC)

Representative of CMC is charge of data assessment about 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

Representative of pharmacology is 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

Representative of clinical is charge of data assessment about 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.

Biostatistics

Representative of biostatistics is charge of data assessment about suitability for collecting, analysing and interpreting study data.

Risk manager (RM)

RM is in charge of central management 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 lifecycle and to ensure consistent safety measures from the development/approval stage to post-marketing.

3.6.3 Expert consultations

During the lifecycle of a drug BRAs are conducted by sponsors and health authorities. In order to address certain topics related to BR 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 in order to receive independent advice from outside experts. These may include consultations with:

- External experts; and
- Internal experts.

External advice may be sought in order 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 in order to evaluate 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 adverse reactions.

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 healthcare systems including the reflection of their needs and expectations in 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.

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 patients' perspective may include:

- Endpoints including patient-reported outcomes 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.

3.6.4 Capability needs at regulatory agencies, sponsors, and in academia

All of the capabilities listed below (Table X) are necessary, at some point, in the conduct of comprehensive BRAs. We wish to highlight that these represent capabilities. We do 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 document. 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, Delphi Process. The same methods can be used to collect patient preferences and incorporate input into the B/R 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 17: Capabilities to support BRA

Source: CIOMS Working Group XII

Stakeholders will need to have expertise in:
• BR frameworks (See Chapter 2 on Structured BR approach / framework)
• Structured strategic stakeholder engagement / BR cross-functional workshops
• Statistics
• RWE and data
• Patient engagement

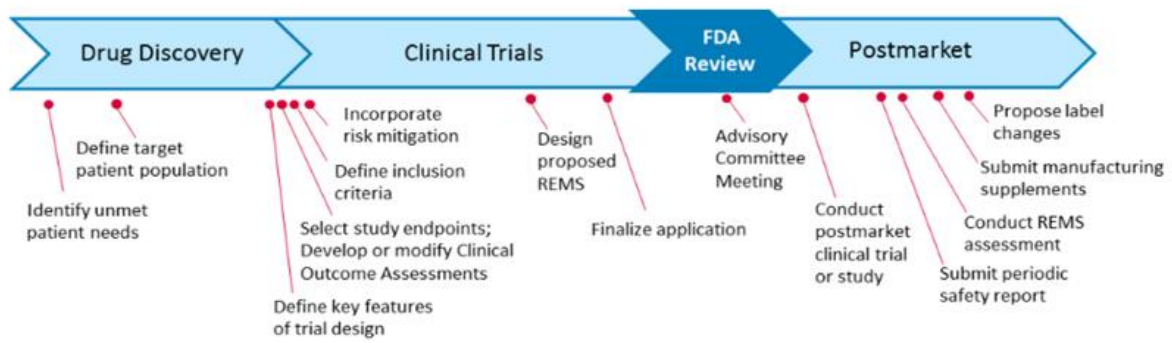
- Data visualisation
- Decision-science

3.6.5 Company Benefit-Risk Assessment Document (BRAD)

A number of key events during the drug development process impact the BR profile (Figure 14). These events start early in the development process and highlights the opportunity to initiate the BRA process early in a product's lifecycle. Several companies have introduced a company SBRF and management process, documented in a document containing company's comprehensive BRA of a product at a given timepoint in the product's lifecycle. This 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 BR management team and starts sometimes as early as prior to First in Human studies. (See section 3.6 on The multidisciplinary BRMT). We will refer to this document generically as the Benefit-Risk Assessment Document (BRAD). It gives a company a clear picture of product's potential benefits and risks and helps in developing strategic plans and establishing go/no-go criteria. A BRAD also enables a company to develop risk mitigation strategy 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 product success. For example, during the product development stage, the BRAD could mandate implementation of risk mitigation measures such as product-specific inclusion/exclusion criteria and toxicity management in all clinical trials. In addition, a BRAD assists a company with effective, consistent and transparent communication with regulatory agencies, investigators, and trial participants; for example, a BRAD facilitates a company's preparation for end of phase meeting with regulatory agencies. In summary, a BRAD will be vital for product development program planning, execution, strategic decision making, and communication. See Appendix for an Example of a company benefit risk assessment document (BRAD).

Figure 14: Key events that have an impact on BRA of a product

Source:[304]



A BRAD contains key elements, including the characteristics of the targeted disease and patient population, description of unmet medical need, key benefits and risks with discussion of strengths and limitations and uncertainties of the available data, risk mitigation measures, and 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 BRA). A BRAD would need to discuss special populations, such as paediatrics. Also, if more than one indication is investigated for a product, a separate BRAD may be considered when development for subsequent indications passes the proof-of-concept stage and the disease and patient population are significantly different from those of the first indication.

A BRAD is a living document throughout a product's lifecycle. Creation of a BRAD prior to an IND helps the company to make investment decision, develop strategic plan, 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 a BRAD at a later stage (e.g. end of Phase 1 or 2) due to reasons such as scanty data and huge uncertainty. The important milestones for BRAD updates include prior to Phase 2 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 adverse reactions 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 a BRAD, but to maintain it throughout the product's lifecycle.

Developing and maintaining a BRAD should involve all relevant parties including, but not limited to, clinical research, patient safety, biometrics, toxicology, regulatory affairs, epidemiology, medical affairs, and health economics. Before creation or update of a BRAD, a cross-functional team is formed or re-established, usually referred at the BRMT, to first determine which data will be examined. Each functional team then gathers and analyses data. 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 and patient safety and regulatory affairs departments.

Each functional team must ensure that a BRAD is incorporated into their relevant documents and practices. For example, the BRA section of the following documents should be in alignment with the BRAD: the IMP Dossier, protocol, Clinical Overview section 2.5.6, regulatory agency meeting briefing document, DSUR, and PBRER.

Understanding the interrelationship between the BRAD and other company core documents such as Development Core Data Sheet (DCDS)/CCDS and Developmental risk management plan (DRMP)/RMP is crucial to 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 a 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 adverse drug reactions listed in CCDS. The core DRMP/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 underdevelopment. Since a BRAD evaluates both key benefits and key risks, it often encompasses the key elements of a core DRMP/RMP. Unlike a BRAD, a core DRMP/RMP does not contain efficacy information. Furthermore, the risks specified in the core DRMP/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 core DRMP serves little purpose and can be omitted in the presence of a BRAD. In short, with the increasing emphasis on BR balance during a product's lifecycle, a BRAD is an important addition to the pool of company core documents and its existence could make certain company core documents such as DRMP obsolete.

CHAPTER 3 ANNEX: EXAMPLES OF FIVE-LEVEL DOOR RANKINGS

Example i

Cardiovascular event prevention trials typically evaluate efficacy based on the time-to-first event where the event could be death, 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 an 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. 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 not fatal events, (ii) events with permanent or disabling sequelae are more important than events with transient sequelae, and (iii) more events is worse than fewer events (Table 18).

Table 18: Five-level DOOR 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 [305]

DOOR 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

These analyses were applied in the acute stroke or transient ischemic attack treated with aspirin or Ticagrelor and patient outcomes study[306],[307] a randomised clinical trial[308],[309] The timing of events can be incorporated into rank-based analyses when comparing two patients in the same category or by evaluating DOOR states longitudinally.

Example ii

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

An analysis[310] 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 4-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 19).

Table 19: A 4-level DOOR

Source: Van Duin, et.al, 2018[311]

DOOR 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 (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.[312]

Example iii

Recent regulatory-industry-academic collaborations have developed and applied DOOR outcomes for complicated intra-abdominal infections (cIAI)[313] based on a US FDA ORISE fellowship[314] and complicated urinary tract infection (cUTI).[315] For example, a DOOR outcome for cUTI was formed on the basis of absence of clinical response, infectious complications, SAEs, and mortality (Table 20).

Table 20: A Generalised DOOR Analysis Strategy

Source: Howard-Anderson J et al. 2023.[316]

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 21: Definitions for cUTI Trials

Source: Howard-Anderson J. et al, 2023.[317]

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.

References

[97] *Kovochich M, Finley BL, Novick R, Monnot AD, Donovan E, Unice KM, et al. Understanding outcomes and toxicological aspects of second generation metal-on-metal hip implants: a state-of-the-art review. Critical Reviews in Toxicology. 2018;48(10):853-901. https://doi.org/10.1080/10408444.2018.1563048*

[98] *The United States Food and Drug Administration (FDA). Metal-on-Metal Hip Implant Systems. (Website accessed 12 May 2023).*

[99] *Australian Government. Department of Health and Aged Care. Metal-on-Metal Hip Replacement Implants. (Website accessed 12 May 2023).*

[100] *European Commission. Final Opinion on Metal-on-Metal Joint Replacements. (Website accessed 12 May 2023).*

[101] *Medicines and Healthcare products Regulatory Agency (MHRA). GOV.UK. All Metal-on-Metal (MoM) Hip Replacements: Updated Advice for Follow-Up of Patients. (Website accessed 12 May 2023).*

[102] *Powell LE, Andersen ES, Nigro LC, Pozez AL, Shah PA. Breast implants: a historical review with implications for diagnosis and modern surgical planning. Annals of Plastic Surgery. 2021;1;87(2):211-21. https://doi.org/10.1097/SAP.0000000000002731*

[103] *Turton P, El-Sharkawi D, Lyburn I, Sharma B, Mahalingam P, Turner SD, et al. UK guidelines on the diagnosis and treatment of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) on behalf of the Medicines and Healthcare products Regulatory Agency (MHRA) Plastic, Reconstructive and Aesthetic Surgery Expert Advisory Group (PRASEAG). European Journal of Surgical Oncology. 2021;1;47(2):199-210. https://doi.org/10.1016/j.ejso.2020.07.043*

[104] *Shoureshi PS, Lee W, Kobashi KC, Sajadi KP. Media coverage of the 2019 United States Food and Drug Administration ordered withdrawal of vaginal mesh products for pelvic organ prolapse. International Urogynecology Journal. 2021;32:375-379. https://doi.org/10.1007/s00192-020-04401-6*

[105] *FDA. How to Determine if Your Product is a Medical Device. (Website accessed 3 June 2023)*

[106] *MasterControl. ISO 14971 Standards. (Website accessed 2 May 2023).*

[107] *Vischer AS, Burkard T. Principles of Blood Pressure Measurement–Current Techniques, Office vs Ambulatory Blood Pressure Measurement. Hypertension: from basic research to clinical practice. 2017:85-96. https://doi.org/10.1007/5584_2016_49*

[108] *Pettersson A, Boström KB, Gustavsson P, Ekselius L. Which instruments to support diagnosis of depression have sufficient accuracy? A systematic review. Nordic journal of psychiatry. 2015;69(7):497-508. https://doi.org/10.3109/08039488.2015.1008568*

[109] *Fraum TJ, Ludwig DR, Bashir MR, Fowler KJ. Gadolinium-based contrast agents: a comprehensive risk assessment. Journal of Magnetic Resonance Imaging. 2017;46(2):338-353. https://doi.org/10.1002/jmri.25625*

[110] *Mitsumori LM, Bhargava P, Essig M, Maki JH. Magnetic resonance imaging using gadolinium-based contrast agents. Topics in Magnetic Resonance Imaging. 2014;23(1):51-69. https://doi.org/10.1097/RMR.0b013e31829c4686*

[111] *Grobner T. Gadolinium–a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? Nephrology Dialysis Transplantation. 2006;21(4):1104-1108. https://doi.org/10.1093/ndt/gfk062*

[112] *Cowper SE, Robin HS, Steinberg SM, Su LD, Gupta S, LeBoit PE. Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. The Lancet. 2000;16;356(9234):1000-1001. https://doi.org/10.1016/S0140-6736(00)02694-5*

[113] *Galan A, Cowper SE, Bucala R. Nephrogenic systemic fibrosis (nephrogenic fibrosing dermopathy). Current opinion in rheumatology. 2006;18(6):614-617. https://doi.org/ 10.1097/01.bor.0000245725.94887.8d*

[114] *Kuo PH, Kanal E, Abu-Alfa AK, Cowper SE. Gadolinium-based MR contrast agents and nephrogenic systemic fibrosis. Radiology 2007;242:647. https://doi.org/10.1148/radiol.2423061640*

[115] *Attari H, Cao Y, Elmholdt TR, Zhao Y, Prince MR. A systematic review of 639 patients with biopsy-confirmed nephrogenic systemic fibrosis. Radiology. 2019;292(2):376-386. https://doi.org/10.1148/radiol.2019182916*

[116] *Kanda T, Ishii K, Kawaguchi H, Kitajima K, Takenaka D. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. Radiology. 2014;270(3):834-841. https://doi.org/10.1148/radiol.13131669*

[117] *Errante Y, Cirimele V, Mallio CA, Di Lazzaro V, Zobel BB, Quattrocchi CC. Progressive increase of T1 signal intensity of the dentate nucleus on unenhanced magnetic resonance images is associated with cumulative doses of intravenously administered gadodiamide in patients with normal renal function, suggesting dechelation. Investigative Radiology. 2014;49(10):685-690. https://doi.org/10.1097/RLI.0000000000000072*

[118] *Semelka RC, Ramalho J, Vakharia A, AlObaidy M, Burke LM, Jay M, Ramalho M. Gadolinium deposition disease: initial description of a disease that has been around for a while. Magnetic Resonance Imaging. 2016;34(10):1383-1390. https://doi.org/10.1016/j.mri.2016.07.016*

[119] *Burke LM, Ramalho M, AlObaidy M, Chang E, Jay M, Semelka RC. Self-reported gadolinium toxicity: a survey of patients with chronic symptoms. Magnetic Resonance Imaging. 2016;34(8):1078-1080. https://doi.org/10.1016/j.mri.2016.05.005*

[120] *Cheng Y, Wang C, Wang Y, Dai L. Soluble PD-L1 as a predictive biomarker in lung cancer: A systematic review and meta-analysis. Future Oncology. 202;18(2):261-273. https://doi.org/10.2217/fon-2021-0641*

[121] *McKean WB, Moser JC, Rimm D, Hu-Lieskovan S. Biomarkers in precision cancer immunotherapy: promise and challenges. American Society of Clinical Oncology Educational Book. 2020;40:275-291.*

[122] *Jørgensen JT, Winther H, Askaa J, Andresen L, Olsen D, Mollerup J. A companion diagnostic with significant clinical impact in treatment of breast and gastric cancer. Frontiers in Oncology. 2021;11:676939. https://doi.org/10.3389/fonc.2021.676939*

[123] *Meehan RT, Amigues IA, Knight V. Precision medicine for rheumatoid arthritis: the right drug for the right patient—companion diagnostics. Diagnostics. 2021;29;11(8):1362. https://doi.org/10.3390/diagnostics11081362.*

[124] *Meehan RT, Amigues IA, Knight V. Precision medicine for rheumatoid arthritis: the right drug for the right patient—companion diagnostics. Diagnostics. 2021;29;11(8):1362. https://doi.org/10.3390/diagnostics11081362.*

[125] *Guymer R, Wu Z. Age-related macular degeneration (AMD): More than meets the eye. The role of multimodal imaging in today's management of AMD—A review. Clinical & Experimental Ophthalmology. 2020;48(7):983-995. https://doi.org/10.1111/ceo.13837*

[126] *Du-Harpur X, Watt FM, Luscombe NM, Lynch MD. What is AI? Applications of artificial intelligence to dermatology. British Journal of Dermatology. 2020;183(3):423-430. https://doi.org/10.1111/bjd.18880.*

[127] *Leclercq C, Witt H, Hindricks G, Katra RP, Albert D, Belliger A, Cowie MR, Deneke T, Friedman P, Haschemi M, Lobban T. Wearables, telemedicine, and artificial intelligence in arrhythmias and heart failure: Proceedings of the European Society of Cardiology Cardiovascular Round Table. Europace. 2022;24(9):1372-1383. https://doi.org/10.1093/europace/euac052*

[128] *Primorac D, Bach-Rojecky L, Vađunec D, Juginović A, Žunić K, Matišić V, et al. Pharmacogenomics at the center of precision medicine: challenges and perspective in an era of Big Data. Pharmacogenomics. 2020;21(2):141-156. https://doi.org/10.2217/pgs-2019-0134*

[129] *Doukky R, Golzar Y. Safety of stress testing in patients with elevated cardiac biomarkers: Are all modalities created equal? Journal of Nuclear Cardiology. 2017;24:735-737. https://doi.org/10.1007/s12350-016-0440-4.*

[130] *Evans SR, Pennello G, Pantoja-Galicia N, Jiang H, Hujer AM, Hujer KM, et al. Benefit-risk evaluation for diagnostics: a framework (BED-FRAME). Clinical Infectious Diseases. 2016;63(6):812-817. https://doi.org/10.1093/cid/ciw329*

[131] *Perez MV, Mahaffey KW, Hedlin H, Rumsfeld JS, Garcia A, Ferris T, et al. Large-scale assessment of a smartwatch to identify atrial fibrillation. New England Journal of Medicine. 2019;381(20):1909-1917. https://doi.org/ 10.1056/NEJMoa1901183.*

[132] *Glines KR, Haidari W, Ramani L, Akkurt ZM, Feldman SR. Digital future of dermatology. Dermatology Online Journal. 2020;26(10). https://doi.org/10.5070/D32610050455*

[133] *Tan CH, Kyaw BM, Smith H, Tan CS, Tudor Car L. Use of smartphones to detect diabetic retinopathy: scoping review and meta-analysis of diagnostic test accuracy studies. Journal of Medical Internet Research. 2020;22(5):16658. https://doi.org/10.2196/16658*

[134] *Meisters R, Putrik P, Ramiro S, Hifinger M, Keszei AP, van Eijk-Hustings Y, Woolf AD, Smolen JS, Stamm TA, Stoffer-Marx M, Uhlig T. EULAR/eumusc. net standards of care for rheumatoid arthritis: cross-sectional analyses of importance, level of implementation and care gaps experienced by patients and rheumatologists across 35 European countries. Annals of the Rheumatic Diseases. 2020;79(11):1423-1431. http://dx.doi.org/10.1136/annrheumdis-2020-217520*

[135] *Kow CS, Hasan SS, Wong PS, Verma RK. Concordance of recommendations across clinical practice guidelines for the management of hypertension in Southeast Asia with internationally reputable sources. BMC Cardiovascular Disorders. 2021;21(1):1-7. https://doi.org/10.1186/s12872-021-02054-x*

[136] *Mahajan A, Butala A, Okun MS, Mari Z, Mills KA. Global Variability in Deep Brain Stimulation Practices for Parkinson's Disease. Frontiers in Human Neuroscience. 2021;15:667035. https://doi.org/10.3389/fnhum.2021.667035*

[137] *Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. New England Journal of Medicine. 2009;360(10):961-972. https://doi.org/10.1056/NEJMoa0804626*

[138] *Banning AP, Serruys P, De Maria GL, Ryan N, Walsh S, Gonzalo N, et al. Five-year outcomes after state-of-the-art percutaneous coronary revascularization in patients with de novo three-vessel disease: final results of the SYNTAX II study. European Heart Journal. 2022;43(13):1307-1316. https://doi.org/10.1093/eurheartj/ehab703.*

[139] *Chou YY, Hwang JJ, Tung YC. Optimal surgeon and hospital volume thresholds to reduce mortality and length of stay for CABG. Plos 0ne. 2021;16(4):e0249750. https://doi.org/10.1371/journal.pone.0249750.*

[140] *Gutacker N, Bloor K, Cookson R, Gale CP, Maynard A, Pagano D, et al. Hospital surgical volumes and mortality after coronary artery bypass grafting: using international comparisons to determine a safe threshold. Health Services Research. 2017;52(2):863. https://doi.org/10.1111/1475-6773.12508.*

[141] *Health Quality Ontario. Robotic surgical system for radical prostatectomy: a health technology assessment. Ontario Health Technology Assessment Series. 2017;17(11):1.*

[142] *Maynou L, Mehtsun WT, Serra-Sastre V, Papanicolas I. Patterns of adoption of robotic radical prostatectomy in the United States and England. Health Services Research. 2021;56:1441-1461. https://doi.org/10.1111/1475-6773.13706*

[143] *Ramsay C, Pickard R, Robertson C, Close A, Vale L, Armstrong N, et al. Systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of laparoscopic surgery and robotic surgery for removal of the prostate in men with localised prostate cancer. Health Technology Assessment (Winchester, England). 2012;16(41):1. https://doi.org/10.3310/hta16410*

[144] *Close A, Robertson C, Rushton S, Shirley M, Vale L, Ramsay C, Pickard R. Comparative cost-effectiveness of robot-assisted and standard laparoscopic prostatectomy as alternatives to open radical prostatectomy for treatment of men with localised prostate cancer: a health technology assessment from the perspective of the UK National Health Service. European Urology. 2013;64(3):361-369. https://doi.org/10.1016/j.eururo.2013.02.040*

[145] *Parackal A, Tarride JE, Xie F, Blackhouse G, Hoogenes J, Hylton D, et al. Economic evaluation of robot-assisted radical prostatectomy compared to open radical prostatectomy for prostate cancer treatment in Ontario, Canada. Canadian Urological Association Journal. 2020;14(8):E350. https://doi.org/10.5489/cuaj.6376.*

[146] *Sandner S, Redfors B, Angiolillo DJ, Audisio K, Fremes SE, Janssen PW, et al. Association of dual antiplatelet therapy with ticagrelor with vein graft failure after coronary artery bypass graft surgery: a systematic review and meta-analysis. JAMA. 2022;328(6):554-562. https://doi.org/10.1001/jama.2022.11966*

[147] *Rao SV, Ohman EM. Balancing the Risks and Benefits of Antiplatelet Therapy After Coronary Artery Bypass Graft Surgery. JAMA. 2022;328(6):532-533. https://doi.org/10.1001/jama.2022.12444*

[148] *Lee EL, Richards N, Harrison J, Barnes J. Prevalence of Use of Traditional, Complementary and Alternative Medicine by the General Population: A Systematic Review of National Studies Published from 2010 to 2019. Drug Safety. 2022;45(7):713-735. https://doi.org/10.1007/s40264-022-01189-w*

[149] *Kristoffersen AE, Nilsen JV, Stub T, Nordberg JH, Wider B, Mora D, Nakandi K, Bjelland M. Use of Complementary and Alternative Medicine in the context of cancer; prevalence, reasons for use, disclosure, information received, risks and benefits reported by people with cancer in Norway. BMC Complementary Medicine and Therapies. 2022;22(1):202. https://doi.org/10.1186/s12906-022-03606-0*

[150] *Wallace J, Lollo A, Duchowny KA, Lavallee M, Ndumele CD. Disparities in health care spending and utilization among Black and White Medicaid enrollees. JAMA Health Forum. 2022;3,6: e221398-e221398). https://doi.org/ 10.1001/jamahealthforum.2022.1398*

[151] *Yang Z, Takahashi T, Terada Y, Meyers BF, Kozower BD, Patterson GA, et al. A comparison of outcomes after lung transplantation between European and North American centers. The Journal of Heart and Lung Transplantation. 2022;41(12):1729-1735. https://doi.org/10.1016/j.healun.2022.07.014*

[152] *Li H, Liang H, Wei L, Shi D, Su X, Li F, Zhang J, Wang Z. Health Inequality in the Global Burden of Chronic Obstructive Pulmonary Disease: Findings from the Global Burden of Disease Study 2019. International Journal of Chronic Obstructive Pulmonary Disease. 2022;1695-1702. https://doi.org/10.2147/COPD.S369120*

[153] *Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA Oncology. 2017;3(4):524-548. https://doi.org/ 10.1001/jamaoncol.2016.5688*

[154] *Rand LZ, Kesselheim AS. An international review of health technology assessment approaches to prescription drugs and their ethical principles. Journal of Law, Medicine & Ethics. 2020;48(3):583-594. https://doi.org/ 10.1177/1073110520958885*

[155] *Padula WV, Kreif N, Vanness DJ, Adamson B, Rueda JD; et al. Machine Learning Methods in Health Economics and Outcomes Research—The PALISADE Checklist: A Good Practices Report of an ISPOR Task Force. Value in Health. 2022;25(7):1063-1080. https://doi.org/10.1016/j.jval.2022.03.022*

[156] *Touré M, Kouakou CR, Poder TG. Dimensions used in instruments for QALY calculation: a systematic review. International Journal of Environmental Research and Public Health. 2021;18(9):4428. https://doi.org/10.3390/ijerph18094428.*

[157] *Cowles E, Marsden G, Cole A, Devlin N. A review of NICE methods and processes across health technology assessment programmes: why the differences and what is the impact? Applied Health Economics and Health Policy. 2017;15:469-477. https://doi.org/10.1007/s40258-017-0309-y*

[158] *Menon D. Health technology assessment: the journey continues. CMAJ. 2015;187(1):E19-20. https://doi.org/10.1503/cmaj.140698*

[159] *Ronquest NA, Paret K, Gould IG, Barnett CL, Mladsi DM. The evolution of ICER's review process for new medical interventions and a critical review of economic evaluations (2018-2019): how stakeholders can collaborate with ICER to improve the quality of evidence in ICER's reports. Journal of Managed Care & Specialty Pharmacy. 2021;(11):1601-1612. https://doi.org/10.18553/jmcp.2021.27.11.1601*

[160] *Kruzikas DT, Malone DC, Pham S, Reinsch TK, Akehurst R. HTA and economics in the United States: a systematic review of ICER reports to evaluate trends, identify factors associated with recommendations, and understand implications. Journal of Managed Care & Specialty Pharmacy. 2020;26(12):1548-1557. https://doi.org/10.18553/jmcp.2020.26.12.1548*

[161] *Butcher L. Can ICER bring cost-effectiveness to drug prices?. Managed Care (Langhorne, Pa.). Applied Health Economics and and Health Policy. 2019;28(6):30-33. https://doi.org/10.1111/dom.14021*

[162] *Sussman M, Yu JC, Menzin J. Do Research Groups Align on an Intervention's Value? Concordance of Cost-Effectiveness Findings Between the Institute for Clinical and Economic Review and Other Health System Stakeholders. Applied Health Economics and Health Policy. 2020;18(4):477-489. https://doi.org/10.1007/s40258-019-00545-9*

[163] *Thokala P, Carlson JJ, Drummond M. HTA'd in the USA: A comparison of ICER in the United States with NICE in England and Wales. Journal of Managed Care & Specialty Pharmacy. 2020;26(9):1162-1170. https://doi.org/10.18553/jmcp.2020.26.9.1162*

[164] *Angelis A, Kanavos P, Phillips LD. ICER value framework 2020 update: recommendations on the aggregation of benefits and contextual considerations. Value in Health. 2020;23(8):1040-1048. https://doi.org/10.1016/j.jval.2020.04.1828*

[165] *Vreman RA, Naci H, Goettsch WG, Mantel-Teeuwisse AK, Schneeweiss SG, Leufkens HG, Kesselheim AS. Decision making under uncertainty: comparing regulatory and health technology assessment reviews of medicines in the United States and Europe. Clinical Pharmacology & Therapeutics. 2020;108(2):350-357. https://doi.org/10.1002/cpt.1835*

[166] *Cuan-Baltazar JY, Muñoz-Perez MJ, Robledo-Vega C, Pérez-Zepeda MF, Soto-Vega E. Misinformation of COVID-19 on the internet: infodemiology study. JMIR Public Health and Surveillance. 2020;6(2):e18444. https://doi.org/10.2196/18444*

[167] *Tasnim S, Hossain MM, Mazumder H. Impact of rumors and misinformation on COVID-19 in social media. Journal of Preventive Medicine and Public Health. 2020;53(3):171-174. https://doi.org/10.3961/jpmph.20.094*

[168] *The United Stated Food and Drug Administration (FDA). Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs. Guidance for Industry. 2020. (PDF accessed 2 May 2023).*

[169] *Doyle PW, Kavoussi NL. Machine learning applications to enhance patient specific care for urologic surgery. World Journal of Urology. 2022;40(3):679-686. https://doi.org/10.1007/s00345-021-03738-x*

[170] *Yao L, Cai M, Chen Y, Shen C, Shi L, Guo Y. Prediction of antiepileptic drug treatment outcomes of patients with newly diagnosed epilepsy by machine learning. Epilepsy & Behavior. 2019;96:92-97. https://doi.org/10.1016/j.yebeh.2019.04.006*

[171] *Papageorgiou EI, Subramanian J, Karmegam A, Papandrianos N. A risk management model for familial breast cancer: A new application using Fuzzy Cognitive Map method. Computer Methods and Programs in Biomedicine. 2015;122(2):123-135. https://doi.org/10.1016/j.cmpb.2015.07.003*

[172] *Jones T, Silverman T, Guzman A, McGuinness JE, Trivedi MS, Kukafka R, Crew KD. Qualitative analysis of shared decision-making for chemoprevention in the primary care setting: provider-related barriers. BMC Medical Informatics and Decision Making. 2022;22(1):208. https://doi.org/10.1186/s12911-022-01954-y*

[173] *Li X, Wang Y, Xu J. Development of a machine learning-based risk prediction model for cerebral infarction and comparison with nomogram model. Journal of Affective Disorders. 2022;314:341-348. https://doi.org/10.1016/j.jad.2022.07.045*

[174] *Momtazmanesh S, Nowroozi A, Rezaei N. Artificial Intelligence in Rheumatoid Arthritis: Current Status and Future Perspectives: A State-of-the-Art Review. Rheumatology and Therapy. 2022;9(5):1249-1304. https://doi.org/10.1007/s40744-022-00475-4*

[175] *Singh D, Hurst JR, Martinez FJ, Rabe KF, Bafadhel M, Jenkins M, et al. Predictive modeling of COPD exacerbation rates using baseline risk factors. Therapeutic Advances in Respiratory Disease. 2022;16:17534666221107314. https://doi.org/10.1177/17534666221107314*

[176] *Newman DH, Ackerman B, Kraushar ML, Lederhandler MH, Masri A, Starikov A, et al. Quantifying patient-physician communication and perceptions of risk during admissions for possible acute coronary syndromes. Annals of Emergency Medicine. 2015;66(1):13-18. https://doi.org/10.1016/j.annemergmed.2015.01.027.*

[177] *Mikkonen K, Yamakawa M, Tomietto M, Tuomikoski AM, Utsumi M, Jarva E, et al. Randomised controlled trials addressing how the clinical application of information and communication technology impacts the quality of patient care—a systematic review and meta-analysis. Journal of Clinical Nursing. 2022;18. https://doi.org/10.1111/jocn.16448*

[178] *Way D, Blazsin H, Löfstedt R, Bouder F. Pharmaceutical benefit–risk communication tools: a review of the literature. Drug Safety. 2017;40:15-36. https://doi.org/10.1007/s40264-016-0466-1*

[179] *Mikkonen K, Yamakawa M, Tomietto M, Tuomikoski AM, Utsumi M, Jarva E, et al. Randomised controlled trials addressing how the clinical application of information and communication technology impacts the quality of patient care—a systematic review and meta-analysis. Journal of Clinical Nursing. 2022;18. https://doi.org/10.1111/jocn.16448.*

[180] *CIOMS XI, Way D, Blazsin H, Löfstedt R, Bouder F. Pharmaceutical benefit-risk communication tools: a review of the literature. Drug Safety. 2017;40(1):15-36. https://doi.org/10.1007/s40264-016-0466-1.*

[181] *DeMets DL, Califf RM. A historical perspective on clinical trials innovation and leadership: where have the academics gone? JAMA. 2011;16;305(7):713-714. https://doi:10.1001/jama.2011.175*

[182] *Evans SR, Bigelow R, Chuang-Stein C, Ellenberg SS, Gallo P, He W, Jiang Q, Rockhold F. Presenting risks and benefits: helping the data monitoring committee do its job. Annals of Internal Medicine. 2020;21;172(2):119-125. https://doi.org/10.7326/M19-1491*

[183] *Evans S, Rubin DB, Powers JH, Follmann D. Analysis populations in anti-infective clinical trials: whom to analyze? Statistical Communications in Infectious Diseases. 2018;1;10(1). https://doi.org/10.1515/scid-2017-0002*

[184] *Johnston SC, Amarenco P, Denison H, Evans SR, Himmelmann A, James S, Knutsson M, et al. Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. New England Journal of Medicine. 2020;16;383(3):207-217. https:// doi:10.1056/NEJMoa1916870*

[185] *Evans S. When and how can endpoints be changed after initiation of a randomized clinical trial. PLoS ClinicalTrials. 2007;13;2(4):e18. https://doi.org/10.1371/journal.pctr.0020018*

[186] *Evans, S., and Ting, N. Fundamental Concepts for New Clinical Trialists. Boca Raton, FL: CRC Press; 2016.*

[187] *Doernberg SB, Tran TT, Tong SYC, Paul M, Yahav D, Davis JS, et al. Good studies evaluate the disease while great studies evaluate the patient: Development and application of a DOOR endpoint for Staphylococcus aureus bloodstream infection. Clinical Infectious Diseases. 2019;2;68(10):1691-1698. https://doi.org/10.1093/cid/ciy766*

[188] *Evans SR, Follmann D. Using outcomes to analyze patients rather than patients to analyze outcomes: a step toward pragmatism in benefit: risk evaluation. Statistics in Biopharmaceutical Research. 2016;1;8(4):386-393. https://doi.org/10.1080/19466315.2016.1207561*

[189] *Clinical Trials Transformation Initiative. CTTI recommendations: Data Monitoring Committees. (PDF accessed 20 April 2023).*

[190] *Evans SR, Bigelow R, Chuang-Stein C, Ellenberg SS, Gallo P, He W, Jiang Q, Rockhold F. Presenting risks and benefits: helping the data monitoring committee do its job. Annals of Internal Medicine. 2020;21;172(2):119-125. https://doi.org/10.7326/M19-1491*

[191] *Evans SR, Rubin D, Follmann D, Pennello G, Huskins WC, Powers JH, et al. Desirability of outcome ranking (DOOR) and response adjusted for duration of antibiotic risk (RADAR). Clinical Infectious Diseases. 2015;1;61(5):800-806. https://doi.org/10.1093/cid/civ495*

[192] *Doernberg SB, Tran TT, Tong SYC, Paul M, Yahav D, Davis JS, et al. Good studies evaluate the disease while great studies evaluate the patient: Development and application of a DOOR endpoint for Staphylococcus aureus bloodstream infection. Clinical Infectious Diseases. 2019;2;68(10):1691-1698. https://doi.org/10.1093/cid/ciy766*

[193] *Kinamon T, Gopinath R, Waack U, Needles M, Rubin D, Collyar D, et al. Exploration of a potential DOOR endpoint for complicated intra-abdominal infections using nine registrational trials for antibacterial drugs. Clinical Infectious Diseases. 2023;ciad239. https://doi.org/10.1093/cid/ciad239*

[194] *Howard-Anderson J, Hamasaki T, Dai W, Collyar D, Rubin D, Nambiar S, et al. Improving traditional registrational trial end points: development and application of a desirability of outcome ranking end point for complicated urinary tract infection clinical trials. Clinical Infectious Diseases. 2023;1;76(3):e1157-1165. https://doi.org/10.1093/cid/ciac692*

[195] Buyse M. Generalized pairwise comparisons of prioritized outcomes in the two-sample problem. Statistics in Medicine. 2010;30;29(30):3245-3257. https://doi.org/10.1002/sim.3923

[196] Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. European Heart Journal. 2012;1;33(2):176-182. https://doi.org/10.1093/eurheartj/ehr352

[197] Follmann DA. Regression analysis based on pairwise ordering of patients' clinical histories. Statistics in Medicine. 2002;30;21(22):3353-3367. https://doi.org/10.1002/sim.1272

[198] Follmann D, Fay MP, Hamasaki T, Evans S. Analysis of ordered composite endpoints. Statistics in Medicine. 2020;28;39(5):602-616. https://doi.org/10.1002/sim.8431

[199] Evans SR, Follmann D. Using outcomes to analyze patients rather than patients to analyze outcomes: a step toward pragmatism in benefit: risk evaluation. Statistics in Biopharmaceutical Research. 2016;1;8(4):386-393. https://doi.org/10.1080/19466315.2016.1207561

[200] Evans SR, Follmann D. Using outcomes to analyze patients rather than patients to analyze outcomes: a step toward pragmatism in benefit: risk evaluation. Statistics in Biopharmaceutical Research. 2016;1;8(4):386-393. https://doi.org/10.1080/19466315.2016.1207561

[201] Mitroiu M, Oude Rengerink K, Teerenstra S, Pétavy F, Roes KC. A narrative review of estimands in drug development and regulatory evaluation: old wine in new barrels?. Trials. 2020;21:1-4. https://doi.org/10.1186/s13063-020-04546-1

[202] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Expert Working Group. ICH harmonised tripartite guideline E9: statistical principles for clinical trials. (PDF accessed 20 April 2023).

[203] Kahan BC, Morris TP, White IR, Tweed CD, Cro S, Dahly D, et al. Treatment estimands in clinical trials of patients hospitalised for COVID-19: ensuring trials ask the right questions. BMC Medicine. 2020;18(1):1-8. https://doi.org/10.1186/s12916-020-01737-0

[204] Unkel S, Amiri M, Benda N, Beyersmann J, Knoerzer D, Kupas K, et al. On estimands and the analysis of adverse events in the presence of varying follow-up times within the benefit assessment of therapies. Pharmaceutical Statistics. 2019;18(2),166-183. https://doi.org/10.1002/pst.1915

[205] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Expert Working Group. ICH harmonised tripartite guideline E9: statistical principles for clinical trials. (PDF accessed April 2023).

[206] Akacha M, Bretz F, Ruberg S. Estimands in clinical trials–broadening the perspective. Statistics in Medicine. 2017;15;36(1):5-19. https://doi.org/10.1002/sim.7033

[207] Unkel S, Amiri M, Benda N, Beyersmann J, Knoerzer D, Kupas K, et al. On estimands and the analysis of adverse events in the presence of varying follow-up times within the benefit assessment of therapies. Pharmaceutical Statistics, 2019;18(2),166-183. https://doi.org/10.1002/pst.1915

[208] The United States Food and Drug Administration (FDA). Endocrinologic and Metabolic Drugs Advisory Committee meeting. 2011. (Website accessed 20 April 2023).

[209] The United States Food and Drug Administration (FDA). Endocrinologic and Metabolic Drugs Advisory Committee meeting. 2011. (Website accessed 20 April 2023).

[210] Yuan SS, Seifu Y, Wang W, Colopy M. Estimands in Safety and Benefit-Risk Evaluation. In Quantitative drug safety and benefit-risk evaluation. Chapman and Hall/CRC, 2021.

[211] Unkel S, Amiri M, Benda N, Beyersmann J, Knoerzer D, Kupas K, et al. On estimands and the analysis of adverse events in the presence of varying follow-up times within the benefit assessment of therapies. Pharmaceutical Statistics, 2019;18(2),166-183. https://doi.org/10.1002/pst.1915

[212] Akacha M, Bretz F, Ruberg S. Estimands in clinical trials–broadening the perspective. Statistics in medicine. 2017;15;36(1):5-19. https://doi.org/10.1002/sim.7033

[213] Yang F, Wittes J, Pitt B. Beware of on-treatment safety analyses. Clinical Trials. 2019;16(1):63-70. https://doi: 10.1177/1740774518812774

[214] Rockhold FW, Lindblad A, Siegel JP, Molenberghs G. University of Pennsylvania 11th annual conference on statistical issues in clinical trials: Estimands, missing data and sensitivity analysis (morning panel session). Clinical Trials. 2019;16(4):350-362. https://doi: 10.1177/1740774519853573

[215] Yuan SS, Seifu Y, Wang W, Colopy M. Estimands in Safety and Benefit-Risk Evaluation. In Quantitative drug safety and benefit-risk evaluation. Chapman and Hall/CRC, 2021.

[216] Thorpe KE, Zwarenstein M, Oxman AD, Treweek S, Furberg CD, Altman DG, et al. A pragmatic–explanatory continuum indicator summary (PRECIS): a tool to help trial designers. Journal of Clinical Epidemiology. 2009;1;62(5):464-475. https://doi.org/10.1016/j.jclinepi.2008.12.011

[217] European Medicines Agency (EMA). International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH Harmonised Guideline. Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials. E9(R1). (PDF accessed 12 May 2023).

[218] Center for Medical Technology Policy (CMTP). Methodological guidance for the design of more informative (or pragmatic) pharmaceutical clinical trials, CTMP Expert Working Group Meeting Summary May 2009. (PDF accessed 12 May 2023).

[219] Reynolds RF, Lem JA, Gatto NM, Eng SM. Is the large simple trial design used for comparative, post-approval safety research? A review of a clinical trials registry and the published literature. Drug Safety. 2011;34(10):799-820. https://doi.org/10.2165/11593820-000000000-00000

[220] European Medicines Agency (EMA). International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH Harmonised Guideline. Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials. E9(R1). (PDF accessed 12 May 2023).

[221] Eapen, Z.J., Lauer, M., and Temple, R.J. (2014). The Imperative of overcoming barriers to the conduct of large, simple trials. JAMA. 311(14):1397-1398. https://doi:10.1001/jama.2014.1030

[222] Center for Medical Technology Policy (CMTP). Resource Center. Pragmatic Explanatory continuum indicator summary. (Website accessed 20 April 2023).

[223] Tosh G, Soares-Weiser K, Adams CE. Pragmatic vs explanatory trials: the pragmascope tool to help measure differences in protocols of mental health randomized controlled trials. Dialogues in Clinical Neuroscience. 2011;13(2):209-215. https://doi.org/10.31887/DCNS.2011.13.2/gtosh

[224] Kim HS, Lee S, Kim JH. Real-world evidence versus randomized controlled trial: clinical research based on electronic medical records. Journal of Korean Medical Science. 2018;33(34):e213. https://doi.org/10.3346/jkms.2018.33.e213

[225] Sugarman J., Califf R.M., Califf R.M. and Sugarman J.Exploring the ethical and regulatory issues in pragmatic clinical trials. Clinical Trials. 2015;12 (5):436-441. https://DOI:10.1177/1740774515598334.

[226] Reynolds RF, Lem JA, Gatto NM, Eng SM. Is the large simple trial design used for comparative, post-approval safety research? A review of a clinical trials registry and the published literature. Drug Safety. 2011;34(10):799-820. https://doi.org/10.2165/11593820-000000000-00000

[227] Reynolds RF, Lem JA, Gatto NM, Eng SM. Is the large simple trial design used for comparative, post-approval safety research? A review of a clinical trials registry and the published literature. Drug Safety. 2011;34(10):799-820. https://doi.org/10.2165/11593820-000000000-00000

[228] Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. Journal of Pharmacology and pharmacotherapeutics. 2010;1(2):100-107. https://doi:10.1371/journal.pmed.1000251

[229] PRagmatic Explanatory Continuum Indicator Summary (PRECIS). PRECIS-2. (Website accessed 12 May 2023).

[230] Tosh G, Soares-Weiser K, Adams CE. Pragmatic vs explanatory trials: the pragmascope tool to help measure differences in protocols of mental health randomized controlled trials. Dialogues in Clinical Neuroscience. 2022;1. https://doi.org/10.31887/DCNS.2011.13.2/gtosh

[231] Reynolds RF, Lem JA, Gatto NM, Eng SM. Is the large simple trial design used for comparative, post-approval safety research? A review of a clinical trials registry and the published literature. Drug Safety. 2011;34(10):799-820. https://doi.org/10.2165/11593820-000000000-00000

[232] Peto, R., Collins, R., and Gray, R. (1995). Large Scale Randomized Evidence: Large Simple Trials and Overview of Trials. Journal of Clinical Epidemiology, 48(1):23-40. https://doi.org/10.1016/0895-4356(94)00150-O

[233] Eapen, Z.J., Lauer, M., and Temple, R.J. (2014). The Imperative of Overcoming Barriers to the Conduct of Large, Simple Trials. JAMA, 311(14): 1397-1398. doi:10.1001/jama.2014.1030

[234] Thorpe KE, Zwarenstein M, Oxman AD, Treweek S, Furberg CD, Altman DG, et al. A pragmatic–explanatory continuum indicator summary (PRECIS): a tool to help trial designers. Journal of Clinical Epidemiology. 2009;1;62(5):464-475. https://doi.org/10.1016/j.jclinepi.2008.12.011

[235] Koehler M, Donnelly ET, Kalanovic D, Dagher R, Rothenberg ML. Pragmatic randomized clinical trials: a proposal to enhance evaluation of new cancer therapies with early signs of exceptional activity. Annals of Oncology. 2016;27(7):1342-1348. https://doi.org/10.1093/annonc/mdw143

[236] Bombardier C, Maetzel A. Pharmacoeconomic evaluation of new treatments: efficacy versus effectiveness studies? Annals of the Rheumatic Diseases. 1999;58;Suppl1:I82-5.:I82-I85 http://dx.doi.org/10.1136/ard.58.2008.i82

[237] Baumfeld Andre E, Reynolds R, Caubel P, Azoulay L, Dreyer NA. Trial designs using real-world data: The changing landscape of the regulatory approval process. Pharmacoepidemiology and Drug Safety. 2020;29(10):1201-1212. https://doi.org/10.1002/pds.4932

[238] The United States Food and Drug Administration (FDA). Framework for FDA's. Real-World Evidence Program. (PDF accessed 20 April 2023).

[239] *The United States Food and Drug Administration (FDA). Framework for FDA's. Real-World Evidence Program. (PDF accessed 20 April 2023).*

[240] *Patient Involvement in the Development, Regulation and Safe Use of Medicines. CIOMS WG XI report. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2022. https://doi.org/10.56759/iiew8982 (PDF accessed 20 April 2022).*

[241] *Whichello C, Bywall KS, Mauer J, Stephen W, Cleemput I, Pinto CA, et al. An overview of critical decision-points in the medical product lifecycle: Where to include patient preference information in the decision-making process? Health Policy. 2020;124(12):1325-1332. https://doi.org/10.1016/j.healthpol.2020.07.007.*

[242] *Patient involvement in the development, regulation and safe use of medicines. CIOMS Working Group report. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2022.* https://doi:10.56759/iiew8982

[243] *Patient involvement in the development, regulation and safe use of medicines. CIOMS Working Group report. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2022.* https://doi:10.56759/iiew8982

[244] *Janssens R, Russo S, van Overbeeke E, Whichello C, Harding S, Kübler J, et al. Patient preferences in the medical product life cycle: what do stakeholders think? Semi-structured qualitative interviews in Europe and the USA. The Patient-Patient-Centered Outcomes Research. 2019;1;12:513-526. https://doi.org/10.1007/s40271-019-00367-w*

[245] *Mühlbacher A, Juhnke C, Beyer A, Garner S. Patient-focused benefit-risk analysis to inform regulatory decisions: the european union perspective. Value in Health. 2016;19(6):734–740. https://doi.org/10.1016/j.jval.2016.04.006*

[246] *Patient Involvement in the Development, Regulation and Safe Use of Medicines. CIOMS WG XI report. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2022. https://doi.org/10.56759/iiew8982 (PDF accessed 20 April 2022).*

[247] *Patient Involvement in the Development, Regulation and Safe Use of Medicines. CIOMS WG XI report. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2022. https://doi.org/10.56759/iiew8982 (PDF accessed 20 April 2022).*

[248] *Patient Involvement in the Development, Regulation and Safe Use of Medicines. CIOMS WG XI report. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2022. https://doi.org/10.56759/iiew8982 (PDF accessed 20 April 2022).*

[249] *Patient Involvement in the Development, Regulation and Safe Use of Medicines. CIOMS WG XI report. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2022. https://doi.org/10.56759/iiew8982 (PDF accessed 20 April 2022).*

[250] *European Medicines Agency (EMA), Stakeholders and Communication Division. The patient's voice in the evaluation of medicines. 2013. (PDF accessed 2 May 2023).*

[251] *Bøgelund M, Vilsbøll T, Faber J, Henriksen JE, Gjesing RP, Lammert M. Patient preferences for diabetes management among people with type 2 diabetes in Denmark–a discrete choice experiment. Current Medical Research and Opinion. 2011;1;27(11):2175-2183. https://doi.org/10.1185/03007995.2011.625404*

[252] *Soekhai V, Whichello C, Levitan B, Veldwijk J, Pinto CA, Donkers B, et al. Methods for exploring and eliciting patient preferences in the medical product lifecycle: a literature review. Drug Discovery Today. 2019;1;24(7):1324-1331. https://doi.org/10.1016/j.drudis.2019.05.001*

[253] *Soekhai V, Whichello C, Levitan B, Veldwijk J, Pinto CA, Donkers B, et al. Methods for exploring and eliciting patient preferences in the medical product lifecycle: a literature review. Drug Discovery Today. 2019;1;24(7):1324-1331. https://doi.org/10.1016/j.drudis.2019.05.001*

[254] *Soekhai V, Whichello C, Levitan B, Veldwijk J, Pinto CA, Donkers B, et al. Methods for exploring and eliciting patient preferences in the medical product lifecycle: a literature review. Drug Discovery Today. 2019;1;24(7):1324-1331. https://doi.org/10.1016/j.drudis.2019.05.001*

[255] *Soekhai V, Whichello C, Levitan B, Veldwijk J, Pinto CA, Donkers B, et al. Methods for exploring and eliciting patient preferences in the medical product lifecycle: a literature review. Drug Discovery Today. 2019;1;24(7):1324-1331. https://doi.org/10.1016/j.drudis.2019.05.001*

[256] *Hauber AB, Fairchild AO, Reed Johnson F. Quantifying benefit–risk preferences for medical interventions: an overview of a growing empirical literature. Applied Health Economics and Health Policy. 2013;11:319-329. https://doi.org/10.1007/s40258-013-0028-y*

[257] *Hazlewood GS, Bombardier C, Tomlinson G, Thorne C, Bykerk VP, Thompson A, Tin D, Marshall DA. Treatment preferences of patients with early rheumatoid arthritis: a discrete-choice experiment. Rheumatology. 2016;1;55(11):1959-1968. https://doi.org/10.1093/rheumatology/kew280*

[258] *Bøgelund M, Vilsbøll T, Faber J, Henriksen JE, Gjesing RP, Lammert M. Patient preferences for diabetes management among people with type 2 diabetes in Denmark–a discrete choice experiment. Current Medical Research and Opinion. 2011;1;27(11):2175-2183. https://doi.org/10.1185/03007995.2011.625404*

[259] *Mühlbacher A, Juhnke C, Beyer A, Garner S. Patient-focused benefit-risk analysis to inform regulatory decisions: the european union perspective. Value in Health. 2016;19(6):734–740. https://doi.org/10.1016/j.jval.2016.04.006*

[260] *Bøgelund M, Vilsbøll T, Faber J, Henriksen JE, Gjesing RP, Lammert M. Patient preferences for diabetes management among people with type 2 diabetes in Denmark–a discrete choice experiment. Current Medical Research and Opinion. 2011;1;27(11):2175-2183. https://doi.org/10.1185/03007995.2011.625404*

[261] *Mühlbacher A, Juhnke C, Beyer A, Garner S. Patient-focused benefit-risk analysis to inform regulatory decisions: the european union perspective. Value in Health. 2016;19(6):734–740. https://doi.org/10.1016/j.jval.2016.04.006*

[262] *Hazlewood GS, Bombardier C, Tomlinson G, Thorne C, Bykerk VP, Thompson A, Tin D, Marshall DA. Treatment preferences of patients with early rheumatoid arthritis: a discrete-choice experiment. Rheumatology. 2016;1;55(11):1959-1968. https://doi.org/10.1093/rheumatology/kew280*

[263] *Hazlewood GS, Bombardier C, Tomlinson G, Thorne C, Bykerk VP, Thompson A, Tin D, Marshall DA. Treatment preferences of patients with early rheumatoid arthritis: a discrete-choice experiment. Rheumatology. 2016;1;55(11):1959-1968. https://doi.org/10.1093/rheumatology/kew280*

[264] *Hazlewood GS, Bombardier C, Tomlinson G, Thorne C, Bykerk VP, Thompson A, Tin D, Marshall DA. Treatment preferences of patients with early rheumatoid arthritis: a discrete-choice experiment. Rheumatology. 2016;1;55(11):1959-1968. https://doi.org/10.1093/rheumatology/kew280*

[265] *Hazlewood GS, Bombardier C, Tomlinson G, Thorne C, Bykerk VP, Thompson A, Tin D, Marshall DA. Treatment preferences of patients with early rheumatoid arthritis: a discrete-choice experiment. Rheumatology. 2016;1;55(11):1959-1968. https://doi.org/10.1093/rheumatology/kew280*

[266] *Whichello C, Levitan B, Juhaeri J, Patadia V, DiSantostefano R, Pinto CA, et al. Appraising patient preference methods for decision-making in the medical product lifecycle: an empirical comparison. BMC Medical Informatics and Decision Making. 2020;20(1):1-5. https://doi.org/10.1186/s12911-020-01142-w*

[267] *Barder O, Levine R. An Introduction to risk an uncertainty. Global Health Forecasting Working Group, Center for Global Development. 2006. (PDF accessed 20 April 2023).*

[268] *Innovative Medicines Initiative (IMI). ADVANCE. Accelerated development of vaccine benefit-risk collaboration in Europe. (Website accessed April 2023).*

[269] *Knight FH., Risk, Uncertainty and Profit, 1921. Houghton Mifflin Company. Che Riverside Press Cambridge.*

[270] *Aspers P. Forms of uncertainty reduction: decision, valuation, and contest. Theory and Society. 2018;47(2):133-149. https://doi.org/10.1007/s11186-018-9311-0*

[271] *Hespanhol L, Vallio CS, Costa LM, Saragiotto BT. Understanding and interpreting confidence and credible intervals around effect estimates. Braz J Phys Ther. 2019 Jul-Aug;23(4):290-301. doi: 10.1016/j.bjpt.2018.12.006. Epub 2018 Dec 31. PMID: 30638956; PMCID: PMC6630113.*

[272] *Bittl JA, He Y. Bayesian Analysis: A Practical Approach to Interpret Clinical Trials and Create Clinical Practice Guidelines. Circ Cardiovasc Qual Outcomes. 2017 Aug;10(8):e003563. doi: 10.1161/CIRCOUTCOMES.117.003563. PMID: 28798016; PMCID: PMC6421843.*

[273] *Evidence Synthesis and Meta-Analysis: Report of CIOMS Working Group X. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS), 2016. https://doi.org/10.56759/lela7055*

[274] *Alizadehsani R, Roshanzamir M, Hussain S, Khosravi A, Koohestani A, Zangooei MH, et al. Handling of uncertainty in medical data using machine learning and probability theory techniques: a review of 30 years (1991-2020). Annals of Operations Research. 2021;21:1-42. https://doi.org/10.1007/s10479-021-04006-2*

[275] *Ghahramani Z. Probabilistic machine learning and artificial intelligence. Nature. 2015;28;521(7553):452-459. https://doi.org/10.1038/nature14541*

[276] *Han PK, Klein WM, Arora NK. Varieties of uncertainty in health care: a conceptual taxonomy. Medical Decision Making. 2011;31(6):828-38.*

[277] *Ghahramani Z. Probabilistic machine learning and artificial intelligence. Nature. 2015;28;521(7553):452-459. https://doi:10.1038/nature14541*

[278] *Mutanga JN, Nukala U, Rodriguez Messan M, Yogurtcu ON, McCormick Q, Sauna ZE, et al. A Retrospective review of center for biologics evaluation and research advisory committee meetings in the context of the FDA's benefit-risk framework. The AAPS Journal. 2023;9;25(1):24. https://doi.org/10.1208/s12248-023-00789-3*

[279] *Aspers P. Forms of uncertainty reduction: decision, valuation, and contest. Theory and Society. 2018;47(2):133-149. https://doi.org/10.1007/s11186-018-9311-0*

[280] *Aspers P. Forms of uncertainty reduction: decision, valuation, and contest. Theory and Society. 2018;47(2):133-149. https://doi.org/10.1007/s11186-018-9311-0*

[281] *Anderson EC, Carleton RN, Diefenbach M, Han PKJ. The relationship between uncertainty and affect. Frontiers in Psychology. 2019;12;10:2504. https://DOI=10.3389/fpsyg.2019.02504*

[282] Han PK, Klein WM, Arora NK. Varieties of uncertainty in health care: a conceptual taxonomy. Medical Decision Making. 2011;31(6):828-38.

[283] Kalke K, Studd H, Scherr CL. The communication of uncertainty in health: a scoping review. Patient Education and Counseling. 2021;104(8):1945-1961. https://doi.org/10.1016/j.pec.2021.01.034

[284] Simonovic N, Taber JM. Psychological impact of ambiguous health messages about COVID-19. Journal of Behavior Medicine. 2021;23:1–13. https://doi.org/10.1007/s10865-021-00266-2

[285] Mishel MH, Germino BB, Lin L, Pruthi RS, Wallen EM, Crandell J, Blyler D. Managing uncertainty about treatment decision making in early stage prostate cancer: a randomized clinical trial. Patient Education and Counseling. 2009;77(3):349-59. https://doi.org/10.1016/j.pec.2009.09.009

[286] Han PK, Reeve BB, Moser RP, Klein WM. Aversion to ambiguity regarding medical tests and treatments: measurement, prevalence, and relationship to sociodemographic factors. Journal of Health Communication. 2009;14(6):556-572. https://doi.org/10.1080/10810730903089630

[287] Han PK, Reeve BB, Moser RP, Klein WM. Aversion to ambiguity regarding medical tests and treatments: measurement, prevalence, and relationship to sociodemographic factors. J Health Commun. 2009 Sep;14(6):556-72. doi: 10.1080/10810730903089630. PMID: 19731127; PMCID: PMC4205160.

[288] Vives ML, FeldmanHall O. Tolerance to ambiguous uncertainty predicts prosocial behavior. Nature Communications. 2018;12;9(1):2156. https://doi.org/10.1038/s41467-018-04631-9

[289] Mishel MH, Germino BB, Lin L, Pruthi RS, Wallen EM, Crandell J, Blyler D. Managing uncertainty about treatment decision making in early stage prostate cancer: a randomized clinical trial. Patient Education and Counseling. 2009;77(3):349-359. https://doi.org/10.1016/j.pec.2009.09.009

[290] Carleton RN, Duranceau S, Shulman EP, Zerff M, Gonzales J, Mishra S. Self-reported intolerance of uncertainty and behavioural decisions. Journal of Behavior Therapy and Experimental Psychiatry. 2016;51:58-65. https://doi.org/10.1016/j.jbtep.2015.12.004

[291] Oglesby ME, Allan NP, Schmidt NB. Randomized control trial investigating the efficacy of a computer-based intolerance of uncertainty intervention. Behaviour Research and Therapy. 2017;95:50-57. https://doi.org/10.1016/j.brat.2017.05.007

[292] Deng X, Guo X, Wu YJ, Chen M. Perceived environmental dynamism promotes entrepreneurial team member's innovation: explanations based on the uncertainty reduction theory. International Journal of Environmental Research and Public Health. 2021;19;18(4):2033. https://doi.org/10.3390/ijerph18042033

[293] Oldeweme A, Märtins J, Westmattelmann D, Schewe G. The Role of transparency, trust, and social influence on uncertainty reduction in times of pandemics: empirical study on the adoption of COVID-19 tracing apps. Journal of Medical Internet Research. 2021;8;23(2):e25893. https://doi.org/10.2196/25893

[294] Oldeweme A, Märtins J, Westmattelmann D, Schewe G. The role of transparency, trust, and social influence on uncertainty reduction in times of pandemics: empirical study on the adoption of COVID-19 tracing apps. Journal of Medical Internet Research. 2021;8;23(2):e25893. https://doi.org/10.2196/25893

[295] Oldeweme A, Märtins J, Westmattelmann D, Schewe G. The Role of Transparency, Trust, and Social Influence on Uncertainty Reduction in Times of Pandemics: Empirical Study on the Adoption of COVID-19 Tracing Apps. J Med Internet Res. 2021 Feb 8;23(2):e25893. doi: 10.2196/25893. PMID: 33465036; PMCID: PMC7872328.

[296] Burke PF, Masters D, Massey G. Enablers and barriers to COVID-19 vaccine uptake: An international study of perceptions and intentions. Vaccine. 2021;23;39(36):5116-5128. https://doi.org/10.1016/j.vaccine.2021.07.056

[297] Levitan B, Cross J. Pharmaceutical benefit-risk assessment in early development. In: Sashegyi A, Felli J, Noel R, eds. Benefit - Risk Assessment in Pharmaceutical Research and Development. Boca Raton: CRC Press, 2014, pp. 3–19

[298] Levitan B, Cross J. Pharmaceutical benefit-risk assessment in early development. In: Sashegyi A, Felli J, Noel R, eds. Benefit - Risk Assessment in Pharmaceutical Research and Development. Boca Raton: CRC Press, 2014, pp. 3–19

[299] Kossmeier M, Tran US, Voracek M. Charting the landscape of graphical displays for meta-analysis and systematic reviews: a comprehensive review, taxonomy, and feature analysis. BMC Medical Research Methodology. 2020;7;20(1):26. https://doi.org/10.1186/s12874-020-0911-9

[300] Hallgreen CE, Mt-Isa S, Lieftucht A, Phillips LD, Hughes D, Talbot S, et al.: PROTECT Benefit-Risk group. Literature review of visual representation of the results of benefit-risk assessments of medicinal products. Pharmacoepidemiology and Drug Safety. 2016;25(3):238-250. https://doi.org/10.1002/pds.3880

[301] Hallgreen CE, Mt-Isa S, Lieftucht A, Phillips LD, Hughes D, Talbot S, et al.: PROTECT Benefit-Risk group. Literature review of visual representation of the results of benefit-risk assessments of medicinal products. Pharmacoepidemiology and Drug Safety. 2016;25(3):238-250. https://doi.org/10.1002/pds.3880

[302] Hallgreen CE, Mt-Isa S, Lieftucht A, Phillips LD, Hughes D, Talbot S, et al.: PROTECT Benefit-Risk group. Literature review of visual representation of the results of benefit-risk assessments of medicinal products. Pharmacoepidemiology and Drug Safety. 2016;25(3):238-250. https://doi.org/10.1002/pds.3880

[303] *Management of Safety Information from Clinical Trials. CIOMS Working Group VI report. Genevca: Switzerland Council for International Organizations of Medical Sciences (CIOMS), 2005. (PDF accessed 20 April 2023).*

[304] *Rodriguez L, Renz C, Edwards B and Wang WB; "Trends and Recent Progress in Benefit-Risk Assessment Planning for Medical Products and Devices," Drug Safety and Benefit-Risk Evaluation, Chapman and Hall/CRC, Boca Raton 2021; https://doi.org/10.1201/9780429488801)*

[305] *Evans SR, Knutsson M, Amarenco P, Albers GW, Bath PM, Denison H, et al. Methodologies for pragmatic and efficient assessment of benefits and harms: application to the SOCRATES trial. Clinical Trials. 2020;17(6);617-626. https://doi: 10.1177/1740774520941441*

[306] *Evans SR, Knutsson M, Amarenco P, Albers GW, Bath PM, Denison H, et al. Methodologies for pragmatic and efficient assessment of benefits and harms: application to the SOCRATES trial. Clinical Trials. 2020;17(6);617-626. https://doi: 10.1177/1740774520941441*

[307] *Simonovic, N., Taber, J.M. Psychological impact of ambiguous health messages about COVID-19. Journal of Behavioural Medicine. 2022;45;159–171. https://doi.org/10.1007/s10865-021-00266-2*

[308] *Evans SR, Knutsson M, Amarenco P, Albers GW, Bath PM, Denison H, et al. Methodologies for pragmatic and efficient assessment of benefits and harms: application to the SOCRATES trial. Clinical Trials, 2020;17(6);617-626. https://doi: 10.1177/1740774520941441*

[309] *J Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, et al. Ticagrelor versus aspirin in acute stroke or transient ischemic attack. New England Journal of Medicine. 2016;7;375(1):35-43. https:// doi:10.1056/NEJMoa1603060*

[310] *Van Duin D, Lok JJ, Earley M, Cober E, Richter SS, Perez F, et al. Colistin versus ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant Enterobacteriaceae. Clinical Infectious Diseases. 2018; 6;66(2):163-171. https://doi.org/10.1093/cid/cix783*

[311] *Van Duin D, Lok JJ, Earley M, Cober E, Richter SS, Perez F, et al. Colistin versus ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant Enterobacteriaceae. Clinical Infectious Diseases. 2018; 6;66(2):163-171. https://doi.org/10.1093/cid/cix783*

[312] *Duin D, Lok JJ, Earley M, Cober E, Richter SS, Perez F, et al. Colistin versus ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant Enterobacteriaceae. Clinical Infectious Diseases. 2018; 6;66(2):163-171. https://doi.org/10.1093/cid/cix783*

[313] *Kinamon T, Gopinath R, Waack U, Needles M, Rubin D, Collyar D, et al. 223. Development and analysis of a novel DOOR endpoint for complicated intra-abdominal infections (cIAI) Using 10 registrational trials for antibacterial drugs. Open Forum Infectious Diseases. 2022;9;2. https://doi.org/10.1093/ofid/ofac492.301*

[314] *Oak Ridge Institute for Science and Education (ORISE). FDA Antibacterial Drug Resistance (DOOR) Fellowship. (Website accessed 2 May 2023).*

[315] *Howard-Anderson J, Hamasaki T, Dai W, Collyar D, Rubin D, Nambiar S, et al. Improving traditional registrational trial end points: development and application of a desirability of outcome ranking end point for complicated urinary tract infection clinical trials. Clinical Infectious Diseases. 2023;1;76(3):e1157-1165. https://doi.org/10.1093/cid/ciac692*

[316] *Howard-Anderson J, Hamasaki T, Dai W, Collyar D, Rubin D, Nambiar S, et al. Improving traditional registrational trial end points: development and application of a desirability of outcome ranking end point for complicated urinary tract infection clinical trials. Clinical Infectious Diseases. 2023;1;76(3):e1157-1165. https://doi.org/10.1093/cid/ciac692*

[317] *Howard-Anderson J, Hamasaki T, Dai W, Collyar D, Rubin D, Nambiar S, et al. Improving traditional registrational trial end points: development and application of a desirability of outcome ranking end point for complicated urinary tract infection clinical trials. Clinical Infectious Diseases. 2023;1;76(3):e1157-1165. https://doi.org/10.1093/cid/ciac692*

Chapter 4: Specificities of BR methods for special situations

4.1 Introduction

This chapter aims to reflect situations where there is an important lack of information on benefits and risks and such uncertainty over the magnitude of benefits and risks creates a need to consider their balance in a different way. These situations are not rare and may cover up to half of recently approved drugs or vaccines. The chapter covers situations impacting the way to evaluate the BR balance due to the medicine itself, the targeted population or the regulatory status.

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

Table 22: Overview of main special situations and related key challenge and methods

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 efficacy and safety
Accelerated /conditional approval	Pending more mature efficacy data	Simulation and extrapolation methods
Legacy product	No clinical data, heterogeneity of sources of information	Synthetise data from multiple sources
Special population: Rare disease	Limited number of patients exposed, limited knowledge on risks	Use of RWD to complement evidence
Special population: paediatric	Limited exposure and heterogeneity	Use of RWD to complement evidence
Advanced Therapy Medicinal Products	Uncertainty on benefits and risks	Simulation and extrapolation methods combined with post-marketing monitoring

4.2 Emergency use and/or repurposing

Major issues / challenges

Managing with lack of evidence and urgency

Following the essential principles of evidence-based medicine and regulatory decision making remain key also in times of public health emergencies. As it 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 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 expanded surveillance should include appropriate, evidence-generating or adverse reaction monitoring strategies such as: Phase 4 clinical studies; observational studies; developer-run patient registries and/or patient support programs; patient focus groups. 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 risks may be different than in non-emergency use circumstances.

When the public health emergency is lifted, the standard measures of monitoring will 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

Major issues / challenges

Managing with uncertainty and pending evidence

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

Specific considerations

At time of initial evaluation

- Uncertainty linked to limited data on benefits and risks, more uncertainty of risks.
    - Consider methods to simulate effects and sensitivity analyses.
- Uncertainty of treatment effect.
    - Provide quantitative measure of sampling variability associated with estimates from a single trial or a meta-analysis of trials.
    - Consider methods to extrapolate the available measures (e.g. surrogate endpoints) into clinical outcomes.

In post-marketing

- Reassessment of BR based on new data collected through planned post-marketing activities (clinical trials, observational studies, etc…).

- Consider synthesising data from multiple sources.

4.4 Legacy products

Major issues / challenges

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

For legacy products, treatment paradigm, data standards and clinical guidelines may have evolved over time since the MA of the product was granted.

Another big challenge with mature products is missing information. The regulatory paradigm was likely not as robust as it is today, resulting in less comprehensive documentation of evidence at time of approval. In addition, there are 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 adverse events – only became a standard in AE reporting since 1999 had seen through over 20 versions since its inception.

In this context, generic compounds are also available with even less evidence on efficacy and safety.

Specific considerations

In post-marketing

- Limited or absence of comparative efficacy data.
  - Leverage from real world evidence effectiveness data.
- Upcoming post market information mainly on risks:
  - Consider methods to address uncertainties (e.g. on drug use in special population such as elderly, pregnant women, children, etc.);
  - Consider synthesising data from multiple sources (network meta-analysis);
  - Consider impact of results on effectiveness of risk minimisation measures.
- Define relevant new information that triggers the need for re-evaluation of BR.

4.5 Special populations

4.5.1 D.1 Patients with rare diseases

Major issues / challenges

Managing with limited data and known heterogeneity

While overall, the BRAs for common disease can also be applied to rare disease, 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 disease is an area where patient preferences would bring additional value to the assessments.

Specific considerations

At time of initial evaluation

- No approved treatment, comparator is absence of treatment;
- Consider use of RWD such as patient registries and methods to build synthetic control arm (retrospective natural history disease registry) as described in regulatory guidance.[318]
- Lack of knowledge on epidemiology of disease and of frequency of background risks
    - Consider use of RWD such as patient registries and methods to predict natural history of disease.
- Uncertainty linked to limited data on benefits and risks and limited comparison;
- Consider methods to address uncertainties (such as sensitivity analysis, Monte Carlo simulation (for more details, refer to case study C in appendix)[319] (Efficacy endpoints may be lab values or imaging data that are not validated as surrogates of clinical benefits
    - Consider methods to validate endpoints to extrapolate clinical results
    - Consider post-market study to validate clinical benefit.
- Heterogeneity in disease phenotypes
    - Consider BRA by disease phenotype sub-groups
    - Consider any biomarker/measurement to identify the individuals with greater benefit or risk.
- Unmet medical need, lack of alternative treatment
    - Consider higher risk acceptance with a threshold of tolerability.
    - Consider measurement of patient perceptions and expectations and conduct patient focused BRA as a key decision-making factor that integrate benefit expectations and risk acceptance from patients' perspective.

In post-marketing setting

- Remaining uncertainties on benefits and risks
    - Consider continued collection of data on risks in treated and untreated patients (epidemiology and case reports), continued measurement on beneficial effects in RWD, Consider synthesising data from multiple sources;
    - Evaluate risk monitoring and risk mitigation strategy.
- Reassess BR when there is significant safety issue post-market.

4.5.2 D.2 Paediatric population

Major issues / challenges

Managing with uncertainty and heterogeneity

The BRA for paediatric population draws more uncertainty than the one in adult population 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 time of initial evaluation

- Limited data on benefits and risks and heterogeneity
    - Consider methods to address uncertainties (e.g. evaluation of long-term effectiveness to confirm durability/persistence of treatment response)

- Consider any potential impact of the formulation of the product on children's compliance, potential overdose, medication error
- Consider specificities of paediatric forms of diseases and alternative treatments
    - Disease progression in the paediatric population as compared to adult (more severe, harder to manage, more complication, etc.).
    - Alternative treatments approved in paediatric population may be more limited than in adults, off label use may also be an important part of the assessment of unmet medical need
    - Clinical registries of off label use in paediatrics may have sufficient evidence for a full BRA, or otherwise can identify the knowledge gap in the unmet medical need where more data are required
    - Dependent on indications, the data in routine clinical databases may be heavily influenced by parents' behaviour / experience. Less experienced parents may tend to over-report adverse events that may bias the analysis. Methodologies to identify and address such biases would prove worthy when dealing with these types of data.

In post-marketing

- Remaining uncertainties on benefits and risks
    - Consider continued collection of data on risks in treated and untreated patients (epidemiology and case reports), continued measurement on beneficial effects in real world data, and risk monitoring and risk management
    - Consider synthesising data from multiple sources

4.6 Advanced therapy medicinal products

Major issues / challenges

Managing with uncertainty and lack of guidance

The BRA of advanced therapy medicinal products such as gene therapy or cell therapy draws more uncertainty regarding long-term efficacy and long term-safety potentially related to the product itself, the associated procedures, the required conditioning measures and/or the background disease to treat. BRA is also impacted by lack of standards for these novel therapeutic products and their huge uncertainty of risks.

Specific considerations

At time of initial evaluation

- Limited number of patients.
- Not validated endpoints.
- Lack of representativity of population: Trial setting with limited number of sites, countries.
- Uncertainty linked to limited data on risks and understanding of potential mechanisms of risks:
    - Consider methods to address uncertainties (such as sensitivity analysis, Monte Carlo simulation, for more details please refer to Case study A.2. in appendix);
    - Consider translational safety methods for comprehensive analysis of correspondence and validity of animal data to better identify the potential risks;[320]
    - In post-marketing setting;
- Remaining uncertainties on benefits and risks.

- Consider continued collection of data on risks in treated and untreated patients (epidemiology and case reports), continued measurement on beneficial effects in RWD, consider synthesising data from multiple sources.
- Evaluate risk monitoring and risk mitigation strategy.

References

[318] *The United States Food and Drug Administration (FDA). Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products. Draft Guidance. 2023. (PDF accessed 20 April 2023).*

[319] *Pognan F, Steger-Hartmann T, Díaz C, Blomberg N, Bringezu F, Briggs K, et al The eTRANSAFE project on translational safety assessment through integrative knowledge management: achievements and perspectives. Pharmaceuticals. 2021;8;14(3):237. https://doi.org/10.3390/ph14030237*

[320] *Pognan F, Steger-Hartmann T, Díaz C, Blomberg N, Bringezu F, Briggs K, et al The eTRANSAFE project on translational safety assessment through integrative knowledge management: achievements and perspectives. Pharmaceuticals. 2021;8;14(3):237. https://doi.org/10.3390/ph14030237*

APPENDIX II: CASE STUDIES A - D

A.1ROTAVIRUS VACCINE: HOW TO INFORM BR 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.[321] 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 uncertain severe risk emerging in post-marketing setting and the BR 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, RT-associated GE (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.[322]
Information on the drug being used to treat the patient	Two RVs have been approved in US since 2006, including: 1. 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. 2. Rotarix™: a live, oral, monovalent RV (RV1) indicated for the prevention of RTGE caused by G1, G3, G4 and G9 types, manufactured by GlaxoSmithKline plc, and approved by US FDA in 2008. Rare cases of intussusception, a potentially life-threatening intestinal blockage, have been reported worldwide in 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 BR 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.
BRA principle/method and reference	Two Probabilistic Monte Carlo models were used to evaluate the BR of RV in children from birth to five 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.
BRA 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 BRA	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.[323]
BR conclusion and risk minimisation strategies	The analysis concludes that the benefits of RVs substantially exceed its potential risk in infants.

Introduction to the case study example

Rotavirus (RT) infection is the most common cause of diarrhoea in infants and children resulting in over 215,000 deaths annually worldwide. Before the Rotavirus vaccines (RVs) were developed, most children in the US and other countries had been infected with the RT at least once before age of two.[324]

Two RVs were approved by US FDA, Rotateq™ (RV5, 3-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 rotavirus-associated gastroenteritis (RTGE) and reducing the severity of the cases.[325,326] By the time this analysis[327] was published, the US post-approval 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.[328] 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 Centers for Disease Control & Prevention (CDC) researchers to incorporate different sources of data. The number of deaths, hospitalisations and emergency department (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.

BR methodology

Probabilistic Monte Carlo simulations were performed to:

- (A) Estimate the RT disease burden such as: number of deaths, hospitalisations and ED visits, with verses without a fully implemented vaccine program (Model-1);
- (B) 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[329] 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 from birth to five years of age.

The RV vaccine effectiveness for full (3 doses) and incomplete doses (< 3 doses) were estimated based on RV5 data from a large post-licensure study[330] 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)[331] of three states (Minnesota, Georgia and Connecticut) in the Emergent Infections Program Network.[332] 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-24).

The RV vaccination of 2009 birth cohort with number of doses completed under a hypothetical fully mature vaccine program (Table-24) was assumed based on the data from the 2009 NIS on RV vaccine (either RV5 or RV1), DTaP (Diphtheria, Tetanus, Pertussis Vaccine)/diphtheria and tetanus toxoid vaccines.

Table 23: Model input variables for vaccine effectiveness

Source: Modified from Desai R, Cortese MM, Meltzer MI, Shankar M, et al [333]

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

Table 24. Model input variables for birth cohort and vaccine coverage

Source: Modified from Desai R, Cortese MM, Meltzer MI, Shankar M, et al.[334]

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 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 relative risk 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 relative risk observed in Mexico (point estimate of 5.3) and weekly baseline incidence of intussusception during the first year of life. Table 25 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 sum of RV-related surgery and death episodes.

Table 25. Model input variables for intussusception risk

Source: Modified from Desai R, Cortese MM, Meltzer MI, Shankar M, et al.[335]

Model input variable ***Potential RV 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 hospitalizations requiring surgery	52.8% (51.1-55.4%)
Percent of intussusception hospitalizations 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 relative risk of RV associated intussusception, a key model input assumed based on international data. The study indicates even with a conservative assumption about relative risk 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,[336] which make the estimates of vaccination benefits conservative. However, this study is informative for BRA of RV and management of RV program.

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.

References

[321] *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:10.1097/INF.0b013e318270362c*

[322] 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:10.1097/INF.0b013e318270362c

[323] Glass RI. Unexpected benefits of rotavirus vaccination in the United States. *Journal of Infectious Diseases.* 2011;1;204(7):975-977. https://doi.org/10.1093/infdis/jir477

[324] The United Stated Food and Drug Administration (FDA). *RotaTeg (Rotavirus Vaccine) Questions and Answers.* 2018. (Website accessed 20 April 2023).

[325] Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, Abate H, Breuer T, Clemens SC, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *New England Journal of Medicine.* 2006;5;354(1):11-22. https://doi:10.1056/NEJMoa052434

[326] Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z, et al. Safety and efficacy of a pentavalent human–bovine (WC3) reassortant rotavirus vaccine. *New England Journal of Medicine.* 2006;5;354(1):23-33. https://doi:10.1056/NEJMoa052664

[327] 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:10.1097/INF.0b013e318270362c

[328] 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:10.1097/INF.0b013e318270362c

[329] Widdowson MA, Meltzer MI, Zhang X, Bresee JS, Parashar UD, Glass RI. Cost-effectiveness and potential impact of rotavirus vaccination in the United States. *Pediatrics.* 2007;119(4):684-697. https://doi.org/10.1542/peds.2006-2876

[330] Cortese MM, LeBlanc J, White KE, Jerris RC, Stinchfield P, Preston KL, et al. Leveraging state immunization information systems to measure the effectiveness of rotavirus vaccine. *Pediatrics.* 2011;128(6):e1474-81. https://doi.org/10.1542/peds.2011-1006

[331] Centers for Disease Control and Prevention (CDC). Morbidity and Mortality Weekly Report. Progress in Immunization Information Systems — United States, 2011. 2013. (Website accessed 20 April 2023).

[332] Pinner RW, Rebmann CA, Schuchat A, Hughes JM. Disease surveillance and the academic, clinical, and public health communities. *Emerging Infectious Diseases.* 2003;9(7):781. https://doi:10.3201/eid0907.030083

[333] *Desai R, Cortese MM, Meltzer MI, Shankar M, 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:10.1097/INF.0b013e318270362c*

[334] *Desai R, Cortese MM, Meltzer MI, Shankar M, 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:10.1097/INF.0b013e318270362c*

[335] *Desai R, Cortese MM, Meltzer MI, Shankar M, 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:10.1097/INF.0b013e318270362c*

[336] Glass RI. Unexpected benefits of rotavirus vaccination in the United States. *Journal of Infectious Diseases.* 2011;1;204(7):975-977. https://doi.org/10.1093/infdis/jir477

A.2 ROTAVIRUS VACCINE: FOCUSING ON BR METHODS INCLUDING MONTE CARLO SIMULATION

Introduction

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

Benefit evaluation

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 effectiveness data of RV5, which accounted for more than 90% of all RV vaccinations from February 2006 through August 2010 and vaccine coverage for an assumptive matured vaccine program based on the 2009 NIS on RV (either RV5 or RV1), DTaP/diphtheria and tetanus toxoid vaccines. Model inputs for vaccine efficacy used for this estimation are shown in **Error! Reference source not found.**23.

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 hospital and ED discharge database. Baseline intussusception hospitalisation rates by week of age during the first year of life were obtained from the State Inpatient Databases maintained by the Healthcare Cost and Utilisation Project containing data from 22 states, which comprises about 67% of the US birth cohort from 2000 to 2005. The ED databases from 14 states include nearly 20% of the US birth cohort from 2003 to 2005.

The relative risk of RV-associated intussusception was assumed same as the relative risk reported in Mexico (point estimate of 5.3, see Table 25). The intussusception incidence was calculated by multiplying baseline incidence of intussusception in the 2009 US birth cohort with the relative risk.

Integrated BRA of the BR 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 relative risk was examined through sensitivity analysis with incremental change of relative risk 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 26).

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 26). The BR ratio column in Table 26 shows the median number of vaccine-adverted events for each vaccine-caused event.

Table 26: Benefits and potential risks of a RV program in a birth cohort for a period up to age five

Source: Modified from Desai R, Cortese MM, Meltzer MI, Shankar M, et al.[337]

Events	Benefit RV-associated sequalae prevented with vaccine [95% CIs]	Risk Excess intussusception cases and sequalae with vaccine	BR ratio
Deaths	14 [10-19]	0.2 (0.1-0.3)*	71 (48-112)+
Hospitalizations	53,444 [37,622-72,882]	45 (21-86)*	1093 (688-1902)+
ED 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 relative risk 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 events would be 48, 618 and 6922 respectively. Even with this most conservative assumption the benefits of RV still outweigh its potential risk.

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:

- Continuing evaluation of BR 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 post-licensure. The model results indicate the benefits of RVs outweigh their risks, which help to inform the management 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.[338,339,340] However, the BR conclusion from this study remains unchanged.

- 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.

- Computational techniques can be used to capture the data uncertainty and assess their impact on the benefits-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 relative risk of RV associated intussusception, a key model input assumed based on international data. The study indicates even with a conservative assumption about relative risk 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)[341], which make the estimates of vaccination benefits conservative. However, this study is informative for BRA of RV and management of RV program.

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.

References

[337] *Desai R, Cortese MM, Meltzer MI, Shankar M, 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:10.1097/INF.0b013e318270362c*

[338] *Centers for Disease Control and Prevention (CDC). Cortese M. Summary of intussusception risk and benefits of rotavirus vaccination in the United States. ACIP Meeting Rotavirus Vaccine. 2013. (Website accessed 20 April 2023).*

[339] *Yih WK, Lieu TA, Kulldorff M, Martin D, McMahill-Walraven CN, Platt R, et al. Intussusception risk after rotavirus vaccination in US infants. New England Journal of Medicine. 2014;370(6):503-512. https://doi:10.1056/NEJMoa1303164*

[340] *Weintraub ES, Baggs J, Duffy J, Vellozzi C, Belongia EA, Irving S, et al. Risk of intussusception after monovalent rotavirus vaccination. New England Journal of Medicine. 2014;370(6):513-519. https://doi.org/10.1056/NEJMoa1311738*

[341] *Glass RI. Unexpected benefits of rotavirus vaccination in the United States. Journal of Infectious Diseases. 2011;1;204(7):975-977. https://doi.org/10.1093/infdis/jir477*

B. BR BALANCE FOR ORAL ANTICOAGULANTS

The case study of Hsu et al.,[342] compared BR of different oral anticoagulants (OACs) (Warfarin, dabigatran, rivaroxaban and apixaban) and dosages for treatment of non-valvular atrial fibrillation using MCDA. The key benefits of the drugs 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. Furthermore, the benefits and risks are varied by condition and characteristics of the patients. This case study demonstrates how MCDA can help inform decision associated with complex BR trade-off.

Case study example summary table

TOPIC	SUMMARY INFORMATION
Purpose/Objective of the case study example	To demonstrate the use of MCDA to compare benefits-risks of different drugs to inform clinicians and patient's decision about the treatment options in situation of complex BR trade-off.
Drug indication	Oral anticoagulants (OACs) are for treatment of nonvalvular atrial fibrillation (NVAF). The treatments of NVAF included in this study are new 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.[343] Rivaroxaban is a new oral, direct, and selective inhibitor of the Factor Xa of the coagulation cascade.[344] Apixaban is an oral, direct factor Xa inhibitor that inhibits both free and clot-bound factor Xa^3.
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	Selected benefit endpoints for patient groups/conditions scenarios: General population (70 to79 years old): prevention of ischemic stroke and prevention of systemic embolism. Patients with higher risk of stroke: prevention of stroke or systemic embolism. Primary/secondary stroke prevention: prevention of stroke or systemic embolism, and prevention of death from vascular causes.
Risks/endpoints	Selected risk endpoints for patient groups/conditions scenarios: General population (70 to 79 years old): intracranial bleeding and extracranial bleeding. Patients with higher risk of stroke: major bleeding. Primary/secondary stroke prevention: intracranial bleeding and other local bleeding.
Integrated BR endpoints (if applicable)	Integrated BRA for comparison of different anticoagulant drugs and dosage using MCDA.

BRA principle/method and reference	This study used value tree to summarise the key benefits and 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 performance scores for individual drugs.
BRA results	Results suggest that overall, NOACs had a higher performance score than warfarin. Among NOACs, apixaban had the highest performance score for patients with a higher risk of stroke. Dabigatran 150 mg had the highest performance score for primary stroke prevention and dabigatran 110 mg had the highest performance score for secondary prevention.
Strengths & Limitations of the BRA	The MCDA approach allows to integrate multiple criteria explicitly for BR trade-offs; thus, inform decision on use of drugs under different clinical conditions. A limitation of this study is that limited patient groups/conditions (general, high risk of stroke, primary and secondary stroke prevention) were evaluated. The results and recommendations may not apply to other patient groups/conditions (e.g. patients without AF or patients less than 70 years old or more than 79 years old). Also, additional PPS may help to fill in the gaps about the health utilities and weights of some BR endpoints and better inform the BR trade-off. A methodological drawback of this study is using hazard ratio in the analysis (see Chapter 3 on BR methodology considerations). This can be misleading without considering the magnitude of baseline risks. ARs may be more appropriate (see more discussion in Chapter 3 on BR methodology considerations).
BR conclusion and risk minimisation strategies	Optimal choice of drugs may be different depending on patient's clinical condition.

Introduction to the case study example

Atrial fibrillation (AF) is the most common type of treated heart arrhythmia.[345] Currently in the U.S., more than 454,000 hospitalisations with AF as the primary diagnosis occur each year.[346] It is estimated that more than 12 million people in the United States will have AF in 2030.[347,348,349] Also, 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.[350] Other patients' characteristics and comorbidities increase the risk of stroke in patients with AF.[351]

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 yearly high number of AF diagnosis in U.S., OACs are commonly prescribed for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF).[352] Available OACs include warfarin and Novel oral anticoagulants (NOACs). Warfarin has been used for decades and has been known to be highly effective for stroke prevention in AF. The NOACs such as apixaban, dabigatran and rivaroxaban have also become available more recently. They have become the primary choice of therapy due to their efficacy, ease of use, and low risk of bleeding complications.[353] In this case study, we describe how MCDA was used to compare the benefits and risk of warfarin and NOACs (dabigatran, rivaroxaban, and apixaban) for treatment of NVAF.

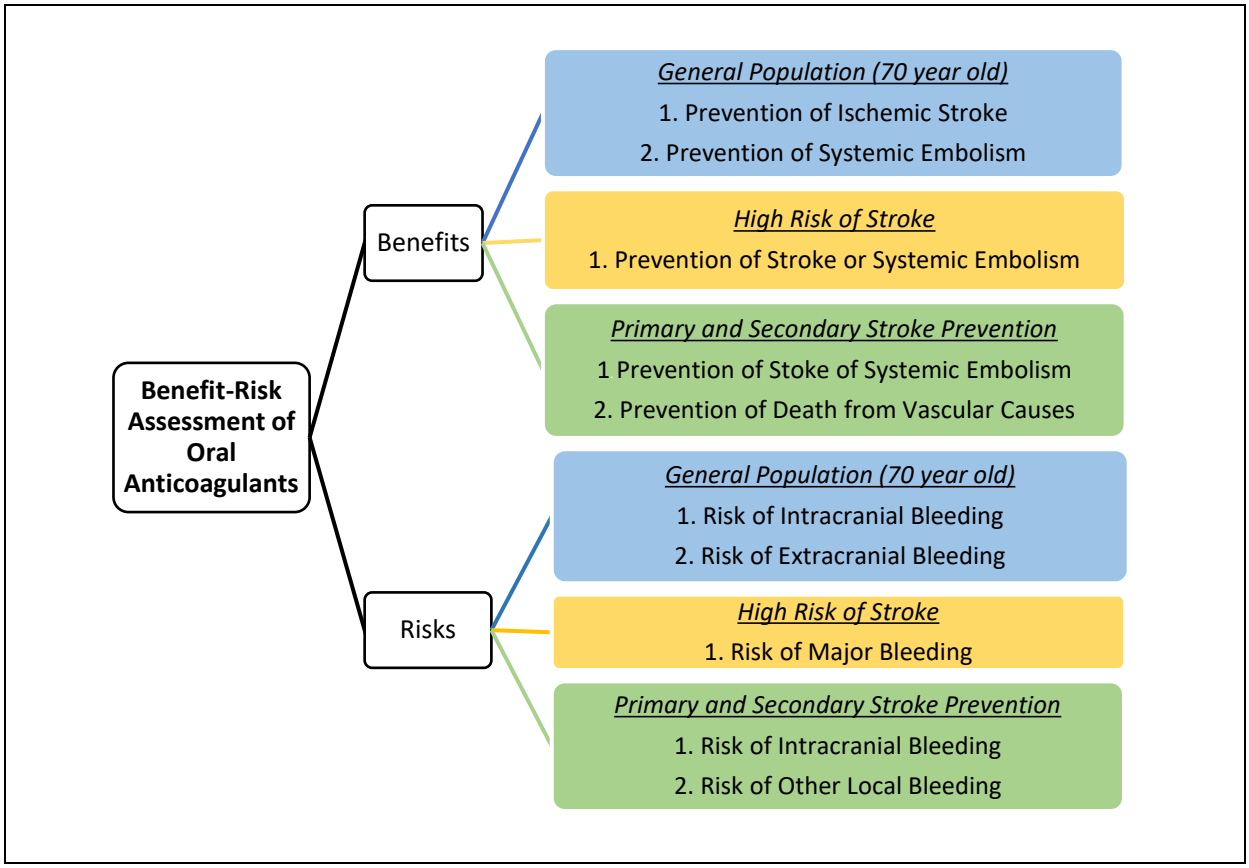
BR methodology

In this study MCDA is 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 15) representing the key benefits and risks of NOACs and warfarin under four different scenarios: (1) the general population (70-year-old, blue), (2) patients with a higher risk of stroke ($CHADS_2$ score ≥3, yellow), (3) for primary stroke prevention (green), and (4) for secondary stroke prevention (green). **Error! Reference source**

not found. In the value tree, Benefits and Risks represents the decision criteria and specific endpoints such as Prevention of Ischemic Stroke and Risk of Intracranial bleeding represents the sub-criteria for benefit and risk, respectively.

Figure 15. BR value tree by four scenarios

Source: Modified from Hsu JC, Hsieh CY, Yang YH, and Lu CY [354]



The second step of the study is to obtain the effect size values (with 95% CIs) of each BR endpoint of the drugs. The values were pulled from three studies[355,356,357] of large RCTs and/or meta-analysis of RCTs. Model used mean, 2.5th and 97.5th percentile of Hazard Ratios (HRs, for risk) and reciprocal of HRs (for benefits) reported in the literature as the mean, lowest and highest values of model inputs. The third step involves rescaling and normalising the effect size (Table 27), such that the value of specific endpoint of a drug was expressed as a ratio relative to a selected baseline drug (Warfarin for General (70-year-old) and High risk of stroke; Rivaroxaban 20 mg one per day or quaque die (QD) for Primary and Secondary Stroke Prevention). Next, the weight for each benefit and risk sub-criteria is estimated using the Analytic Hierarchy Process[358,359,360] based on the values of health utilities[361,362] (Table 28 and Table 32). The weights for specific benefit and risk sub-criteria calculated based on this approach are shown in Table 29 and Table 33. The last step is to calculate the performance score for each drug using the MCDA method and the standardised effect sizes and estimated weights of BR endpoints as inputs. The drugs with higher performance score are more preferred. Furthermore, sensitivity analysis was conducted to evaluate the impact on the performance scores of the different drugs by varying weights of two highest ranked endpoint, prevention ischemic stroke (benefit) and intracranial bleeding (risk).

Benefit evaluation

To compare the benefits of drugs, the effect size of each benefit endpoints (Table 27) were standardised (i.e. scaled and normalised). The effect sizes in Table 27 are the reciprocal of hazard ratio (HR) obtained from.[363,364,365]For the general and high risk of stroke scenarios, warfarin is used as

a baseline with standardised effect size of 1. The effect sizes of NOACs are estimated as ratios relative to warfarin. However, note that under the primary and secondary stroke prevention scenarios effect sizes for warfarin are not presented since the study by Rasmussen et al.[366] only made comparisons among NOACs. In this case, rivaroxaban 20 mg QD is used as a baseline with effect size of 1.

Table 27. Standardised effect sizes for benefit endpoints as model inputs

Source: Modified from Hsu JC, Hsieh CY, Yang YH, and Lu CY [367]

Scenarios	Benefit endpoints *Prevention of*	Units	Oral Anticoagulant agents					Reference
			Warfarin	Dabigatran 150 mg BID	Dabigatran 110 mg BID	Rivaroxaban 20 mg QD	Apixaban 5 mg BID	
General (70-year-old)	Ischemic stroke	1/HR	1	1.32 (1.02-1.67)	n/a	1.06 (0.85-1.33)	1.09 (0.89-1.35)	10
	Systemic embolism	1/HR	1	1.20 (0.93-1.72)	n/a	4.35 (1.64-11.11)	1.15 (0.57-2.27)	10
High risk of stroke	Stroke or systemic embolism	1/HR	1	1.43 (1.05-1.92)	1.27 (0.95-1.69)	1.14 (0.95-1.35)	1.47 (1.14-1.92)	12
Primary stroke prevention	Stroke or systemic embolism	1/HR	n/a	1.28 (0.87-1.89)	0.83 (0.57-1.19)	1	0.94 (0.65-1.35)	11
	Death from vascular causes	1/HR	n/a	1.11 (0.87-1.47)	0.91 (0.69-1.19)	1	1.02 (0.79-1.33)	11
Secondary stroke prevention	Stroke or systemic embolism	1/HR	n/a	1.25 (0.83-1.92	1.12 (0.74-1.69)	1	1.23 (0.85-1.79)	11
	Death from vascular causes	1/HR	n/a	1.00 (0.68-1.47)	1.56 (1.01-2.38)	1	1.00 (0.68-1.45)	11
High risk of stroke: patients with $CHADS_2$ score ≥3. HR = hazard ratio; 1/HR = the reciprocal of hazard ratio. QD: Once a day; BID: twice a day.								

Health utilities measures (mean and ranges) of benefit endpoints were obtained from the literature[368] and summarised in Table 28**.** If no health utility value available in literature, assumptions are made as noted in the table.

Table 28. Health utilities for benefit endpoints for different scenarios

Source: Modified from Hsu JC, Hsieh CY, Yang YH, and Lu CY [369]

Criteria	Scenario	Endpoints	Health Utility	Reference
Benefit		*Prevention of:*		
	General (70-year-old)	Ischemic stroke	0.27 (0.22-0.32)	15
		Systemic embolism	0.575 (0.45-0.7)	15
	High risk of stroke	Stroke or systemic embolism	0.50 (0.22-0.70)	assumed
	Primary/Secondary stroke prevention	Stroke or systemic embolism		
		Death from vascular causes	0.10	assumed

Note that the weight of overall benefits is the sum of the weights for all benefit endpoints in each scenario. The weights of each benefit endpoint (Table 29) are calculated using the above health utilities and the Analytic Hierarchy Process.[370,371,372]

Table 29: Weights for benefit endpoints in descending order

Source: Modified from Hsu JC, Hsieh CY, Yang YH, and Lu CY [373]

Criteria	Scenarios	Endpoints	Weight	Overall weight
Benefit	*General (70-year-old)*	Prevention of ischemic stroke	0.43	0.631
		Prevention of systemic embolism	0.202	
	High risk of stroke	Prevention of stroke or systemic embolism	0.615	0.615
	Primary/Secondary stroke prevention	Prevention of stroke or systemic embolism	0.659	0.791
		Prevention of death from vascular causes	0.132	

Performance scores for the benefits of each drug under each scenario are calculated with the standardised effect sizes and the weights of sub-criteria. For general and high risk of stroke scenario, warfarin was used as a baseline for comparison of NOAC. For the primary and secondary stroke prevention scenarios, rivaroxaban was used as a baseline for comparison of NOACs including the two different doses of dabigatran.

Table 30: Calculated mean performance scores of drugs for four scenarios by benefit endpoints

Source: Modified from Hsu JC, Hsieh CY, Yang YH, and Lu CY [374]

Scenario	*Weight*		*Warfarin*	*Dabigatran 150 mg BID*	*Dabigatran 110 mg BID*	*Rivaroxaban 20 mg QD*	*Apixaban 5 mg BID*
General (70-year-old)							
Overall Benefits	0.631	Score	0.284	**0.57**	n/a	0.506	0.393
		Ranking	4	**1**		2	3
Prevention of ischemic stroke	0.43	Score	0.372	**0.769**	n/a	0.456	0.511
		Ranking	4	**1**	n/a	3	2
Prevention of systemic stroke	0.202	Score	0.096	0.147	n/a	**0.613**	0.143
		Ranking	4	2	n/a	**1**	3
High risk of stroke							
Benefits: Prevention of stroke of systemic embolism	0.615	Score	0.120	0.697	0.535	0.372	**0.748**
		Ranking	5	2	3	4	**1**
Primary stroke prevention							
Overall Benefits	0.791	Score	n/a	**0.753**	0.468	0.642	0.629
		Ranking	n/a	**1**	4	2	3
Prevention of stroke or systemic embolism	0.132	Score	n/a	**0.758**	0.383	0.575	0.503
		Ranking	n/a	**1**	4	2	3
Prevention of death from vascular causes	0.659	Score	n/a	**0.752**	0.485	0.655	0.654
		Ranking	n/a	**1**	4	2	3
Secondary stroke prevention							
Overall Benefits	0.791	Score	n/a	0.616	**0.923**	0.642	0.614
		Ranking	n/a	2	**1**	4	3
Prevention of stroke or systemic embolism	0.132	Score	n/a	**0.739**	0.652	0.575	0.731
		Ranking	n/a	**1**	3	4	5
Prevention of death from vascular causes	0.659	Score	n/a	0.592	**0.978**	0.655	0.590
		Ranking	n/a	3	**1**	2	4

Risk evaluation

A similar approach for as described above for benefit evaluation was used to compare the risks of drugs. Table 31 contains the standardised effect size for each risk endpoint derived from hazard ratios obtained from.[375,376,377]

4395 ***Table 31: Standardised effect size for risk endpoint as model inputs***

4396 Source: Hsu et al, 2015.[378]

Scenarios	Risk endpoint *Risk of*	Units	Oral Anticoagulant agents					Reference
			Warfarin	Dabigatran 150 mg BID	Dabigatran 110 mg BID	Rivaroxaban 20 mg QD	Apixaban 5 mg BID	
General (70-year-old)	Intracranial bleeding	HR	1	0.40 (0.27-0.60)	n/a	0.67 (0.47-0.93)	0.42 (0.30-0.58)	10
	Extracranial bleeding	HR	1	1.07 (0.92-1.25)	n/a	0.42 (0.29-0.55)	0.79 (0.68-0.93)	10
High risk of stroke	Major bleeding	HR	1	1.05 (0.86-1.30)	0.82 (0.66-1.03)	1.01 (0.87-1.18)	0.69 (0.55-0.87)	12
Primary stroke prevention	Intracranial bleeding	HR	n/a	0.75 (0.38-1.52)	0.61 (0.30-1.27)	1	0.77 (0.40-1.49)	11
	Other local bleeding	HR	n/a	1.67 (0.76-3.70)	1.57 (0.71-3.48)	1	1.23 (0.55-2.72)	11
Secondary stroke prevention	Intracranial bleeding	HR	n/a	0.55 (0.25-1.23)	0.27 (0.10-0.73)	1	0.50 (0.24-1.04)	11
	Other local bleeding	HR	n/a	2.56 (1.12-5.88)	1.74 (0.75-4.04)	1	1.92 (0.83-4.46)	11
High risk of stroke: patients with CHADS₂ score ≥3. HR = hazard ratio QD: Once a day; BID: twice a day.								

4397

4398 The health utilities in Table 32 for risk endpoint under each scenario were also obtained from
4399 Meenan et al., 2007.[379]

4400 ***Table 32: Health utilities for risk endpoints in each scenario***

4401 Source: Hsu et al, 2015.[380]

Criteria	Scenario	Endpoints	Health Utility	Reference
Risk		*Risk of:*		
	General (70-year-old)	Intracranial bleeding	0.46 (0.22-0.9)	15
		Extracranial bleeding	0.997 (0.98-1.00)	15
	High risk of stroke	Major bleeding	0.80 (0.5-0.99)	16
	Primary/Secondary stroke prevention	Intracranial bleeding	0.46 (0.22-0.9)	15
		Other local bleeding	0.997 (0.98-1.00)	15

4402

4403 Note that the weight of overall risks for each scenario is the sum of the weights for all risk endpoints.
4404 The weights of each risk endpoint (Table 33) are calculated using the Analytic Hierarchy
4405 Process[381,382,383] based on health utility.

4406
4407

Table 33: Weights for risk endpoints in descending order

Source:

Criteria	Scenario	Endpoints	Weight	Overall weight
Risk	General (70-year-old)	Risk of intracranial bleeding	0.252	0.369
		Risk of extracranial bleeding	0.116	
	High risk of stroke	Risk of major bleeding	0.385	0.385
	Primary/Secondary stroke prevention	Risk of intracranial bleeding	0.143	0.209
		Risk of other local bleeding	0.066	

Similarly, performance scores for the risks of each drug under each scenario are calculated with the standardised effect sizes and the weights of risk endpoints. For general and high risk of stroke scenario, warfarin was used as a baseline for comparison of NOACs. For the primary and secondary stroke prevention scenarios, effect sizes of warfarin were not available in the literature, thus rivaroxaban was used as a baseline for comparison of NOACs including the two different doses of dabigatran.

Table 34: Calculated performance scores of drugs for four scenarios by risk endpoints

Source:

Scenario	*Weight*		*Warfarin*	*Dabigatran 150 mg BiD*	*Dabigatran 110 mg BID*	*Rivaroxaban 20 mg QD*	*Apixaban 5 mg BID*
General (70-year-old)							
Risks	0.369	Score	0.030	0.458	n/a	0.386	**0.483**
		Ranking	4	2	n/a	3	**1**
Risk of intracranial bleeding	0.252	Score	0.000	**0.639**	n/a	0.230	0.598
		Ranking	4	**1**	n/a	3	2
Risk of extracranial bleeding	0.116	Score	0.097	0.066	n/a	**0.724**	0.234
		Ranking	3	4	n/a	**1**	2
High risk of stroke							
Risks: Risk of major bleeding	0.385	Score	0.109	0.085	0.165	0.109	**0.586**
		Ranking	3	5	2	3	**1**
Primary stroke prevention							
Risks	0.209	Score	n/a	0.396	**0.496**	0.353	0.438
		Ranking	n/a	3	**1**	4	2
Risk of intracranial bleeding	0.143	Score	n/a	0.393	**0.525**	0.194	0.377
		Ranking	n/a	2	**1**	4	3
Risk of other local bleeding	0.066	Score	n/a	0.402	0.433	**0.697**	0.570
		Ranking	n/a	4	3	**1**	2
Secondary stroke prevention							
Risks	0.209	Score	n/a	0.467	**0.817**	0.353	0.554
		Ranking	n/a	3	**1**	4	2
Risk of intracranial bleeding	0.143	Score	n/a	0.594	**1.017**	0.194	0.656
		Ranking	n/a	3	**1**	4	2
Risk of other local bleeding	0.066	Score	n/a	0.194	0.383	**0.697**	0.332
		Ranking	n/a	4	2	**1**	3

Results

The overall BR of different anticoagulant drugs were compared using an integrated performance score (the higher score represents a more preferable drug) calculated using effect sizes (Table 27 and Table 31) and weights (**Error! Reference source not found.** 29 and **Error! Reference source not found.** 33). The results of MCDA performance score and ranking integrated benefits and risks of the drugs for four scenarios are summarised in Table 35 based on weight presented in Table 30 and Table 34. Note that the NOAC with the highest ranking and performance score is bolded for easy distinction. Dabigatran 150 mg BID had the highest performance score for two scenarios, general population and primary stroke prevention (Table 35). For patients with high risk of stroke and secondary stroke prevention, dabigatran 110 mg BID and apixaban 5 mg BID, had the highest performance score, respectively (Table 35).

The sensitivity analysis was conducted to vary the weights for one benefit endpoint (prevention of ischemic stroke) and one risk endpoint (intracranial bleeding). These two endpoints have the highest weights among benefit and risk endpoints, respectively. The results of this analysis suggested that if the weight for prevention of ischemic stroke was between 0.05 and 0.65, dabigatran 150 mg BID and rivaroxaban 20 mg QD had the highest performance scores. However, when the weight for prevention of intracranial bleeding was less than 0.32, the optimal choices are dabigatran 150 mg BID and rivaroxaban 20 mg QD.

Table 35: Calculated performance scores of drugs for four scenarios by integrated BRA

Source: Modified from Hsu JC, Hsieh CY, Yang YH, and Lu CY [384]

Scenario		*Warfarin*	*Dabigatran 150 mg BID*	*Dabigatran 110 mg BID*	*Rivaroxaban 20 mg QD*	*Apixaban 5 mg BID*
General (70-year-old)	Score	0.191	**0.529**	n/a	0.462	0.426
	Ranking	4	**1**	n/a	2	3
High risk of stroke (CHADS₂≥3)	Score	0.116	0.462	0.392	0.271	**0.686**
	Ranking	5	2	3	4	**1**
Primary stroke prevention	Score	n/a	**0.678**	0.474	0.581	0.589
	Ranking	n/a	**1**	4	3	2
Secondary stroke prevention	Score	n/a	0.585	**0.901**	0.581	0.601
	Ranking	n/a	3	**1**	4	2

Discussion

This case study demonstrates use of some BRA tools such as value tree to list BR sub-criteria, effect able to summarise the data/evidence for benefits and risks, and MCDA to calculate performance score integrating the benefits and risks to support decision making in different situations and scenarios.

The study has several limitations. In general, decision models are a simplification of decision making in real-life scenarios. In this study, a limited number of scenarios were considered (general, high risk of stroke, primary and secondary stroke prevention), thus, the results and recommendations of this study should not be applied to other scenarios such as patients without AF or less than 70 years old or more than 79 years old. Moreover, additional studies to compare the effect sizes of warfarin and NOACs for primary and secondary stock prevention are needed for a more consistent comparison of drugs across groups/scenarios. Also, BR endpoints measured did not consider impact of drug use in real-life. For example, interactions with other drugs, patient adherence rate, risk of switching medications, off-label or inappropriate use of drugs were not considered in the model. Also, this model considered the most important clinical outcomes as benefit or risks endpoints but did not consider other factors that may impact the patients such as availability of reversal agent, administration frequency or food interactions that were found to have impact on the BR balance.[385] Lastly, time-dependent risks and benefits may need to be considered.

Another limitation is lack of health utility for some benefit endpoints such as health utilities for prevention of stroke or systemic embolism for patients with high risk of stroke and heath utilities for prevention of stroke or systemic embolism and death from vascular causes for primary/secondary stroke prevention. Assumptions had to be made in the study for estimation of the weights for those benefit endpoints in specific scenarios. Additional PPSs may have value to provide AF patients perspectives towards these benefit endpoints and help to fill the gaps and cover multiple factors that may impact patients.

A methodological drawback of this study is using hazard ratio in the analysis (see Chapter III). This can be misleading without considering the magnitude of baseline risks. ARs may be more appropriate (see more discussion in Chapter 3 on BR methodology considerations).

Conclusion and risk minimisation

MCDA quantitative method can be used to integrate benefits and risks of the drugs and compare multiple treatment options under different scenarios (or clinical endpoints of interest) when BR trade-off is complex. This type of study helps clinicians and patients to make a better choice of drug/treatment for patients with different clinical conditions and different risk factors.

References

[342] *Hsu JC, Hsieh CY, Yang YH, Lu CY. Net clinical benefit of oral anticoagulants: a multiple criteria decision analysis. PLoS One. 2015;10(4):e0124806. https://doi.org/10.1371/journal.pone.0124806*

[343] *Ganetsky M, Babu KM, Salhanick SD, Brown RS, Boyer EW. Dabigatran: review of pharmacology and management of bleeding complications of this novel oral anticoagulant. Journal of Medical Toxicology. 2011;7:281-287. https://doi.org/10.1007/s13181-011-0178-y*

[344] *Mismetti P, Laporte S. Rivaroxaban: clinical pharmacology. In Annales Francaises D'anesthesie et de Reanimation 2008;27:16-21). https://doi.org/10.1016/S0750-7658(08)75142-6*

[345] *Centers for Disease Control and Prevention (CDC). What is Atrial Fibrillation? (Website accessed 2 May 2023).*

[346] *Centers for Disease Control and Prevention (CDC). What is Atrial Fibrillation? (Website accessed 2 May 2023).*

[347] *Centers for Disease Control and Prevention (CDC). Division for Heart Disease and Stroke Prevention. (Website accessed 20 April 2023).*

[348] *Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation. 2006;114(2):119-125. https://doi.org/10.1161/CIRCULATIONAHA.105.595140*

[349] *Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the US adult population. The American Journal of Cardiology. 2013;112(8):1142-1147. https://doi.org/10.1016/j.amjcard.2013.05.063*

[350] *Alkhouli M, Noseworthy PA, Rihal CS, Holmes DR. Stroke prevention in nonvalvular atrial fibrillation: a stakeholder perspective. Journal of the American College of Cardiology. 2018;71(24):2790-2801. https://doi.org/10.1016/j.jacc.2018.04.013*

[351] *Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137(2):263-272. https://doi.org/10.1378/chest.09-1584*

[352] *Tervonen T, Ustyugova A, Bhashyam SS, Lip GY, Verdecchia P, Kwan R, Gropper S, Heinrich-Nols J, Marsh K. Comparison of oral anticoagulants for stroke prevention in nonvalvular atrial fibrillation: a multicriteria decision analysis. Value in Health. 2017;20(10):1394-1402. https://doi.org/10.1016/j.jval.2017.06.006*

[353] *Tervonen T, Ustyugova A, Bhashyam SS, Lip GY, Verdecchia P, Kwan R, Gropper S, Heinrich-Nols J, Marsh K. Comparison of oral anticoagulants for stroke prevention in nonvalvular atrial fibrillation: a multicriteria decision analysis. Value in Health. 2017;20(10):1394-1402. https://doi.org/10.1016/j.jval.2017.06.006*

[354] *Hsu JC, Hsieh CY, Yang YH, Lu CY. Net clinical benefit of oral anticoagulants: a multiple criteria decision analysis. PLoS One. 2015;10(4):e0124806. https://doi.org/10.1371/journal.pone.0124806*

[355] *Canestaro WJ, Patrick AR, Avorn J, Ito K, Matlin OS, Brennan TA, Shrank WH, Choudhry NK. Cost-effectiveness of oral anticoagulants for treatment of atrial fibrillation. Circulation: Cardiovascular Quality and Outcomes. 2013;6(6):724-731. https://doi.org/10.1161/CIRCOUTCOMES.113.000661*

[356] *Rasmussen LH, Larsen TB, Graungaard T, Skjøth F, Lip GY. Primary and secondary prevention with new oral anticoagulant drugs for stroke prevention in atrial fibrillation: indirect comparison analysis. Bmj. 2012;345. https://doi.org/10.1136/bmj.e7097*

[357] *Schneeweiss S, Gagne JJ, Patrick AR, Choudhry NK, Avorn J. Comparative efficacy and safety of new oral anticoagulants in patients with atrial fibrillation. Circulation: Cardiovascular Quality and Outcomes. 2012;5(4):480-486. https://doi.org/10.1161/CIRCOUTCOMES.112.965988*

[358] *Lee S, Mullin R, Blazawski J, Coleman CI. Cost-effectiveness of apixaban compared with warfarin for stroke prevention in atrial fibrillation. PLos One. 2012; 7(10): e47473. https://doi.org/10.1371/journal.pone.0047473*

[359] *Meenan RT, Saha S, Chou R, Swarztrauber K, Pyle Krages K, O'Keeffe-Rosetti MC, et al. Cost-effectiveness of echocardiography to identify intracardiac thrombus among patients with first stroke or transient ischemic attack. Medical Decision Making. 2007;27(2):161-177. https://doi.org/10.1177/0272989X06297388*

[360] *O'Brien CL, Gage BF. Costs and effectiveness of ximelagatran for stroke prophylaxis in chronic atrial fibrillation. JAMA. 2005;293(6):699-706. https://doi.org./10.1001/jama.293.6.699*

[361] *Meenan RT, Saha S, Chou R, Swarztrauber K, Pyle Krages K, O'Keeffe-Rosetti MC, et al. Cost-effectiveness of echocardiography to identify intracardiac thrombus among patients with first stroke or transient ischemic attack. Medical Decision Making. 2007;27(2):161-177. https://doi.org/10.1177/0272989X06297388*

[362] *O'Brien CL, Gage BF. Costs and effectiveness of ximelagatran for stroke prophylaxis in chronic atrial fibrillation. JAMA. 2005;293(6):699-706. https://doi.org./10.1001/jama.293.6.699*

[363] *Canestaro WJ, Patrick AR, Avorn J, Ito K, Matlin OS, Brennan TA, Shrank WH, Choudhry NK. Cost-effectiveness of oral anticoagulants for treatment of atrial fibrillation. Circulation: Cardiovascular Quality and Outcomes. 2013;6(6):724-731. https://doi.org/10.1161/CIRCOUTCOMES.113.000661*

[364] *Rasmussen LH, Larsen TB, Graungaard T, Skjøth F, Lip GY. Primary and secondary prevention with new oral anticoagulant drugs for stroke prevention in atrial fibrillation: indirect comparison analysis. Bmj. 2012;345. https://doi.org/10.1136/bmj.e7097*

[365] *Schneeweiss S, Gagne JJ, Patrick AR, Choudhry NK, Avorn J. Comparative efficacy and safety of new oral anticoagulants in patients with atrial fibrillation. Circulation: Cardiovascular Quality and Outcomes. 2012;5(4):480-486. https://doi.org/10.1161/CIRCOUTCOMES.112.965988*

[366] *Rasmussen LH, Larsen TB, Graungaard T, Skjøth F, Lip GY. Primary and secondary prevention with new oral anticoagulant drugs for stroke prevention in atrial fibrillation: indirect comparison analysis. BMJ. 2012;345. https://doi.org/10.1136/bmj.e7097*

[367] *Hsu JC, Hsieh CY, Yang YH, Lu CY. Net clinical benefit of oral anticoagulants: a multiple criteria decision analysis. PLoS One. 2015;10(4):e0124806. https://doi.org/10.1371/journal.pone.0124806*

[368] *Meenan RT, Saha S, Chou R, Swarztrauber K, Pyle Krages K, O'Keeffe-Rosetti MC, et al. Cost-effectiveness of echocardiography to identify intracardiac thrombus among patients with first stroke or transient ischemic attack. Medical Decision Making. 2007;27(2):161-177. https://doi.org/10.1177/0272989X06297388*

[369] *Hsu JC, Hsieh CY, Yang YH, Lu CY. Net clinical benefit of oral anticoagulants: a multiple criteria decision analysis. PLoS One. 2015;10(4):e0124806. https://doi.org/10.1371/journal.pone.0124806*

[370] *Schneeweiss S, Gagne JJ, Patrick AR, Choudhry NK, Avorn J. Comparative efficacy and safety of new oral anticoagulants in patients with atrial fibrillation. Circulation: Cardiovascular Quality and Outcomes. 2012;5(4):480-486. https://doi.org/10.1161/CIRCOUTCOMES.112.965988*

[371] *Feeny D, Furlong W, Torrance GW, Goldsmith CH, Zhu Z, DePauw S, et al. Multiattribute and single-attribute utility functions for the health utilities index mark 3 system. Medical Care. 2002;40(2):113-128.*

[372] *Lee S, Mullin R, Blazawski J, Coleman CI. Cost-effectiveness of apixaban compared with warfarin for stroke prevention in atrial fibrillation. PLos One. 2012;7(10):e47473. https://doi.org/10.1371/journal.pone.0047473*

[373] *Hsu JC, Hsieh CY, Yang YH, Lu CY. Net clinical benefit of oral anticoagulants: a multiple criteria decision analysis. PLoS One. 2015;10(4):e0124806. https://doi.org/10.1371/journal.pone.0124806*

[374] *Hsu JC, Hsieh CY, Yang YH, Lu CY. Net clinical benefit of oral anticoagulants: a multiple criteria decision analysis. PLoS One. 2015;10(4):e0124806. https://doi.org/10.1371/journal.pone.0124806*

[375] *Canestaro WJ, Patrick AR, Avorn J, Ito K, Matlin OS, Brennan TA, et al. Cost-effectiveness of oral anticoagulants for treatment of atrial fibrillation. Circulation: Cardiovascular Quality and Outcomes. 2013;6(6):724-731. https://doi.org/10.1161/CIRCOUTCOMES.113.000661*

[376] *Rasmussen LH, Larsen TB, Graungaard T, Skjøth F, Lip GY. Primary and secondary prevention with new oral anticoagulant drugs for stroke prevention in atrial fibrillation: indirect comparison analysis. Bmj. 2012;345. https://doi.org/10.1136/bmj.e7097*

[377] *Schneeweiss S, Gagne JJ, Patrick AR, Choudhry NK, Avorn J. Comparative efficacy and safety of new oral anticoagulants in patients with atrial fibrillation. Circulation: Cardiovascular Quality and Outcomes. 2012;5(4):480-486. https://doi.org/10.1161/CIRCOUTCOMES.112.965988*

[378] *Hsu JC, Hsieh CY, Yang YH, Lu CY. Net clinical benefit of oral anticoagulants: a multiple criteria decision analysis. PLoS One. 2015;10(4):e0124806. https://doi.org/10.1371/journal.pone.0124806*

[379] *Meenan RT, Saha S, Chou R, Swarztrauber K, Pyle Krages K, O'Keeffe-Rosetti MC, et al. Cost-effectiveness of echocardiography to identify intracardiac thrombus among patients with first stroke or transient ischemic attack. Medical Decision Making. 2007;27(2):161-177. https://doi.org/10.1177/0272989X06297388*

[380] *Hsu JC, Hsieh CY, Yang YH, Lu CY. Net clinical benefit of oral anticoagulants: a multiple criteria decision analysis. PLoS One. 2015;10(4):e0124806. https://doi.org/10.1371/journal.pone.0124806*

[381] *Schneeweiss S, Gagne JJ, Patrick AR, Choudhry NK, Avorn J. Comparative efficacy and safety of new oral anticoagulants in patients with atrial fibrillation. Circulation: Cardiovascular Quality and Outcomes. 2012;5(4):480-486. https://doi.org/10.1161/CIRCOUTCOMES.112.965988*

[382] *Feeny D, Furlong W, Torrance GW, Goldsmith CH, Zhu Z, DePauw S, Denton M, Boyle M. Multiattribute and single-attribute utility functions for the health utilities index mark 3 system. Medical Care. 2002;40(2):113-128.*

[383] *Lee S, Mullin R, Blazawski J, Coleman CI. Cost-effectiveness of apixaban compared with warfarin for stroke prevention in atrial fibrillation. PLos One. 201;7(10):e47473. https://doi.org/10.1371/journal.pone.0047473*

[384] *Hsu JC, Hsieh CY, Yang YH, Lu CY. Net clinical benefit of oral anticoagulants: a multiple criteria decision analysis. PLoS One. 2015;10(4):e0124806. https://doi.org/10.1371/journal.pone.0124806*

[385] *Tervonen T, Ustyugova A, Bhashyam SS, Lip GY, Verdecchia P, Kwan R, et al. Comparison of oral anticoagulants for stroke prevention in nonvalvular atrial fibrillation: a multicriteria decision analysis. Value in Health. 2017;20(10):1394-1402. https://doi.org/10.1016/j.jval.2017.06.006*

C. TWO REGULATORY AGENCIES CONDUCT BR DIFFERENTLY ON NERLYNX NERATINIB

Summary table of the case study[386]

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 Nerlynx (neratinib) as a single agent for the extended adjuvant treatment of adult patients with early stage HER2[9]-positive breast cancer to follow adjuvant trastuzumabbased 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 Nerlynx, 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 Nerlynx 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 Nerlynx lived for one further year after stopping Nerlynx 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 Nerlynx lived another year without the cancer coming back versus 91% of those given placebo.
Known risks	The most common, serious side effect with Nerlynx 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. Nerlynx must not be used in patients with severely reduced liver function. It must also not be used with certain medicines that affect the way Nerlynx is broken down in the body. For the full list of restrictions, see the package leaflet.
BRA 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

[9] HER2: human epidermal growth factor receptor 2

	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 rates at five years were consistent with those of the two-year findings from the pivotal study. The Committee for Medicinal Products for Human (CHMP) of 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 Nerlynx 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, Nerlynx 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 Nerlynx be refused MA. Major efficacy findings (CHMP's initial assessment) For the primary endpoint of invasive disease-free survival (iDFS) in the intention-to-treat (ITT) population, the 2-year and 5-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 hazard ratios are imprecise as demonstrated by wide 95% CIs including values close to unity. Importantly, the 5-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. 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 Nerlynx do not outweigh the risks.

	Re-examination procedure The applicant requested a re-examination on detailed grounds. Clinical ground 1. The applicant 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 applicant 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 oestrogen receptor (ER) and with HER2 and 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, Nerlynx 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 Nerlynx with less patients discontinuing Nerlynx treatment. Data from the post approval 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). 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 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 sub-groups (including node positive and HR positive breast cancer) had an observed benefit that was substantially increased relative to the ITT population. Other than diarrhoea, Nerlynx 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. Diarrhoea is the most frequently reported adverse event, 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 diarrhoe. 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 Nerlynx 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 Nerlynx. 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 CHMPre-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 Nerlynx after surgery and trastuzumab would be a reasonable option. The agency therefore decided that Nerlynx'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 CHMP adopted a positive opinion recommending MA for the medicinal product Nerlynx 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.

4481

References

[386] EMA 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 EMA approach 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 is a genetically modified autologous cell-based product containing T cells transduced ex vivo using a retroviral vector expressing an 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. Limitations of Use: Not indicated for the treatment of patients with primary central nervous system lymphoma. Adult patients with relapsed or refractory follicular lymphoma (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 {YESCARTA® Kite Pharma}[387] 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 evaluated the efficacy of a single infusion of YESCARTA[387] in adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma, 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 (7 patients) or PR (7 patients), with a median time to improvement of 2.1 months (range: 1.6 to 5.3 months). Relapsed or Refractory Follicular Lymphoma {YESCARTA® Kite Pharma}[387] Efficacy in follicular lymphoma 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

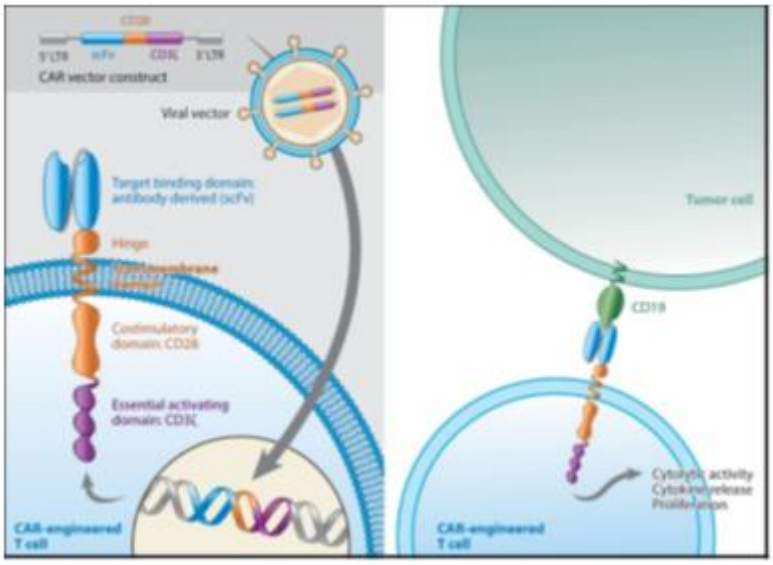
	efficacy population was 1.0 month (range: 0.8 to 3.1 months). The overall Objective Response Rate was 91% [95% CI 83-96].
Known Risks	The known risks – important identified risks – include Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions; neurologic toxicities, including 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.
BRA 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, 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 marketing authorisation 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 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. 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 16). 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 16. Replication-deficient murine γ-retroviral vector stably integrates the anti-CD19 CAR transgene into the T cell genome

Source: 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 was minimised to reduce the likelihood of any recombination events), these findings have been the basis for the RCR screening requirements issued by the 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 life-long 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 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 g-retroviral 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 should be monitored annually for 15 years. Further, quantitative polymerase chain reaction (PCR) should 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 should 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 develops a secondary malignancy during the study, every effort should be made to test for RCR in blood and a biopsy sample of the neoplastic tissue.

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

Post-marketing experience

RCR

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 European Society for Blood and Marrow Transplantation (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 additional 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 the regulators prefer to keep this risk in the RMP.

Secondary malignancies

To characterise the risk post-marketing, 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-RMP UPDATE during the five-year MA renewal

The five-year MA renewal was a good opportunity to reflect on the EU-RMP and determine whether the risks made sense and if the pharmacovigilance plan and risk minimisation measures 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 that:

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 adverse event rate is less than 0.0068 per person-year, or equivalently, no more than one event in every ~147 years.[388] 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 (CAT) response

The 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.[389,390,391] 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 regulators' expectations of the pharmacovigilance plan seem to exceed its ability to produce a meaningful risk characterisation.

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 marketing authorisation 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 post-marketing setting in determining the appropriate and feasible routine and additional pharmacovigilance activities for 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 healthcare 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.

References

[387] *YESCARTA® Kite Pharma. YESCARTA® (axicabtagene ciloleucel) suspension for intravenous infusion. US Prescribing Information (USPI). Santa Monica, CA. Revised: November 2022. (Website accessed 29 May 2023)*

[388] *Scholler J, Brady TL, Binder-Scholl G, Hwang WT, Plesa G, Hege KM, et al. Decade-Long Safety and Function of Retroviral-Modified Chimeric Antigen Receptor T Cells. Science translational medicine 2012;4 (132):132ra53.*

DOI: 10.1126/scitranslmed.3003761

[389] *Emery P, Furst DE, Kirchner P, Melega S, Lacey S, Lehane PB. Risk of Malignancies in Patients with Rheumatoid Arthritis Treated with Rituximab: Analyses of Global Postmarketing Safety Data and Long-Term Clinical Trial Data. Rheumatol Ther 2020;7 (1):121-31. doi: 10.1007/s40744-019-00183-6*

[390] *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. doi: 10.3899/jrheum.150051.*

[391] *Winthrop KL, Saag K, Cascino MD, Pei J, John A, Jahreis A, et al. Long-Term Safety of Rituximab in Rheumatoid Arthritis: Analysis From the SUNSTONE Registry. Arthritis care & research 2018;71 (8):993-1003. doi: 10.1002/acr.23781.*

Example of a company Benefit risk assessment document (BRAD)

EXAMPLE OF A COMPANY BENEFIT-RISK ASSESSMENT DOCUMENT (BRAD)

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*.)

EXECUTIVE SUMMARY

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

[Investigational/Trade Name] is a [describe the therapeutic class] that is being administered[insert route(s) of administration] 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* **List of Abbreviations**]

[Investigational/Trade Name] [Indication]
BRAD [Draft # or Final]

1. MODULE 1 – 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)

CONFIDENTIAL [DD Month YYYY]

4658

4659

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 Key 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						

4660
4661

4. MODULE IV –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

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

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

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

CIOMS WG XII statement

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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.