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REPUBLIC OF KENYA

Ministry of Health

# PHARMACY AND POISONS BOARD

## GUIDELINES ON BENEFIT-RISK ASSESSMENT OF HEALTH PRODUCTS AND TECHNOLOGIES

**JANUARY 2023**

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## Abbreviations and Acronyms

| | |
|---|---|
| **ASF** | Ashby and Smith Framework |
| **BRA** | Benefits Risk Assessment |
| **BRAT** | Benefit Risk Action Team |
| **BRF** | Benefit Risk Framework |
| **CMRCASS** | Center for Medicines Research Canada Australia therapeutic goods administration SwissMedic Singapore Health Science Authority |
| **COBRA** | Consortium on Benefit Risk Assessment |
| **DALY** | Disability Adjusted Life Years |
| **EMA** | European Medicines Agency |
| **EUA** | Emergency Use Authorisation |
| **HALE** | Health Adjusted Life Expectancy |
| **HPT** | Health Products and Technologies |
| **INHB** | Incremental Net Health Benefit |
| **LMIC** | Low- and Middle-Income Countries |
| **MAH** | Market Authorisation Holder |
| **NCE** | New Chemical Entities |
| **NDA** | New Applications Applications |
| **NTD** | Neglected Tropical Diseases |
| **PPB** | Pharmacy and Poisons Board |
| **QALY** | Quality Adjusted Life Years |
| **Q-TWIST** | Quality Adjusted Time without Toxicity and Symptoms |
| **RMP** | Risk Management Program |
| **SABRE** | South East Asia Benefit Risk Evaluation |
| **TURBO** | Transparent Uniform Benefit Risk Overview |
| **UMBRA** | Unified Methodologies for Benefits Risk Assessment |
| **US-FDA** | United States Federal Drugs Agency |

**Glossary of terms**

**Benefit:** Refers to a gain (positive result) for an individual or a population. It can also refer to the improvement attributable to the drug, in terms of human health, health-related quality of life, and/or economic benefit to the individual or group.

**Risk**: The probability or threat of quantifiable damage, injury, liability, loss, or any other negative occurrence that is caused by external or internal vulnerabilities, and that may be avoided through preemptive action.

**Benefit-risk assessment:** It's a formal process that quantitatively and/or qualitatively weighs the benefits of a drug against the known risk with a view of deciding if the former substantially outweighs the risk for continued use.

**Pharmacovigilance Expert Review and Advisory Committee (PERAC):** This is an Ad hoc committee of the Pharmacy and Poisons Board charged with the review of safety signals arising from spontaneous reports, regulatory pharmacovigilance submissions and medication events in the public domain.

**PrOACT-URL:** Refers to a decision-making framework with eight steps: Problems, Objectives, Alternatives, Consequences, Trade-offs, Uncertainty, Risk attitudes, and Linked decisions. It has been adapted by the European Medicines Agency for the benefit risk assessment of medicines. It continuously undergoes review.

**Metric**: This is a summary quantitative measure of the benefit risk balance.

**Threshold index:** This is a summary measure of the benefit risk assessment. They are derived from statistical manipulation of probabilities and utilities and are termed threshold because they are cut offs used in deciding the best treatment options.

**Health utility indices**: These are measures of benefits that incorporate patient preferences. They include but are not limited to QALYs Q-TWIST HALE, DALY.

**Trade off Indices:** These are a group of quantitative measures of the benefit risk assessment. They integrate the value of a tradeoff. They include TURBO and Incremental Net Health Benefit (INHB)

**Therapeutic context of drug use**: Refers to the nature and severity of the condition the drug is intended to prevent, treat, cure, mitigate, or diagnose, and how well patients' needs are being met by currently available treatments.

**Uncertainty:** Refers to factors that lead to errors in benefit risk assessment. These errors may arise from methodological differences, lack of internal and external validity of studies used to derive measures of benefit and harm as well as subjective aspects of the analysis such as assignment of utilities and weights.

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# 1. INTRODUCTION

## 1.1. Background

The benefit–risk assessment of medicines is a critical process in making regulatory decisions, throughout their lifecycle. The product's benefits and risks often change over time as new information about the product's effectiveness or safety becomes available. Post market evidence to inform benefit-risk assessments can come from a diverse set of sources, such as the clinical data, nonclinical data, patient experience data, medical literature, post marketing studies, adverse event reports, epidemiologic data, medication error reports, product quality reports, and in some cases, from new data obtained from drugs of the same class.

Kenya, like many other African countries, is gradually enhancing its technical capacity in conducting benefit risk assessment. In addition, New Chemical Entities (NCE) are not developed in the country and therefore the need for complex methods for Benefit risk assessment (BRA) may not arise in the drug development phase. The importance of these contextual factors is that the selection of methodologies for conducting BRA should be biased towards simple and easy to use methods.

For this reason, during application for marketing authorization for new chemical entities, there is heavy reliance on the decisions of stringent regulatory authorities. Nonetheless, there is a need to conduct BRA in the local context because of the burden of Neglected Tropical Diseases (NTD) and use of repurposed drugs for management of pandemics, which necessitate the need for local capacity to conduct BRA.

The recent COVID pandemic led to the use of vaccines and drugs that did not go through rigorous drug registration processes. These vaccines received Emergency Use Authorization (EUA) which placed a burden on regulatory agencies to conduct BRA. In addition, there was public concern about the risks of these vaccines and this was highlighted by vaccine hesitancy during the COVID-19 pandemic. This demonstrated the need to share findings of objective benefit risk assessments with both health care professionals and policy makers and the public in a manner that is easily understood by all.

### 1.2. Legal framework for conducting benefit-risk assessment

Under the Cap 244, the Pharmacy and Poisons Board is responsible for ensuring that health products and technologies (HPTs) marketed in Kenya are of quality, safe and efficacious. The Board therefore is required to conduct benefit risk evaluation of these products.

Benefit-risk assessment in the drug regulatory context entails "making a judgment as to whether the expected benefits (with their uncertainties) of the drug outweigh the potential risks (with their uncertainties and approaches to manage risks) associated with its expected use". (ICH M4E(R2)).

The key benefits are favorable effects identified during pre-clinical and clinical phases of drug development or during use post marketing approval. "Key risks are unfavorable effects that are important from a clinical and/or public health perspective in terms of their frequency and/or severity and/or seriousness" (ICH M4E(R2))

The evidence submitted in the premarket application and/or generated in the post market setting informs PPB's understanding of the benefits and risks of the drug.

The guidelines for submitting applications for registration of drugs, require the Marketing Authorization Holder (MAH) to submit conclusions about the benefits and risks of the drug. It is key that Product Evaluation and Registration Department to critically appraise these decisions (Guidelines on Medicines Evaluation and Registration, January 2022).

### 1.3. Objectives of the guidelines

The objective of this guidance is to describe a standardized systematic approach for evaluation and reporting the balance between the benefits and risks of marketed Health Products and Technologies (HPTs).

This shall also include investigational entities undergoing clinical trial application and a critical appraisal of submitted reports that is appropriate for low- and middle-income countries (LMIC).

In addition, these guidelines describe how a critical appraisal of a BRA can be conducted by a regulator or a sponsor.

### 1.4. Scope for the guidance

The purpose of this guidance is to provide a framework for the sponsors, drug developers, reviewers, marketing authorization holders and researchers to systematically evaluate, report and communicate the balance between benefits and risks of a medicinal product in a standardized format. This guidance also includes the decision-making framework at the end of a benefit risk assessment.

This guidance applies to:

- New Chemical Entities and Health Products Technologies assessment.
- Marketed drugs with a new safety signal or a new indication.
- Clinical trials.

## 2. PRINCIPLES OF BENEFITS RISK ASSESSMENT

Any benefit risk assessment shall adhere to the four principles of transparency; independence; timeliness; systematic, comprehensive and relevant. The components of the process that feed to these four core principles is represented in figure 1.

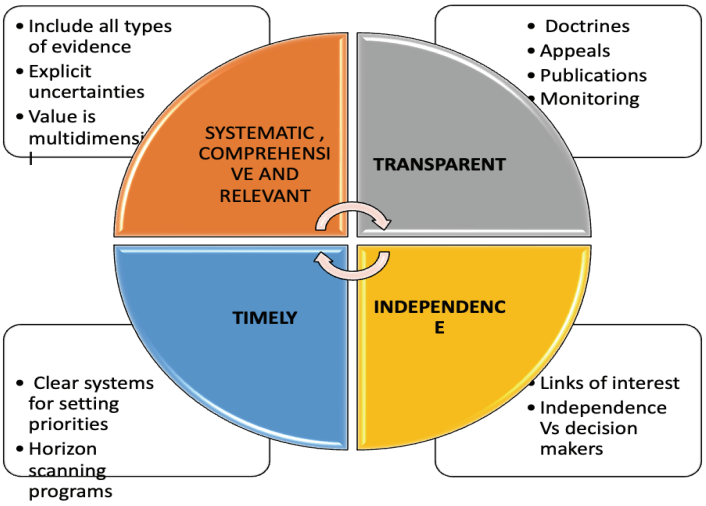


*Figure 1: Principles of Benefit Risk Assessment*

### 2.1 Triggers for the conduct of a Benefit Risk Assessment

In the pre-authorization phase of the drug cycle BRA is mandatory. The triggers for subsequent review and updating of the BRA is when new data is received regarding:

i. Safety concern or a change in the existing safety information of a health product or technology;
ii. The product's efficacy (or, in the post market context, its real-world effectiveness);
iii. Marketing application for a new indication;
iv. Public Health concern.

The iterative process of reviewing and updating the BRA in light of new evidence should be tied to similar updates made to the product's RMP, thus emphasizing the interrelationship between the two documents as strategic, lifecycle management tools for risk management.

On the contrary, there shall be no need for conducting a BRA under the following circumstances:

i. Where a BRA has been conducted by stringent NRA;
ii. Generic brands for which no safety concerns have been raised or associated with the product or products within the same therapeutic class, and/or;
iii. The effectiveness of specified risk management activities.

### 2.2 Structural Requirements for the conduct of a Benefits Risk Assessment

There are three elements for determining the benefit risk framework namely: selection of a structured benefit risk framework, human resource and Standard Operating Procedure (SOP) for benefit risk assessment.

#### 2.1.1 Selection of a structured benefit risk assessment framework

There are many frameworks for conducting BRA. Some are purely descriptive and many are quantitative. Examples of these frameworks are presented in table 1.

**Table 1: Examples of Benefit Risk Assessment frameworks**

| NAME OF THE FRAMEWORK | TYPE OF THE FRAMEWORK |
|---|---|
| FDA5-step framework | Semi-qualitative |
| EMA PrOACT-URL. | Qualitative |
| US-FDA BRAT | Quantitative |
| ASF | Quantitative |
| SABRE | Quantitative |
| UMBRA 8-step framework | Quantitative |
| CMR-CASS | Qualitative |

There are substantial methodological differences employed by these frameworks and they differ in complexity. No one framework is comprehensive and universally applicable. Selection of a framework is governed by the following considerations:

i. The level of experience and expertise of the NRA or MAH;
ii. The stage of the drug development cycle with early phases requiring more complex methodologies;
iii. The urgency of the problem at hand. Urgent issues to be addressed calls for application of a framework that can rapidly be deployed;
iv. Availability of software to conduct analysis, which is widely used by the BRAT framework;
v. The audience for the BRA.

The PPB shall make no recommendation on which framework to use; this shall be left at the discretion of the team conducting BRA and the MAH**.**

### 2.1.2 Human resource for conducting Benefit Risk Assessment

It shall be a cross functional team with a mix of expertise composed of Clinical Development/translational medicine, Pharmacoepidemiologists, Pharmacoeconomists, Epidemiologists, Biostatistics, Regulatory specialist. Management level reviewers - should have received training on the conduct of Benefit Risk Assessment. The core team may co-opt other members if additional expertise is required.

### 2.1.3 Standard Operating Procedures

The MAH/ regulator, shall have an SOP for the conduct of BRA. The SOP shall have the following components:

1. The triggers and timing for document development.
2. Responsibilities.
3. Nature of contributions from each representative of the cross-functional group.

A contemporary structured benefit–risk evaluation (cSBRA) aims at providing an objective assessment of the benefit–risk profile of health products and a higher transparency for decision making purposes. The triggers for subsequent review and updating of the cSBRA aims at providing an objective - when new data is received regarding:

1. The product's efficacy (or, in the post market context, its real-world effectiveness),
2. Risks associated with the product or products within the same therapeutic class, and/or
3. The effectiveness of specified risk management activities. These triggers would facilitate an update to the cSBRA prior to any marketing application submission for a new indication.

### 2.1.4 Target Audience for BRA

In The conduct of a BRA identification of the target audience is important as it determines identification of the key outcomes of interest as well as presentation and communication of the findings. The key audience include:

i. NRA who responsible for reviewing submissions;
ii. MAHs;
iii. Policy makers who use the findings to make decisions on change on treatment guidelines;
iv. Public and patients.

## 3. HOW TO CONDUCT THE BENEFIT RISK ASSESSMENT

The benefit risk assessment shall be conducted by the Pharmacovigilance Unit at the PPB. The Division may co-opt members into the benefit risk assessment team as needed. As a minimum requirement, the members of the team shall have training on benefit-risk assessment of medicines within the last three years.

Benefit risk assessment of cases that are of public health interest shall be conducted by the Pharmacovigilance Expert Review and Advisory Committee (PERAC). In the case of an emergency where the PPB cannot constitute a team, a team of three shall be considered acceptable.

### 3.1 The general approach for the conduct of a BRA

Regardless of the framework, a BRA has five key steps as illustrated in figure 2 namely: planning; evidence gathering and data preparation; analysis; exploration; conclusion and dissemination.

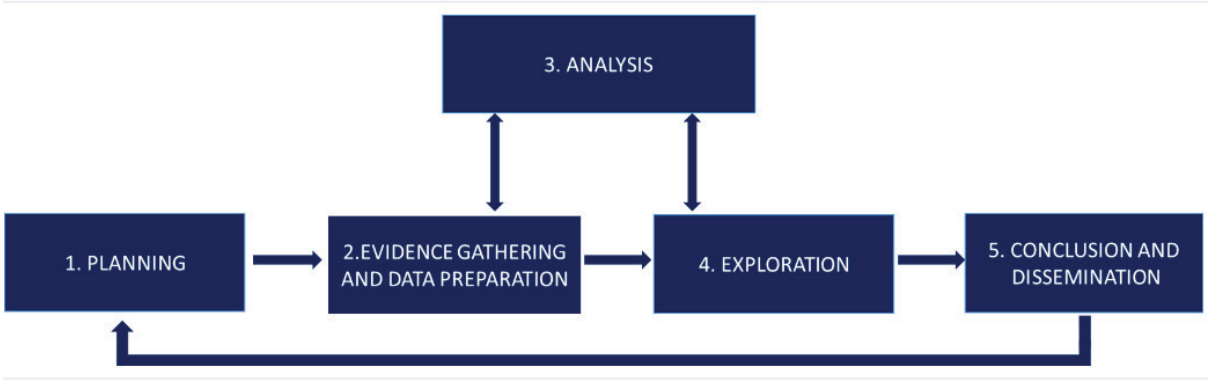


*Figure 2. General approach for conduct of a BRA*

### 3.2 Planning

This is done by identifying and documenting the following details that are fundamental to the decision and the evidence supporting the analysis. A more comprehensive description is available within the PrOACT-URL framework **(Annex 1).**

Planning involves describing the following:

- The decision problem;
- The comparators;

- The benefits and risks to include;
- The perspectives that should be taken into account;
- The sources of evidence;
- The resources available to the decision maker;
- Time horizon (short-term versus long-term benefits and risks).

The process for conducting the Benefit Risk Assessment (BRA) shall be divided into 12 key steps using PrOACT-URL framework as follows:

i. Identify the problem and its context;
ii. Identify objectives of the BRA that indicate the overall purposes to be achieved;
iii. Identify the treatment options in the market against which the medicinal product can be compared;
iv. Outline the key primary and secondary outcomes that shall be used to assess the product under review and the acceptable trade-offs during the review;
v. Assessment of the therapeutic context in which the drug is used, including the nature and severity of the condition the drug is intended to prevent, treat, cure, mitigate, or diagnose, and how well patients' needs are being met by currently available treatments;
vi. The favorable and unfavorable events shall then be prioritized using an appropriate method, which can be assessed using the principles of three grading systems as shown in **Annex 2**.

### 3.3 Gathering and Assessment of the available evidence

Post market evidence to inform benefit-risk assessments includes sources, such as the medical literature, post market studies, adverse event reports, medication error reports, product quality reports, and in some cases, from new data obtained from health products of the same class.

This can also include the effects table. An example of an effects table has been provided in **Annex 3.** It shall be provided by the sponsor or the MAH in case of marketed drugs. The effects tables shall include summaries of the beneficial effects of the medicines from clinical studies and observational studies.

### 3.4 Scoring of the assessed risk and benefits

A preliminary score shall be done by a co-opted member/ PV unit of the PERAC using the Transparent Uniform Risk/Benefit Overview (TURBO) model for benefit-risk analysis **(Annex 4)**. A review and discussion of the preliminary score to prioritize the risk based on seriousness and frequency shall then be conducted. Given that there are multiple approaches for benefit risk assessment, the PERAC shall be allowed to use methods described in the CIOMS. The TURBO model shall be preferred because of its simplicity.

### 3.5 Analysis and expert judgment

The data table shall provide a summary of the incidences and prevalence, benefits and risks. An example is shown in **Annex 5**.

The committee shall then decide whether to conduct a qualitative or quantitative assessment. Some of the considerations in the qualitative assessment shall be the economic, ethical and societal concerns of the effects.

The discussions can be guided and presented using the table on expert judgement as presented in **Annex 6.** This table may also be used for effects prioritization.

The quantitative analysis shall be based on the data table and shall entail assignments of weights to the effects based on the prioritization, followed by computation of a composite metric as the one listed in **Annex 7.**

### 3.6 Exploration and Uncertainty

The exploration may incorporate patients' perception of the effects of the treatment through patient representative involvement in the benefit risk assessment or by use of composite measures that are based on utilities.

Advanced statistical models can be used to address uncertainty. These models include sensitivity analysis and the recommended probabilistic simulation methods. The effects of uncertainty shall be displayed using visualization methods such as the box, forest plots and tornado diagram.

### 3.7 Regulatory decision making

The committee shall be expected to consider the consistency of this decision with similar past decisions, and assess whether taking this decision could impact future decisions.

Examples of regulatory decisions that may be informed by such assessments include addition, modification, or removal of a risk evaluation and mitigation strategies, initiation or release of post marketing study requirements, labeling changes (e.g., addition, revision, or removal of a boxed warning), and, rarely, marketing withdrawal. The PPB benefit-risk assessment in the post market setting generally considers the strength of the evidence evolving in the post market setting, remaining uncertainties about the drug's benefits and risks, how the drug is used in the post market setting, the evolving therapeutic context, and the availability of alternative treatments.

### 3.8 Communication of the decisions

The communications shall include:

a. A technical report that contains the summaries of the risks prioritized and the decisions. The format of the reporting template is shown in **Annex 8**. If need be, the technical report can be accompanied with a policy brief to be shared with government and other agencies.

b. A written communication to the sponsor or the MAH.

c. If the BRA was as a result of a major public health concern, the report shall be shared with the Ministry of Health.

The communication shall be appropriately prepared and disseminated to the target audience/relevant stakeholders using the established channels.

## 4. CRITICAL APPRAISAL OF BENEFIT AND RISKS ASSESSMENT

The appraisal for the various methodologies of Benefit Risk Assessments submitted by MAH's shall be done as guided by the checklist in (**Annex 9).**

The important findings shall be summarized and the deficiencies of BRA communicated to either the MAH or the team that conducted the analysis. The following recommendations can be made depending on the findings:

a. The BRA was well conducted and no amendments are required.

b. The BRA has minor deficiencies which may not substantially change the conclusion. If possible, the deficiencies can be addressed.

c. The BRA has major deficiencies that may substantially affect the conclusion therefore a repeat BRA is advised.

## 5. REFERENCES

1. CIOMS 1998. Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals.
2. Benefit-Risk Assessment Throughout the Drug Lifecycle: FDA Discussion Document. May 3, 2019.
3. EMEA. 6 February 2014 EMA/74168/2014 Human Medicines Development and Evaluation Benefit-risk methodology project Update on work package 5: Effects Table pilot (Phase I)
4. IMI-PROTECT Benefit-Risk Group recommendations report-Recommendations for the methodology and visualization techniques to be used in the assessment of benefit and risk of medicines
5. Report of the chmp working group on benefit-risk assessment models and methods doc. ref. EMEA/CHMP/15404/2007-ANNEX 1:TABLE 1) -https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/report-chmp-working-group-benefit-risk-assessment-models-methods_en.pdf
6. Smith, Meredith & Benattia, Isma & Strauss, Carmit & Bloss, Laura & Jiang, Qi. (2017). Structured Benefit-Risk Assessment Across the Product Lifecycle: Practical Considerations. Therapeutic Innovation & Regulatory Science. 51. 216847901769627. 10.1177/2168479017696272.
7. PROTECT, the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium. Metric indices. https://protectbenefitrisk.eu/MetricIndices.html

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## 7. ANNEXES

### Annex 1: PrOACT-URL framework

| STEP | DESCRIPTION | INFORMATION SOURCES |
|---|---|---|
| PrOBLEM<br>1. Determine the nature of the problem and its context | 1a. The medicinal product (e.g., new or marketed chemical or biological entity, device, generic).<br>1b. Indication(s) for use.<br>1c. The therapeutic area and disease epidemiology<br>1d. The unmet medical need, severity of condition, affected population, patients' and physicians' concerns, time frame for health outcomes.<br>1e. The decision problem (what is to be decided and by whom, e.g., industry, regulator, prescriber, patient) | Assessment history, Initial Marketing authorisation documents, new data obtained on post approval |
| 2. Frame the problem. | 2a. Whether this is mainly a problem of uncertainty, or of multiple conflicting objectives, or some combination of the two, or something else (e.g., health states' time progression).<br>2b. The factors to be considered in solving the problem (e.g., study design, sources and adequacy of data, disease epidemiology, presence of alternative treatments). | 2a. Usually it is a mixture of favourable effect size, unfavourable effect seriousness and their uncertainties. Refer for example to previous BRAs conducted, PBRERs and any other data sources<br>2b. Ideally, only factors that make a difference to a decision need be included. |
| OBJECTIVES<br>3.Establish objectives that indicate the overall purposes to be achieved. | 3. The aim (e.g., to evaluate the benefit-risk balance, to determine what additional information is required, to assess change in the benefit-risk balance, to recommend restrictions). | |

| STEP | DESCRIPTION | INFORMATION SOURCES |
|---|---|---|
| 4. Identify criteria for<br>a) favourable effects<br>b) unfavourable effects | 4. A full set of criteria covering the favourable and unfavourable effects (e.g., endpoints, relevant health states, clinical outcomes). An operational definition for each criterion along with a measurement scale with two points defined to encompass the range of performance of the alternatives (not just reported measures of central tendency, but also confidence intervals). Considerations of the clinical relevance of the criteria—some are of more concern to decision makers than others. | Establishing two points on each measurement criterion facilitates scaling of the alternatives. Usually, data are reported only for the alternatives considered, but quantitative modelling requires definitions of two points on each measurement scale: e.g., lowest and highest practically-realisable measures. Quantitative weights assigned to the scales are based on considerations of relevance, which may not be documented, in which case the relevant stakeholders or key players can provide the information. |
| ALTERNATIVES<br>5. Identify the options to be evaluated against the criteria. | 5a. Pre-approval: dosage, timing of treatment, drug vs. placebo and/or active comparator; the decision or recommendation required (e.g., approve/disapprove, restrict, withdraw).<br><br>5b. post-approval: do nothing, limit duration, restrict indication, suspend. | 5. As above, Step 1. Provide a clear definition of each option. |
| CONSEQUENCES<br>6. Describe how the alternatives perform for each of the criteria, i.e., the magnitudes of all effects, and their desirability or severity, and the incidence of all effects. | 6. The consequences separately for each alternative on each criterion (e.g., efficacy and safety effects that are clinically relevant, positive and negative health outcomes), summarised in an 'Effects Table' with alternatives in columns and criteria in rows. Qualitative and quantitative descriptions of the effects in each cell, including statistical summaries with confidence intervals, and references to source data, graphs and plots. | 6. As above for Steps 3 and 4. It is rare to see all this information in one place. Usually, it is necessary to search for the information. If more than one study is reported, are decisions to be based on a single 'best' study or on combined data? Is a meta-analysis available? Can the effects table be populated with the results from several studies? Head-to-head comparisons are not necessarily needed for quantitative modelling. Report |

| STEP | DESCRIPTION | INFORMATION SOURCES |
|---|---|---|
| | | missing data. A quantitative model will require judgements of value functions, which express the clinical relevance of the data. |
| TRADE-OFFS<br><br>7. Assess the balance between favourable and unfavourable effects | 7. The judgement about the benefit-risk balance, and the rationale for the judgement. | Overall conclusions, benefit/risk assessment and recommendations. A quantitative model will also require judgements of weights associated with the criteria. |
| At this point, only issues concerning the favourable and unfavourable effects, and their balance, have been considered. The next three steps are relevant in considering how the benefit-risk balance is affected by taking account of uncertainties. | | |
| UNCERTAINTY<br><br>8. Report the uncertainty associated with the favourable and unfavourable effects.<br><br>9. Consider how the balance between favourable and unfavourable effects is affected by uncertainty. | 8. The basis for and extent of uncertainty in addition to statistical probabilities (e.g., possible biases in the data, soundness and representativeness of the clinical trials, potential for unobserved adverse effects)<br><br>9. The extent to which the benefit-risk balance in step 7 is reduced by considering all sources of uncertainty, to provide a benefit-risk balance, and the reasons for the reduction. | Overall conclusions (as at Step 7, above). Incidence data, reported at step 6 in the effects table, provide information relevant to the probabilities of realising the effects.<br><br>Judgement plays a key role in this step.<br><br>A quantitative model will explore in sensitivity analyses and scenario analyses (or by explicitly incorporating probability distributions in the model) the effects on the overall benefit-risk balance of all sources of uncertainty. |
| RISK TOLERANCE<br><br>10. Judge the relative importance of the decision maker's risk attitude for this product. | 10. Any considerations that could or should affect the decision maker's attitude toward risk for this product (e.g., orphan drug status, special population, unmet medical need, risk management plan). | Some idea of the risk tolerance can be inferred from any report of step 9—how the favourable-unfavourable effects balance was affected by uncertainty. Another key role for judgement. |
| 11. Report how this | 11. The basis for the decision maker's | see Step 1 |

| STEP | DESCRIPTION | INFORMATION SOURCES |
|---|---|---|
| affected the balance reported in step 9. | decision as to how tolerable the benefit-risk balance is judged to be (taking into account stakeholders' views of risk?). | |
| LINKED DECISIONS<br><br>12. Consider the consistency of this decision with similar past decisions, and assess whether taking this decision could impact future decisions. | 12. How this decision, and the value judgements and data on which it is based, might set a precedent or make similar decisions in the future easier or more difficult. | Conclusions.<br><br>As all decisions are based not only on evidence, but also interpretations of that evidence that invoke value judgements and beliefs about uncertainty, decision makers may wish to reflect on whether those judgements and beliefs are consistent across similar past decisions, allow future changes and can be defended. |

## Annex 2: "Principle of three" grading system

| | **High** | **Medium** | **Low** |
|---|---|---|---|
| **Disease** | | | |
| Seriousness | | | |
| Duration | | | |
| Incidence | | | |
| **LEVEL OF IMPROVEMENT PRODUCED BY THE MEDICINE** | | | |
| Seriousness | | | |
| Duration | | | |
| Incidence | | | |
| **ADVERSE EFFECTS OF THE MEDICINE** | | | |
| Seriousness | | | |
| Duration | | | |
| Incidence | | | |

## Annex 3: Example of an effects table

| | Effect | Short Description | Unit | Placebo | Vandetanib | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|---|
| Favourable | PFS (HR) | From randomization to progression or death (blinded independent review) | N/A | 1 | 0.46 95% CI: (0.31, 0.69) | Large effect in overall population. Consistent and significant effect on PFS but not OS (too early?) | See Discussion on Clinical Efficacy. |
| | PFS (median) | Weibull model | Mo | 19.3 | 30.5 | Only a very low number of patients with definite RET mutation negative status at baseline. Lower efficacy? | Single-arm study in RET negative patients post-approval. |
| | ORR | Proportion of complete or partial responders (>=30% decrease unidimensional) RECIST | % | 13 | 45 | No clear effect on PRO/QoL (missing data) | See Discussion on Clinical Efficacy. |
| Unfavourable | Diarrhoea Grade 3-4 | Increase of ≥7 stools per day over baseline; incontinence; Life-threatening | % | 2.0 | 10.8 | Duration of follow up in the pivotal study is short *vs.* the need for long duration of treatment. | Risk of dehydration and renal/cardiac risks (see SmPC 4.4) Restrict to symptomatic and aggressive disease (see SmPC 4.1). Explore lower dose (see See Table 20. Summary of the RMP) |
| | QTc related events Grade 3-4 | QTc >0.50 second; life threatening; Torsade de pointes | % | 1.0 | 13.4 | Risk of developing further major cardiac SAEs including Torsades de pointe? | |
| | Infections Grade 3-4 | IV antibiotic, antifungal, or antiviral intervention indicated; Life-threatening | % | 36.4 | 49.8 | | |

Abbreviations: PFS, progression-free survival; ORR objective response rate; Mo, months; OS, overall survival; RET, "rearranged during transfection" gene, see text.

## Annex 4: The ‘‘Turbo’’ Model for Benefit-Risk Analysis

Scores are assigned to the risks (R-Score) and the benefits (B-Score) and are then combined into an overall TURBO or “therapeutic” score; the score can be regarded as a measure of the “intrinsic” property of a drug, reflecting the benefit-risk relationship at the population level for a given medication; different indications can, of course, be associated with different benefit-risk balances, usually because of different associated benefits. The challenge is to appropriately quantify the benefits and risks so that the drugs under comparison can be represented in their rightful positions on the graph. As already described, both risks and benefits have two basic determinants, degree and probability, which are quantifiable. In its simplest form:

R-factor = Ro+ Rc

B-factor = Bo + Bc

Where Ro is the risk associated with the medically most serious adverse effect, Rc represents an additional risk (e.g., the next most serious adverse reaction or the most frequent), Bo = primary benefit, and Bc = ancillary benefits(s). As formulated by Amery, scores for Bo and Ro range from 1 to 5, and for Rc and Bc from 0 to 2. Figure 1 represents an R-score grid with possible scores; measurements should reflect the risk in its most severe appearance (e.gTorsade de pointe, not QTc prolongation; hepatitis, not transaminase increase), as determined from the best available data (clinical trials, epidemiological data, etc.). Figure 2 presents suggested scores and associated definitions for risk severity. Figure 3 illustrates how to apply them to yield a value for Rc. A similar approach can be used to deter

Mine the B-factor (see Figures 4-6). Placement of the resultant B-factor and R factor on the Turbo diagram (Figure 7) provides a composite for between drug comparisons.

Figure 1. «R» score associated with the more severe adverse effect (= R)

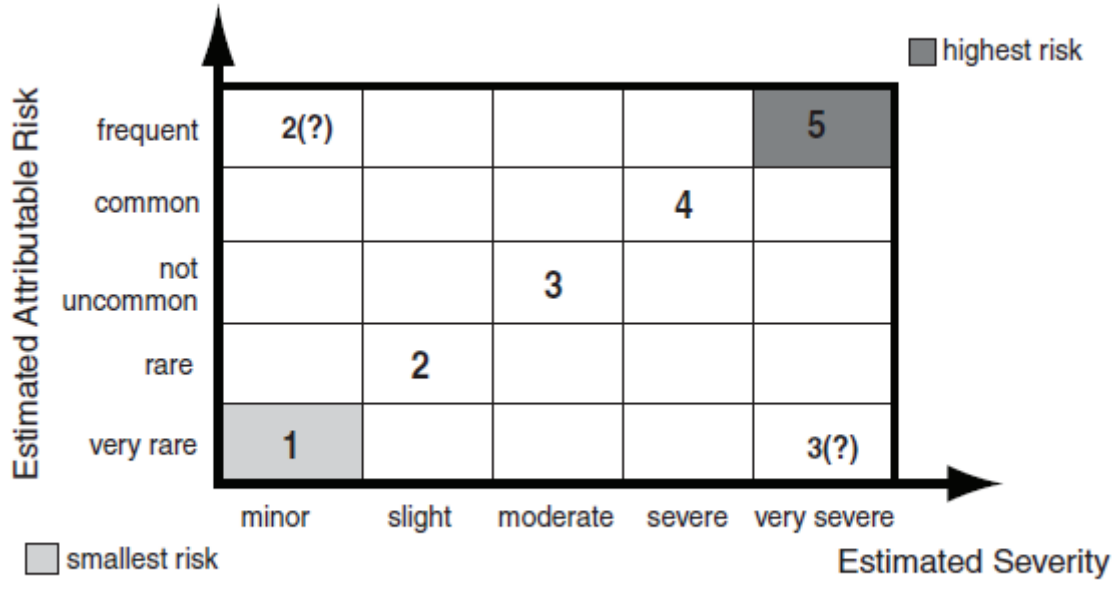


Figure 2. Estimating severity of risk

severity = impact on health status and socio professional capabilities

E.g., five scores (definitions are tentative):

1 = some hindrance, but not really incapacitating

2 = temporarily/intermittently incapacitating

3 = incapacitating, but not life-threatening/-shortening

4 = life-shortening, but not life-threatening

5 = life-threatening

Score should refer to risk if properly managed. For example:

- preventability through monitoring (bleeding due to anticoagulant)
- (full) recovery if appropriately managed (hepatotoxicity in most instances)
- timely detection (presence of warning signs)

Figure 3. The adjusted "R"score = the "R"-factor

Take the next severe adverse effect or, if there is no other severe adverse effect, the most frequent one and estimate "R"score for this adverse

effect = R'

"R"-factor = Ro + correction factor Rc

Correction factor Rc

= +2 ifR'=5

+ 1 if R' = 4

+ 0 if R' $\leq$ 3 (tentative example)

**Figure 4. «B» score associated with the benefit in that indication (=B )**

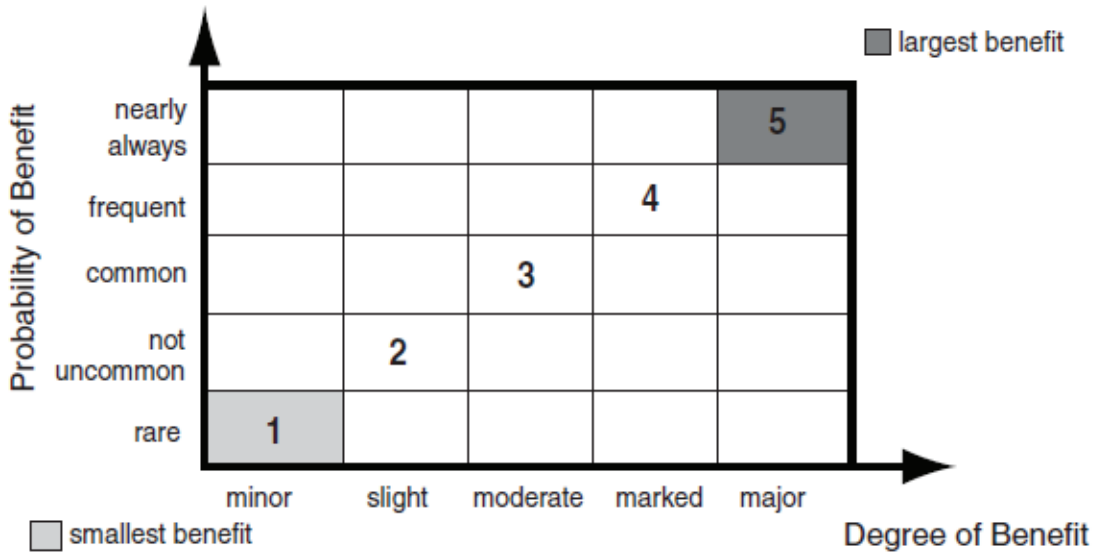


**Figure 5. Estimating degree of benefit (Bo)**

Benefit = impact on indication as reflected by change(s) in health status and socio professional capabilities

E.g., five scores; treated condition becomes (definitions are tentative):

1 = less hindering, but capabilities remain unchanged

2 = less frequently incapacitating or incapability lasts shorter

3 = less incapacitating, but no change in life expectancy

4 = less life-shortening

5 = less immediately life-threatening

Score refers to benefits associated with correctly used medicine (and leaves out aspects such as non-compliance).

**Figure 6. The adjusted "B" score = the "B"-factor**

Consider whether the medicine has relevant ancillary properties and assign a value to the correction factor as indicated below:

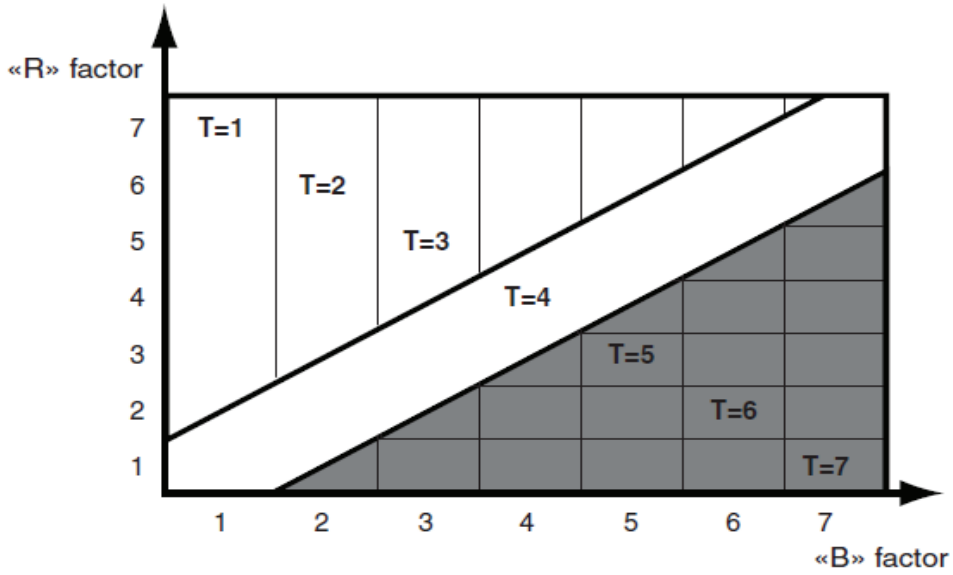
"B"-factor = Bo + correction factor (Bc) for ancillary property

Correction factor Bc (tentative example)

= + 2 if ancillary medical property relevant to the indication (e.g., cholesterol lowering effect for antidiabetic or for antihypertensive medicine)

= + 1 if ancillary practical property (e.g., once-daily dosage schedule or fast onset of action, etc.)

**Figure 7. The intrinsic RB balance: the TURBO diagram**




T-scores (in grid) to be further defined

## Annex 5: Data table

| **Benefits** | **Drug 1** | **Drug 2** |
|---|---|---|
| Reduction in cholesterol | 50% | 40% |
| Weight loss | 20% | 18% |
| **Risks** | | |
| Transient nausea | 15% | 20% |
| Gastric ulcer | 5% | 6% |

## Annex 6: Expert Judgement

| **Key considerations for expert judgement** | **YES** | **NO** |
|---|---|---|
| Is the disease severe or serious from either a patient or public health perspective? | | |
| Are there alternatives that effectively manage the condition? | | |
| Are there financial, ethical or societal concerns about the HPT | | |

## Annex 7: Composite Metric Table

### Threshold metric indices

| | **Interpretation** | **Description of how it is computed** | **References** |
|---|---|---|---|
| Number Needed to Treat (NNT) | The number of patients that need to be treated (on average) for one event to be observed as a result of treatment | Is derived from the probabilities of a favorable effect for the treatment and comparator groups. The difference between the two probabilities, and, gives the increase in certainty, NNT is then calculated as the reciprocal of this difference | Holden, Juhaeri, and Dai, 2003; Laupacis, Sackett, and Roberts, 1988 |
| Number needed to harm (NNH) | Probabilities of unfavorable effects | | |
| Adverse Event Adjusted-NNT (AE-NNT) | See NNT above | Penalizes NNT for the occurrence of AEs in the same patient | Schulzer and Mancini, 1996 |
| Relative Value adjusted NNH (RV-NNH) | See NNH above | incorporates stakeholders' value preferences on the importance of AEs into NNH. | Guyatt et al., 1999 |
| Impact numbers | Estimates of the number of individuals that will be affected by a disease and/or an intervention can be derived. | A group of metrics that generalise the NNT concept to the population level instead of focusing on only those patients who receive treatment. | Attia et al., 2002; Heller et al., 2002; Heller et al., 2003 |

| | **Interpretation** | **Description of how it is computed** | **References** |
|---|---|---|---|
| Minimum Clinical Efficacy (MCE) | The minimal therapeutic benefit for a treatment to be worth considering, accounting for the event probability when untreated. | | Holden, Juhaeri, and Dai, 2003a; Holden, Juhaeri, and Dai, 2003b |
| Relative Value adjusted MCE (RV-MCE) | Determines incorporates stakeholders' value preferences on the importance of AEs into MCE | | |
| Maximum Acceptable Risk (MAR) | | Analogous but opposite to MCE. MAR assumes mutually exclusive benefit and risk events | Johnson et al., 2009 |
| Net Efficacy Adjusted for Risk (NEAR) | Estimates NEAR odds ratio (OR) or relative risk (RR) using the standard formulae for OR and RR | Uses benefit or risk event and non-event count data for two comparative treatments in a table. | Boada et al., 2008; Boada et al., 2009 |

**Health Indices**

| | **Intepretation** | **References** |
|---|---|---|
| Quality Adjusted Life Years (QALY) | The time spent in a particular health state is multiplied by the QoL score in that state. | Sassi, 2006; Ried, 1998 |
| Health Adjusted Life Expectancy (HALE) | It is the sum of QALYs | |

| | **Intepretation** | **References** |
|---|---|---|
| Disability Adjusted Life Years (DALYS) | Is a parallel extension of QALY and is an index quantifying number<br><br>Of years lost from treatment compared to the national life expectancy. | Sassi, 2006 |
| Quality-adjusted Time Without Symptoms and Toxicity (Q-TWiST) | A QALY metric, with explicit definitions of the discrete health states in cancer therapy: toxicity, time without symptoms and toxicity, and relapse. | Gelber et al., 1995; Goldhirsch et al., 1989 |

**Trade off indices**

| | **Intepretation** | **References** |
|---|---|---|
| Utility and Time adjusted NNT (UT-NNT) | Adjusts the benefit-risk event probabilities in NNT for the time saved or lost due to treatment and the utilities associated with the treatment. | Riegelman and Schroth, 1993 |
| INHB (Incremental Net Health Benefit (INHB) | Calculates the difference in the "incremental" change of benefits to that of risks. INHB uses QALY specifically to characterize benefits and risks, but other metrics can be used and generalizes as INB | Garrison, Towse, and Bresnahan, 2007; Lynd, Najafzadeh, et al., 2010; Minelli et al., 2004) |
| Incremental Net Benefit | | Lynd, Marra, et al., 2010 |
| Benefit Risk Ratio (BRR) | Divides benefits by risks, and, therefore, assumes equal importance of benefits and risks. | Chuang-Stein, Entsuah, and Pritchett, 2008; Korting and Schafer-Korting, 1999; Payne and Loken, 1975 |
| Global Benefit Risk (GBR) | Refers to three trade-off metrics constructed around individual patients' outcomes in clinical trials such as linear, ratio | Chuang-Stein, Entsuah, and Pritchett, 2008; Chuang-Stein, Mohberg, and Sinkula, 1991 |

## Annex 8: Benefits Risk Assessment Report Template

I. Analysis of Condition

- *Provide a concise description of the epidemiology, natural history of the disease and the aims of treatment.*
- *Patients' experience with living with disease condition can be added here. Information about disease severity in subpopulations should be provided as it*
- *Relates to differences in how the therapeutic context may be considered in the benefit-risk assessment for the population.*
- *Aspects of the disease that have the greatest impact on patients should be described.*
- *Significant limitations or uncertainties in the understanding of the condition should be discussed.*

II. Current Therapies/Treatment Options

- *Provide a short overview of the major current therapies/treatment options in the intended population (i.e., those used most frequently and/or recommended*
- *In clinical guidelines), and the benefits and risks of these current therapies that are most relevant to the evaluation of the medicinal product in the intended population.*
- *Describe the medical need for a new therapy ("unmet medical need") in terms of efficacy, safety, tolerability, convenience or preference (if applicable).*
- *Significant limitations or uncertainties in the understanding of the current therapies should be discussed.*

III. Benefits

- *Describe key benefits ("drivers") of product. Reference product Value Tree and Effects Table. Consider:*

  *– Nature of the benefit: e.g., preventive, symptomatic, or disease-modifying*

  *– Clinical importance of the benefit itself and its treatment effect (e.g., less frequent hospitalization, prevention of disease progression)*

  *– Absolute difference in effect versus the comparator.*

- *Provide a brief critical evaluation of the strengths and limitations of the evidence for the benefits, considering:*

➔ *The study design(s) and comparator(s) used*

➔ *Treatment effect size and its clinical relevance*

➔ *Time course (time to onset) and duration of effect*

➔ *Validity of surrogate endpoint(s), if used*

➔ *Statistical analysis rigor and limitations*

- ➔ *Consistency of findings across studies for the same or similar endpoints*
- ➔ *Generalizability of treatment response to the proposed patient population*
- ➔ *Variability of treatment effects across population. If treatment effects are significantly greater or lesser in certain subgroups, results for these subgroups should be described.*
- ➔ *Present information on patient preferences relating to key product risks if data are available.*
- *Characterize key uncertainties (e.g., missing information for key endpoints or in the broader patient population, conflicting findings either within or across studies, or marginal treatment effects) in any of the benefits.*

IV. Risks

- Describe key risks ("drivers") of product. Consider:
- *Biological plausibility of the risk, which may include class effects*
- *Medical seriousness/severity of the risk, including the impact on individual patient*
- *Its frequency, time course, predictability, preventability, and reversibility*
- *Requirement for treatment cessation or dose reduction as a result of the risk*
- *Potential impact on public health (frequency; size of treated population)*
- *Public perception of risk where it may impact public health*
- *Present information on patient preferences relating to key product risks if data are available*
- *Highlight the key strengths and limitations of the evidence. Briefly characterize key uncertainties (e.g., adequacy of risk assessment, missing information for key endpoints or in the broader patient population, conflicting findings either within or across studies, relationship between dose/exposure and risk, or marginal treatment effects) in any of the risks.*

V. Risk Management

- *Describe risk minimization activities directed at any of the risks, including "routine" (i.e., labeling) as well as "additional" (i.e., specific activities as outlined in the product's core Risk Management plan) and their ability to prevent or minimize the risks.*
- *Describe the plan to evaluate the effectiveness of any additional risk minimization activities.*

VI. Conclusion

- *Provide a succinct, overall interpretation of the benefit-risk of the product within the indication. This assessment should explain your benefit-risk conclusion using a critical analysis and integration of the information in the previous sections. It should consider relative benefits and risks of the medicinal product, compared with standard of care.*
- *Discussion may include how the combined key benefits are judged to exceed the combined key risks in the target patient population; whether the benefit-risk*

*profile is difference for any subgroups; whether the benefit-risk profile would be expected to change significantly over the treatment course; and where sponsor believes the product will fit within the therapeutic landscape.*

- *A Value Tree and an Effects Table should be referenced here. (Examples provided in Annex 1 and 2). If possible, also include:*
- *A visualization of relative magnitude of benefits and risks in an integrated graphical format (e.g., forest plot, tornado diagram, etc.).*
- *If semi-quantitative or quantitative methods are used to evaluate the relative benefit-risk relationship, the following should be included in this section:*
- *a clear explanation/ rationale of the selected methodology*
- *a justification of the assumptions (e.g., weighting)*
- *methods and rationale for sensitivity analyses*
- *results for the primary and sensitivity analyses*
- *a discussion of strengths and limitations of the methods selected*
- *an interpretation of the analyses and a discussion of how they are supportive of the overall qualitative assessment.*

VII. References

VIII. Appendices

Appendix A: Value Tree

Appendix B: Effects Table

## Annex 9: BRA checklist-critical appraisal

| Dimension | Specific Evaluation Criteria |
|---|---|
| Fundamental principle | 1) Is the method logically sound? This will be determined by the underlying mathematical/empirical reasoning used to build the models, and in the results e.g. the point estimates and construction of associated confidence intervals.<br>2) Does the method offer increased transparency in the assessment allowing reproducibility of the results? We will determine, descriptively, how the methods enforce transparency and whether any insufficient disclosure of the steps taken in the process prohibits reproducibility.<br>3) Does the method also produce statistical uncertainty estimates around the point estimates (using the standard models)? This is satisfied when the method has a technique to produce confidence intervals which are mathematically sound. Otherwise, we will describe whether the methods provide any guideline on how uncertainty is to be dealt with.<br>4) Can the method incorporate other sources of uncertainty in the input parameters? This is assessed by how the approach elicits the input parameters allowing for uncertainty in the response.<br>5) Can the principles of the methods be easily understood by the end users? We will describe to what extent the principles are thought important to be understood before a decision maker can build decision models or interpret the results from a particular method.<br>6) Does the approach appropriately incorporate value judgements, either explicitly or implicitly? Stakeholders' involvement in providing preference value is needed to satisfy this criterion.<br>7) How does the approach handle multiple options? Often in decision making, more than two options (e.g. drug treatments) would be considered. We describe how an approach handles this, and whether there is a natural extension to the approach when it comes to multiple options. |
| Features of respective approaches | 1) Does the method appropriately allow balancing of the benefit-risk profile either numerically or visually? We will also describe whether the assessment benefits and risks are done separately or simultaneously.<br>2) Can the model flexibly include several benefits and risks criteria? We shall also describe whether the method has a technique to handle multiple benefits and risks evidence simultaneously.<br>3) Can the model flexibly include multiple sources of evidence? We shall describe whether the method can incorporate pieces of evidence from different sources of data.<br>4) Does the method naturally allow sensitivity analysis? We will address the feasibility of conducting a sensitivity analysis for each method and what has been suggested e.g. to investigate the best and worst scenarios.<br>5) Can the method incorporate time dimension? We will describe how time variables are dealt with.<br>6) Is the model ready to be formally updated with new/additional data/assumptions? We will describe how feasible it is for a model built to be modified to take into account new evidence or changes in the input parameters.<br>7) Is there any unique feature of a particular method? We will describe any unique feature of a method that gives an added advantage to other methods. Additionally, we will also describe any fatal flaw, if any, of models built from a particular method. Available computer programmes and/or manuals relevant to the methods will also be described. |

| **Dimension** | **Specific Evaluation Criteria** |
|---|---|
| Visual representation of model | 1) Does the model propose potential visualizations of the results? We will describe the proposed visualization techniques and what they are intended to represent. |
| Accessibility and accessibility | 1) Are the parameters and results acceptable and easily interpretable (from the perspective of a non-statistician)? This shall include any interim results, if any, before the final results are reached. We will describe how the methods ensure consistency in the input parameters, if any. We will also describe where we see there are potential misinterpretations of the results.<br>2) How practical is the method when used in real-life decision making? This will address the economic aspects of the methods in terms of their complexity, the time to set up, the (monetary) cost involved if directly applicable, and the ease of rerunning/modifying the models.<br>3) Which perspective are the methods useful for e.g. for regulators, physicians, patients, stakeholders, etc.? We will also address whether a model built to take on one perspective can be easily modified into another.<br>4) In what respect the use of the approach can lead to make better decision making |

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