**The Brighton Collaboration Standardized Module for Vaccine Benefit-Risk Assessment**

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**Keywords:**

Benefit-risk; module; vaccine safety; vaccines; guidelines

**Abstract**

Vaccine Benefit-Risk (B-R) assessment consists of evaluating the demonstrated benefits and risks of a vaccine and making a judgment on whether the expected key benefits outweigh the potential key risks associated with its expected use. B-R supports regulatory and public health decision-making throughout the vaccine’s lifecycle. In August 2021, the Brighton Collaboration’s Benefit-Risk Assessment of VAccines by TechnolOgy (BRAVATO) Benefit-Risk Assessment Module working group was established to develop a standard module to support the planning, conduct and evaluation of a defensible structured B-R assessments for vaccines from different platforms when data from clinical trials or post-marketing studies, including real-world evidence, become available. It enables sharing of relevant information via value trees, effects tables and graphical depictions of B-R trade-offs. It can be used by vaccine developers, funders, regulators and policy makers in high-, middle- or low-income countries to help inform decision-making and facilitate transparent communication concerning development, licensure, deployment and other lifecycle decisions. The module is available electronically at xxx and a case study on COVID-19 vaccines using the module is available at xxx. Vaccine developers, funders, regulators and public health personnel can use the module during vaccine development, submission and/or post-approval.

## 1. Preamble

The Brighton Collaboration ([www.brightoncollaboration.org](http://www.brightoncollaboration.org)) was launched in 2000 to improve the science of vaccine safety1. The Brighton Collaboration formed the Viral Vector Vaccines Safety Working Group (V3SWG) in October 2008 to improve the ability of key stakeholders to anticipate potential safety issues and interpret or assess safety data, thereby facilitating greater public acceptance of newly licensed viral vector vaccines. The mandate of the V3WSG was expanded to all vaccines, and accordingly the Working Group (WG) was renamed the Benefit-Risk Assessment of VAccines by TechnolOgy (BRAVATO) WG in February 2020. To support this mandate, the BRAVATO WG developed standardized templates that describe key considerations for Benefit-Risk (B-R) assessment of other vaccine platforms (e.g., nucleic acid, protein, inactivated, live attenuated and a revised viral vector vaccine template) 2-6. In August 2021, BRAVATO established the Benefit-Risk Assessment Module WG to develop a standard module to support the planning, conduct and evaluation of structured B-R assessments for multiple vaccine platforms. The purpose of this paper is to introduce the module, describe it in detail, and provide instructions for its use. An on-line supplement demonstrates how the B-R assessment module can be utilized in a real-world B-R calculation, using an example of a generic COVID-19 mRNA vaccine versus no vaccination, largely based on CDC analysis from June 2021.

**2. Introduction**

Evaluation of B-R balance is a key element throughout the life cycle of a vaccine product. B-R assessment consists of evaluating the demonstrated benefits and risks of a vaccine and making a judgment on whether the expected key benefits outweigh the potential key risks associated with the vaccine’s expected use.7 B-R assessment supports decision-making during development milestones, regulatory approval, policy recommendations, and following identification of emerging safety (or effectiveness) signals, generally during post-authorization surveillance. Structured B-R assessment aims to provide an objective and defensible characterization of the B-R profile of vaccines. It provides transparent information to ensure informed public-health decision-making and helps maintain or regain trust in vaccination.

The field of B-R assessment has advanced considerably over the past two decades with the application of structured B-R frameworks; growing use of patient preference studies to support B-R assessments and numerous regulatory, academic and public-private partnership initiatives.8-15 With the increased diversity/complexity of the vaccine landscape with many vaccine products available, these advancements are being applied to vaccines.16,17 The advanced planning and standards of a structured B-R module can speed decisions, mitigate risks, provide transparency, simplify B-R communication and, therefore, improve trust in the vaccine development and review process. These considerations are even more important when there is an urgent need to approve a vaccine.

The module serves as a tool, applicable throughout the vaccine life cycle, for planning a vaccine B-R assessment and for conducting a defensible B-R assessment when data from clinical trials or post-marketing studies, including real-world evidence, become available. It enables sharing the evaluation via value trees, effects tables and graphical depictions of B-R trade-offs. It can be used by vaccine developers, funders, regulators and policy makers in high-middle or low-income countries to help inform decision-making and facilitate transparent communication and scientific discourse concerning development, licensure, deployment and other lifecycle decisions. These roles are of particular importance in epidemics and pandemics, as observed in the rapid regulatory decisions needed for COVID-19 vaccines.

The module is shown in table 1. An on-line supplement demonstrates how the B-R assessment module might be used in a real-world B-R calculation, using an example of a generic COVID-19 mRNA vaccine versus no vaccination, largely based on CDC analysis from June 2021.

# **3. Development of the module**

The B-R assessment module WG was formed by invited expressions of interest to the Brighton Collaboration network and to B-R experts. The WG consists of 24 members with a mixture of significant B-R, vaccine safety and vaccine regulatory expertise from industry, regulatory bodies, public health authorities, academia and consulting.

The latest version of the module can be accessed on [xxx](https://brightoncollaboration.us/v3swg/). Vaccine developers and funders are encouraged to use the module for their vaccine candidates in development, submission, or post-approval. Collaboration with the BRAVATO B-R assessment module WG is encouraged and questions about using the module are welcome by the WG.

An accompanying interactive visualization tool is being developed which will also be publicly posted on xxx.

**Instructions for completing the module**

The module includes detailed instructions for completing its technical content, which users are recommended to read before using. Sources for data used in the template should be added to the reference section at the end of the module. Unpublished original data are acceptable, though source and contact information should be included. In general, the module provides the opportunity to commenting on any concerns or limitations of the responses provided. Users can send questions about use of the module and suggestions for its improvement to bc-coordinator@taskforce.org.

We briefly describe each section of the module and give instructions for completing them. Detailed instructions are in the module itself.

Section 1: Decision Context

The decision context can be considered a description of the decision being made and a summary of key background assumptions. The decision context has four parts:

* 1A: In “Authorship and Role”, include the names of all authors of the assessment, the date the module is completed and whether the module is being used for advanced planning, reporting, or reviewing a B-R assessment. If the module is being updated, please provide the date of the original and the new version. These co-authors will be included in the final published module in the journal *Vaccine* once reviewed and approved by the B-R assessment module WG and in subsequent Wiki updates on the Brighton Collaboration website.
* 1B: In “Vaccine of Interest Topics”, describe the vaccine for which B-R is being conducted, including formulation/regimen, lifecycle stage and objective for the vaccine immunization program.
* 1C: In “Disease and Treatments Topics”, describe the disease of interest, population, nature of the condition for which the vaccine is intended, existing vaccines and therapies for this condition and the unmet medical need.
* 1D: In “High-level Benefit-Risk Topics”, describe the purpose/drivers for the B-R assessment being conducted, comparator(s), time horizon after vaccination over which events will be considered and subgroups of special interest.

Section 2: Identifying key endpoints for B-R (Developing a Value Tree)

Identify and define the benefit and risk endpoints used for B-R assessment, including whether the endpoints are key for B-R assessment, potential or identified, their clinical impact, rationale for inclusion and any limitations. Optionally, a B-R value tree figure can be included and replace the example value tree in Appendix 1.

Section 3: Data Sources

List each data source planned to be used for the B-R assessments or that were used for the assessment, the rationale for its selection, its role(s) in the assessment and limitations for B-R. Sources may include randomized controlled trials, observational studies, effectiveness studies, public health surveillance data (e.g., CDC), spontaneous reports, long-term efficacy or safety studies, pharmacovigilance databases, etc.

Section 4: Statistical Methods

Describe the approaches used to calculate rates and cases prevented or caused in Sections 4 and 5, based on data sources in section 3. Provide an outline level explanation sufficient for an informed reader to understand the general approaches used for each endpoint. As appropriate, describe the types of metrics used (e.g., incident proportions, incident rates), analysis sets, time horizon, strata adjustments, methods for pooling of data sources, 95% confidence intervals (CIs) or other measures of uncertainty. List the sensitivity analyses conducted using alternative incident rates and scenarios of special interest.

Alternatively, a report can be attached that demonstrates how the data entered in sections 4 and 5 were derived from data sources listed in section 3.

Section 5: Benefits Data

For each benefit, provide the data to be used in the assessment, including cases per 1,000,000 individuals vaccinated (or other population size) with the vaccine of interest, number of cases per 1,000,000 individuals on the comparator, number of cases caused or prevented by the vaccine of interest vs. comparator per 1,000,000 individuals, and assessment of strengths and uncertainties of evidence. If calculable and relevant to the B-R assessment, 95% confidence intervals for the number of cases caused or prevented can be included. Number needed to vaccinate (NNV) can optionally be included. If multiple comparators, infection/transmission rates, subgroups or scenarios are included, separate versions of the table should be completed for those endpoints affected. These separate tables can be omitted initially and completed as more data becomes available.

Section 6: Risks Data and Mitigations

Provide the same type of data for risks as for benefits in section 5. As appropriate, and if possible, describe the impact of mitigations from the Risk Mitigation Plan on the harms. Mitigations that apply to all combinations of comparators, infection/transmission rates, subgroups and scenarios can be described once in the first table and left blank in other tables. If mitigations can be described numerically, consider using scenarios to describe the risk data to characterize the impact of mitigations.

Summary effects tables with both benefits and risks, forest plots or other graphical depictions of the B-R data (e.g., cases prevented, and cases caused) can be included after section 6.

Section 7: Clinical Impact / Weighting (optional)

Preference studies can assess the relative desirability or acceptability of benefits and risks for alternative health interventions7. If available and relevant, optionally include patient or general population preference data, or other measures of the weight or clinical impact of each event (e.g., relative importance of endpoints, maximum acceptable risk for a given benefit). If preference data is used, a report on the assessment should be attached to the completed module.

Section 8: Integrated B-R Assessment

Using the information and evidence in all prior sections, provide a cogent, transparent, defensible qualitative assessment of whether benefits outweigh risks. If appropriate, use tabular and graphical summaries of benefits and risks that show cases prevented and cases caused for all key benefits and risks. When this module is being used to plan for a B-R assessment, ideally include mock ups of the planned tables and figures. When this module is used to conduct a B-R assessment, these displays will be populated with the data from sections 5 and 6.

Account specially for the severity of the condition, the current unmet medical need, strength of evidence, and statistical and other uncertainties. Also include the acknowledged limitations of the B-R evaluation, specifying, as much as possible, which potential risks and benefits could not be considered and the reasons why. If appropriate, a regulatory benefit-risk framework can be used to structure the integrated B-R assessment.11

**Limitations**

This paper describes the first release of the Brighton vaccine B-R module. The module accommodates a wide range of deterministic vaccine B-R approaches with accompanying sensitivity analyses. However, the module does not specifically support probabilistic approaches, simulations or transmission dynamics models. Such approaches can include reduced transmission due to herd immunity, limited vaccine uptake due to storage limitations, distribution challenges, vaccine hesitancy, the effects of alternative strategies (e.g., lockdowns) especially on subgroups such as children and the elderly, etc. Use of such models is not always required and is at the discretion of the analyst. If such models are used in a B-R assessment, they can be described qualitatively with the model(s) included in an appendix to this module.

There are also numerous tabular and graphical means with which vaccine B-R data can be displayed. The current module does not provide guidance on these displays. The accompanying interactive visualization tool supports a variety of effects tables, forest plots and related displays.

**Conclusions**

Recent advanced in the field of benefit-risk assessment are increasingly being applied to vaccines. The Brighton vaccine B-R module supports planning, conducting and reporting structured vaccine B-R assessments. With the use of this module, the Brighton Collaboration hopes to speed vaccine decisions, mitigate risks, provide transparency, simplify B-R communication and improve trust in the vaccine development and review process.

**Disclaimer:**

The findings, opinions and assertions contained in this consensus document are those of the individual scientific professional members of the working group. They do not necessarily represent the official positions of each participant’s organization. Specifically, the findings and conclusions in this paper are those of the authors and do not necessarily represent the views of their respective institutions.

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**Declaration of interests**

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: BL is an employee of Janssen Research and Development, LLC, is a stockholder in Johnson & Johnson and has a portfolio that at times includes other pharmaceutical, vaccine and health care-related companies. VB is an employee, and own shares options, of GSK. NB is an employee of and stockholder of Novavax, Inc. The remaining authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Table 1- BRAVATO Module for Vaccine Structured Benefit-Risk Assessment**

**Version 1: April 1, 2023**

***Background***

The decision to progress the clinical development, approve, recommend or use any medical intervention, be it a vaccine or a drug, is predicated on showing whether its benefits outweigh its risks. Formal assessment of benefit-risk (B-R) should help guide those decisions at each stage of the vaccine lifecycle. Systematic B-R assessment can provide transparent information to ensure evidence-based public health decisions and to maintain or regain trust in vaccination.

Formally, B-R assessment is the evaluation of the demonstrated benefits and risks of a vaccine or medical product and making a judgment as to whether the expected key benefits outweigh the potential key harms associated with its expected use.7 B-R assessment typically entails a systematic review of the relevant evidence available to date. In some cases, B-R assessment can be done qualitatively by visual inspection of effectiveness and safety data. In other cases, a structured framework approach or quantitative modelling is needed to make a transparent and defensible B-R decision. A range of approaches for vaccine B-R were reviewed in Arlegui et al. 202016, while several more recent examples can be found for the COVID-19 vaccines.18 Increasingly, there are guidelines for B-R, with a draft guidance issued by the FDA being one of the most recent.19

For vaccines, B-R is constantly evolving, as new effectiveness and safety data accrue post-authorization, disease transmission rates and government policies change, vaccine access and logistics improve, and mutations lead to viral or bacterial variants with different infectivity, virulence and susceptibility to vaccines and other preventative and treatment measures. The purpose of this module is to support a structured framework approach to vaccine B-R assessment.

***B-R Assessment Module***

This module was developed within the Brighton Collaboration’s Benefit-Risk Assessment of VAccines by TechnolOgy (BRAVATO) working group, consisting of experts with a wide variety of backgrounds. BRAVATO has developed and published standardized templates that summarize key considerations for vaccine B-R assessment.2-6 These templates summarize information on vaccine effectiveness and safety separately, without support for structured B-R assessment. This module provides that support.

This module can be used as an optional supplemental B-R add-on to these standardized Brighton vaccine templates or as an independent document for planning, conducting, or reporting vaccine B-R assessments. It can be used by developers, regulators, and public health agencies to help make informed decisions concerning development, licensure, deployment, and other lifecycle decisions of vaccines. It can be applied for B-R decisions throughout the vaccine lifecycle, both to describe an approach for B-R that will be conducted when data becomes available or as a formal assessment of B-R based on accumulated data. It can also be used as a “living document” to support revised B-R assessments as evidence accumulates.

The structured approach for vaccines B-R in this module is based on the growing use of structured B-R frameworks in regulatory reviews.8,16,19 A B-R framework is a set of guidelines, processes and tools to select evidence for a B-R assessment, organize that evidence, mathematically summarize it and communicate it to decision-makers. Specific roles for this module include supporting rapid conduct of defensible B-R assessments, transparent communication of those assessments, and facilitating scientific discourse among key stakeholders (including vaccine developers, funders, and regulators and policy makers) in high, middle or low-income countries. These roles are of particular importance in epidemics and pandemics, as observed in the rapid regulatory decisions needed for COVID-19 vaccines for Emergency Use Authorization (EUA), Conditional Marketing Authorisation (CMA) and Emergency Use Listing (EUL) decisions once adverse events were noted.

***When to use this module***

This module can be used at any point in development – when planning a vaccine B-R assessment, when conducting a B-R assessment after top line clinical trial data are available, when reviewing a B-R assessment, or for post-approval B-R assessment as data accrues from real-world use. While many specifics will differ between vaccine platforms, the approach to B-R is generally independent of the platform.

***How to use this module***

If used along with the primary [BRAVATO](https://brightoncollaboration.us/bravato/) vaccine template, information can be referenced rather than duplicated. Sections and specific questions deemed not relevant to the B-R assessment for a particular vaccine can be left blank. When the module is used to plan for a future B-R assessment, the data sections will be left blank. It should be noted in the module, when the document is used for an assessment and data are accumulating but not currently available..

As noted above, B-R assessment is a dynamic process, as the evaluation needs to be updated as feasible each time significant new data emerge. It should be considered as an iterative process. However, there are situations where immediate decisions need to be made at an early phase with several uncertainties or unknowns, such as the detection of a safety signal or B-R for an EUA during a pandemic or epidemic. B-R for EUA data will generally have considerably more unknowns than B-R for submission after pivotal phase 3 studies. This presents challenging situations for all affected parties. Decision-making is a dynamic process that should be based on the best evidence available at the time a decision is required, and the unknowns and assumptions should be made transparent to maintain public confidence in both the decision-making process and public health use of the vaccine in question. It should also be kept in mind that B-R decisions and actions may differ based on country / regional needs, including vaccine supply, disease prevalence and severity, disease burden, vaccine effectiveness, vaccine safety and the availability of alternative vaccines or treatments, which may differ between low- and middle-income (LMICs) and high-income countries (HICs).

Accordingly, this module can be used as a living document. Sections can be skipped initially, when there are many unknowns, and incrementally completed as data accumulate. The parts of the module for which data are unknown can be left blank, potentially with comments that indicate plans to include that information when available. As data accumulate with vaccine usage, these parts can be more fully completed. The module can also be used as a collective repository for a growing body of information for B-R assessment. In that case, it can be used in a shared, collaborative manner, with different stakeholders adding or modifying entries as more data becomes available.

The Statistical Methods section of this module provides a place to describe data sources used and the general approach by which the key effectiveness and safety data are calculated. **This module is not intended to guide users in conducting the statistical or epidemiological calculations that provide the data used in B-R**. These calculations should be conducted by individuals with sound statistical and/or epidemiological skills. A report detailing these calculations can be attached to this module. Models that account for distribution, access, vaccine stability, vaccine hesitancy, herd immunity and other indirect effects can be included in these reports as well, with the resulting impact on effectiveness and safety included in the data entered.

Although other aspects of manufacturing, quality, and implementation can play a role in the B-R assessment of a vaccine/vaccination program, those considerations are out of the scope of the initial version of this module. However, they can be included in the attached calculations if appropriate. Patient preference studies may also be included in attached materials, providing a means to incorporate the patient perspective on acceptable B-R trade-offs in the assessment. Section 7 allows summarizing such studies.

Note that, in the questions below, an “e.g.,” indicates that what follows is a list of example responses. Those lists are not exhaustive, and other responses can be used instead.

This module also includes a glossary of key terms. References for the vaccine being assessed should be included in a separate reference section at the end of this module.

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| **Section 1: Decision context**: |

Specify the context for this benefit-risk (B-R) assessment. The context is a description of the decision being addressed and the role for this module, i.e., whether the module is being used for advanced planning of a B-R assessment, to report a completed assessment or to review a completed assessment. The decision context can be considered a summary of key background assumptions including the decision to be made, the comparator(s), the nature and clinical impact of the indication/disease, the expected changes in disease incidence over time, and unmet medical need (the key characteristics and limitations of other existing vaccines or treatments for this indication/disease, if any). Additional details include the assumed time horizon for the B-R assessment, and subgroups of specific interest for the assessment.

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| --- | --- | --- | --- |
| **1A. Authorship and Role** | | | |
| **Author(s) and affiliation(s)** |  | | |
| **Date completed/updated**[[1]](#footnote-1) |  | | |
| **Module role:** Is this module currently being used to plan, report or review a B-R assessment? | Select one:   * Planning * Reporting * Reviewing | | |
|  | | | | | |
| **1B. Vaccine of Interest Topics** | | | | | |
| **Question** | | | **Responses** | **Comments** | |
| **Vaccine of Interest:** What is the vaccine being studied (type or platform, producer)? | | |  |  | |
| **Formulation / Regimen / Schedule of the vaccine of interest:**  Specify the formulation (e.g., oral, IM, IV, IN), schedule (e.g., primary series, booster, homologous or heterologous priming, homologous or heterologous boosting) | | |  |  | |
| **Vaccine Development/Lifecycle stage:**  For what lifecycle stage is this B-R assessment? (e.g., early development, phase 3, submission, emergency use authorization (EUA)/conditional marketing approval (CMA)/emergency use listing (EUL), post-approval, public health decision-making) | | |  |  | |
| **Objective of the vaccine of interest immunization program:**  What are/were the key objectives of the immunization program for the vaccine of interest? If the objective varies by region, describe the objective/s and regions. (e.g., mortality prevention, severe disease (i.e. hospitalization) prevention, preventing health system overload (i.e. hospitalization, ICU), achieving herd immunity, eradication for specific regions, global eradication, preventing outbreaks, etc.) | | |  |  | |
|  | | | | | |
| **1C. Disease and Treatments Topics** | | | | | |
| **Question** | | | **Responses** | **Comments** | |
| **Disease of interest:**  What is the disease (or indication) for which the vaccine will be /is used? | | |  |  | |
| **Population of interest:**  What is the population intended for this vaccine benefit-risk assessment? (e.g., adults ≥18 years worldwide, children 12-17 years). Note that subgroups of interest are listed below.  If relevant, describe potential differences between the trial population and the target population (e.g., difference in baseline risk due to higher level of comorbidities in the target populations in a region / country)  Note: If the rollout will be to prioritized subgroups and gradually expanded, consider whether these subgroups should be listed as subgroups of special interest below. | | |  |  | |

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| --- | --- | --- |
| **Nature of condition:** Briefly describe the natural course of the condition, illness or disease the vaccine is intended to prevent. How serious is this condition? (e.g., requiring hospitalization, severe or life threatening, endemic potential, epidemic potential, pandemic potential, worsening antimicrobial resistance, long term effects of the disease). Note important uncertainties in these characteristics that impact on B-R. |  |  |
| **Existing vaccines and therapies**:  What vaccines, treatments or therapies are currently used to treat or prevent this condition (e.g., existing vaccines, therapeutic medicines, prophylactic medicines) |  |  |
| **Unmet medical need:**  Briefly describe the limitations of currently available therapies for preventing/treating the condition. What are their key adverse effects and uncertainties? Is there sufficient supply of these alternatives and can they be accessed by those who choose to use them?  If relevant, indicate if there are any important differences by region or country for which the vaccine is being considered. Note: It may be easier to complete a separate module for regions / countries with several important differences. |  |  |

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| **1D. High-level Benefit-Risk Topics** | | |
| **Question** | **Responses** | **Comments** |
| **Purpose and drivers for the B-R assessment:**  What is driving the decision to perform this B-R assessment at this time? (e.g., presentation to health or regulatory authorities, identification of a new safety signal post-approval, emergence of a special population of interest, changes in the pathogen (severity, transmission), changes in vaccine effectiveness, concerns with waning immunity, a new competitor vaccine, development of a booster, etc.) |  |  |
| **Comparator(s)**  To what vaccine(s), treatment(s) or therapy(ies) is the vaccine of interest being compared in the B-R assessment? (e.g., no vaccine, other established vaccine, therapies such as monoclonal antibodies (prophylactic or therapeutic) or prophylactic agents), isolation, etc. |  |  |
| **Time horizon for B-R assessment:** Over what time period after vaccination are B-R assessment data being considered? (e.g., six months from primary dose administration date, 1 year from first boost administration date; if in a clinical trial - to end of trial, discontinuation, or follow-up?) |  |  |
| **What is the justification for this time horizon?**  If there is a series of doses, indicate when the time horizon’s data collection period starts (e.g., after first dose, after second dose, etc.) |  |  |
| **Subgroups of special interest:** List subgroups for which B-R assessment is of particular interest (e.g., age, sex, occupation, comorbidities, concomitant medications, concomitant diseases, immune compromised, special settings (schools, long term care), pregnant, neonates, infants, lactating)  If not clear from a subgroup’s name, provide the definition of the subgroup (e.g., age group considered for adolescents, adults, or elderly).  If not self-evident, describe why a subgroup is of special interest.  Indicate if any of these subgroups is likely to be especially small or difficult to study. |  |  |
| Subgroup 1 |  |  |
| Name |  |  |
| Definition |  |  |
| Subgroup 2 |  |  |
| Name |  |  |
| Definition |  |  |
| Subgroup 3 |  |  |
| … |  |  |

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| **Section 2: Identifying key endpoints for B- R (Developing a Value Tree)** |

Identify and define the **key** benefits, **key** risks and other endpoints used for B-R assessment.

Considerations for identifying which endpoints to use for a B-R assessment:

* Clinical trials, registries and observational studies measure numerous endpoints. For B-R, only a subset of endpoints is used - those considered “key” or most likely to have a meaningful impact on the B-R profile. For example, typically only a few endpoints are needed from a larger set of different measures of the same event or among events that are causally dependent. For this reason, **the list of adverse events in risk management plans is typically broader than needed for B-R**. Endpoints whose events are mild, of short-duration and reversible are generally not key for B-R. Often, using endpoints for hospitalized, severe and fatal events is sufficient for B-R. Potential risks (and potential benefits) may also be considered if important for the assessment. In all cases, the rationale used to select the key endpoints should be clearly described. The rationale for excluding endpoints that might have reasonably been included should also be clearly described. Figures 1 and 2 provide some insights into categorizing outcomes by whether they are key/not key and identified/potential.
* Reduction of complications from the disease or disease-related adverse events (e.g. post-acute sequelae) may be regarded as benefits in the benefit-risk balance since the vaccine will reduce their frequency or severity. In contrast, adverse events caused by the vaccine are regarded as risks (e.g., a vaccine may prevent death and hospitalization from the disease caused by a virus, while the vaccine may cause death and hospitalization due to a side effect. These endpoints should be named distinctly to reduce confusion - e.g., “infection-related death” and “vaccine-related death”).
* To enable a clear and fair comparison of the benefits and risks, **it is generally preferable to use outcomes of comparable clinical impact for benefits and risks** (e.g., when risks are immunization-induced hospitalization, ICU admissions or death,

benefits could be reduction of infection-induced hospitalization, ICU admissions or death). However, this is not always possible, and the clinical impact of the benefit and risk events should be described in the endpoint lists below and used to support the Integrated Benefit-Risk Assessment in Section 8. The preference data in Section 7 can also be used to provide preference or other weights for endpoints.

* While adverse events with very low frequency are typically not included in drug B-R assessment, they are often included in vaccine B-R assessment, particularly if they are serious, since the (often very large) population being vaccinated is not suffering from the disease of interest and, thus, has a very low tolerance for adverse events, or the vaccinations may be mandatory for children, which also raises concern for rare adverse events.
* The rationale for which endpoints are considered relevant to the B-R assessment (“key” endpoints) may depend on the objectives of the immunization program (summarized in the Decision Context). The endpoints considered key for a B-R assessment may also differ for particular applications of the module (e.g., for a specific subgroup that has a different risk of disease complications or death).
* Avoid double-counting of an event under more than one endpoint. For example, the endpoint all-cause death and the endpoint stroke both include fatal stroke. To avoid double-counting, stroke could be replaced by non-fatal stroke. In cases where double-counting is inherent in common endpoints for a disease or when it is not possible to completely separate the endpoints, the double-counting should be noted in the analysis plan and acknowledged as a limitation of the analysis.
* While economic benefits and access issues are generally not incorporated into drug B-R assessment, they may have roles in vaccine B-R assessment due to their potential impacts on vaccine storage, stability, and access – particularly in LMICs

To assist with this step, consider including a value tree, a graphical depiction of the benefits, risks and other endpoints used in a B-R assessment (example in Appendix 1). The endpoints must be included below. The order in which endpoints are shown in the value tree can be used to support the B-R assessment - endpoints can be grouped by anatomy or function and can be placed in order from most clinically impactful to least clinically impactful (e.g., in order of clinical impact: death, hospitalization, severe disease, any infection). The value tree in Appendix 1 can optionally be replaced with the value tree for this assessment.

In the table below, endpoints can be placed in the same order as in the value tree, with rows added to show how endpoints are grouped. Alternatively, endpoints can be placed in order of decreasing clinical impact per event. The endpoints should be sequenced to best support the B-R assessment. Extend the table as needed to for additional endpoints.

Considerations for definition of endpoints

* Include the precise definition of the event counted within an endpoint, both for benefits and risks. For example, for hospitalizations caused by the disease prevented by the vaccine, how is this hospitalization distinguished from hospitalizations for other causes, or for an adverse event, as appropriate, indicate whether the Brighton Level 1, 2 or 3 definition is used. If an endpoint is labelled “severe” or “serious”, provide the precise definition of severe/serious used.
* if this information is unavailable, indicate what is known about the events from each data source used. In many cases, investigators decide to categorize hospitalized events as “serious”, which is generally justifiable and saves resources needed to classify the events (Note that, for adverse event reporting in Vaccine Adverse Event Reporting System (VAERS), a hospitalized event is defined as “serious”).20
* For an endpoint measured with an exposure-time rate (event or events per person-year), indicate whether the events are counted once (at least once) per individual or all events that an individual experiences are counted instead. The challenges of obtaining reliable adverse event information and the practical limitations on research resources often lead towards counting events only once per individual. However, this decision could become more complex when events (e.g., adverse event hospitalizations) are investigated for multiple vaccine doses, due to difficulties in assigning a late hospitalization to either dose.
* Indicate the time period from vaccination over which events are collected, the benefit window or risk window for benefits and/or risks, respectively. (If unknown, a reasonable convention for benefits is to use a conservative 6-month period). For risks, investigators can often use prior knowledge regarding the time window (risk window) post-vaccination during which the event can be considered as vaccine-associated (if unknown, reasonable conventions for most risks could be 30 or 42 days post each vaccine dose). Consider including the benefit window or risk window in the endpoint name to lessen ambiguity when communicating results or when multiple windows for the same endpoint are studied.
* Indicate which subjects are assessed in the endpoint. For clinical trials, this could be an intent to treat analysis set, a treatment emergent analysis set, a safety analysis set, etc.
* Indicate the type of measurement. This module uses cases seen in a hypothetical vaccinated population (e.g., 1,000,000 individuals). However, measurements may be proportions or incidence rates and may be in units of decimal (0 - 1), percent (0 - 100) or events in any size of hypothetical population (e.g., 100,000 individuals vaccinated).
* Describe any known limitations for the endpoint itself (e.g., surrogate outcome (a biomarker vs. clinical event that it may reflect), inconsistent reporting of events in different regions, potential misclassification of the endpoint, hospitalizations that may include those due to non-vaccine/non-infection-related events). Limitations on the data sources used for endpoints are described in Section 3: Data Sources.
* Note that the definition of an endpoint is distinct from the statistical metrics that may be computed from it. For example, an endpoint may be defined as a proportion, while the statistical metric could be the risk difference between vaccine and comparator.

|  |  |  |
| --- | --- | --- |
| **Question** | **Responses** | **Comments** |
| **Benefit #1** | | |
| Name  (e.g.  - Any death (or any death within a given time period after vaccination, e.g., 30 days)  - Death due to target pathogen infection  - ICU admission  - Hospitalization due to infection  - Serious disease, if different from hospitalization  - Symptomatic infection  - Asymptomatic infection (if detection is possible)  - Long-term sequelae (e.g., major adverse coronary events, long COVID following SARS CoV-2 infection) |  |  |
| Definition and benefit window (per Statistical Analysis Plan).  (e.g., Number of subjects hospitalized with physician-confirmed infection within one year of dosing per 1,000,000 individuals vaccinated) |  |  |
| Key or not key for B-R and rationale |  |  |
| Identified or potential benefit and rationale |  |  |
| Clinical impact / severity (e.g., most hospitalizations last at least a few days and might require time in an ICU) |  |  |
| Rationale for inclusion (why is this endpoint included in B-R, if not obvious) |  |  |
| Limitations (cannot be avoided) and uncertainties (potentially mitigatable) of this endpoint (e.g. the disease could be difficult to diagnose, not all events may be reported, mild events cannot be obtained reliably). |  |  |
| **Benefit #2** | | |
| Name |  |  |
| Definition and benefit window |  |  |
| Key or not key for B-R and rationale |  |  |
| Identified or potential and rationale |  |  |
| Clinical impact / severity |  |  |
| Rationale for inclusion |  |  |
| Limitations of this endpoint |  |  |
| **Benefit #3** | | |
| … |  |  |
|  | | |
| **Risk #1** | | |
| Name  (e.g., fatal or life-threatening adverse reactions, severe or serious adverse events following immunization (AEFIs) such as intussusception, myocarditis, Guillain-Barre Syndrome (GBS), anaphylaxis, Bell’s palsy, neuritis, convulsion, thrombocytopenia, vasculitis, anaphylaxis) |  |  |
| Definition and risk window, if relevant (e.g., Number of TTS cases as per the Brighton probable case definition within 28 days after vaccination (primary or boosters) per 1,000,000 vaccinated individuals in the ITT analysis set, or Number of myocarditis cases within days 0-7 post-COVID-19 vaccination per 1,000,000 vaccinated individuals) |  |  |
| Key or not key for B-R and rationale |  |  |
| Identified or potential and rationale |  |  |
| Clinical impact / severity (e.g., most events are mild to moderate in severity and can be reversed by over-the-counter treatments) |  |  |
| Rationale for inclusion |  |  |
| Limitations (cannot be avoided) and uncertainties (potentially mitigatable) of this endpoint (e.g., not all events may be reported) |  |  |
| **Risk #2** | | |
| Name |  |  |
| Definition and risk window, if relevant |  |  |
| Key or not key for B-R and rationale |  |  |
| Identified or potential and rationale |  |  |
| Clinical impact / severity |  |  |
| Rationale for inclusion |  |  |
| Limitations and uncertainties of this endpoint |  |  |
| **Risk #3** | | |
| **…** |  |  |

|  |  |
| --- | --- |
| **Other risks considered** | |
| **Question** | **Responses** |
| **Other risks considered**  Were other risks considered and not included in the B-R assessment? | * Yes * No |
| **Which risks were considered?** |  |
| **Rationale for exclusion** |  |

|  |
| --- |
| **Section 3: Data sources**: |

Data sources planned to be used for the B-R assessments or that were used for the assessment, their characteristics, and limitations. As appropriate, describe the general method and criteria used to identify the data sources. List each data source separately and provide the rationale for its selection, its role in the assessment, and its limitations for B-R. Under limitations, if important for the B-R analysis, indicate if any subgroups of interest or scenarios of interest are not included or identified in any of the data sources. These roles for the data sources can be described in the Statistical Methods section below.

Sources may include randomized controlled trials, observational studies, effectiveness studies, public health surveillance data (e.g., CDC), spontaneous adverse event reports, long-term efficacy or safety studies, pharmacovigilance databases, etc. Clinical trial or other data reported through literature publications or public presentations should be clearly identified with the manuscript website or presentation information to differentiate those data reported from a trial database and summarized in a non-public report (e.g., clinical study report, integrated summary, clinical overview, etc.).

|  |  |  |
| --- | --- | --- |
| **Source** | **Role in B-R assessment** | **Rationale and Limitations for B-R** |
|  |  |  |
| … |  |  |

|  |
| --- |
| **Section 4: Statistical methods**: |

Describe the approaches used to give rates and cases prevented or caused in Sections 4 and 5. Alternatively, a report can be attached that demonstrates how the data entered in sections 4 and 5 were derived from data sources.

As appropriate, describe the types of metrics used (e.g., proportions, exposure-time rates), analysis sets, time horizon, strata adjustments, methods for pooling of data sources, 95% confidence intervals or other measures of uncertainty and sensitivity analyses. If different methods are used for different endpoints, the information can be provided for endpoints in groups assessed in a similar manner. Show how data are converted to be expressed as cases per 1,000,000 individuals vaccinated, if appropriate. Note that the denominator of 1,000,000 individuals is shown for providing a public health context to the data and to ease interpretation of cases caused and prevented, however, any useful denominator may be used.

List the sensitivity analyses conducted. In particular, (i) alternative incidence rates (due to varying transmission intensities, different data sources) and (ii) scenarios of special interest. Scenarios[[2]](#footnote-2) refer to combinations of assumptions that provide a sensitivity analysis to baseline assumptions (see glossary). Assessing B-R for different scenarios provides a sensitivity analysis to baseline assumptions. Any set of properties can be used to define a scenario.

This module supports B-R assessment based on the rates and severities of benefits and risks experienced by vaccine recipients. Deterministic or probabilistic population level B-R models can include reduced transmission due to herd immunity, limited vaccine uptake due to storage limitations, distribution challenges, vaccine hesitancy, the effects of alternative strategies (e.g., lockdowns) especially on subgroups such as children and the elderly, etc. If such models are used in the B-R assessment, they can be described qualitatively with the model(s) included in an appendix to this module. A forecast/model can potentially be used to extrapolate data to a group for which information is unavailable.

|  |
| --- |
| **Overview of approach used to give data in Sections 5 and 6** |

|  |  |
| --- | --- |
| **Question** | **Responses** |
| **Date range for data used in analysis:** (Over what time period was the data used in these analyses collected?) |  |
| **Vaccine Effectiveness**  (What assumptions are used for vaccine effectiveness? What is the rationale? If there are multiple periods with different levels of effectiveness assumed, describe the assumptions and the supporting rationale. |  |
| **Type of measurements:** e.g., incidence rate, incidence proportion, case count per 1,000,000 vaccinated |  |
| **Population-level modelling:**  Does this analysis include population-level models (see glossary)? | * Yes * No |
| **Population-level model summary** (if included) |  |
| Adjustment for strata, pooling of data sources, approach for calculation of the 95% CI) |  |
|  | |
| **Alternative incidence rates (due to varying transmission intensities):**  If the analyses for B-R data are done under the assumption of several different rates by which the pathogen targeted by the vaccine is infecting the vulnerable population, or different rates of transmission for the virus, name and define the alternatives and their underlying assumptions (e.g., high transmission intensity, based on US hospitalization rate in week of May 1, 2021). Add rows as needed. | |
| Transmission rate 1 | |
| Name |  |
| Definition |  |
| Transmission rate 2 | |
| … |  |
|  | |
| **Scenarios of special interest**  Scenarios refer to combinations of assumptions that provide a sensitivity analysis to baseline assumptions (see glossary). They may serve as best-case and worst-case scenarios. For example, a best-case scenario might have 100% reporting rate, 80% vaccine effectiveness and no waning of immunity, and a worst-case scenario might have 25% reporting rate, 60% vaccine effectiveness and immunity reducing to 25% after 6 months (see Glossary). List each scenario for which B-R assessment is of particular interest and their definition. Add rows as needed. | |
| Scenario 1 | |
| Name |  |
| Definition |  |
| Scenario 2 | |
| … |  |

|  |
| --- |
| **Section 5: Benefit Data**: |

**For each benefit listed in the value tree (Section 2)**, provide the clinical or observational data to be used in the B-R assessment, including number of cases per 1,000,000 individuals vaccinated with the vaccine of interest, number of cases per 1,000,000 individuals on the comparator, number of cases caused or prevented by the vaccine of interest vs. comparator per 1,000,000 individuals, and assessment of strengths and uncertainties of evidence. If they can be calculated and are relevant to the B-R assessment, 95% confidence intervals for the number of cases caused or prevented can be included as a reflection of statistical uncertainty. Column headings can be changed as needed to reflect the type of data entered. Number needed to vaccinate (NNV) can optionally be included.

If multiple comparators, infection/transmission rates, subgroups or scenarios were listed above, separate versions of the table can be completed for those endpoints affected. These separate tables can be omitted initially and completed as more data becomes available. The titles for the tables can omit the comparator, subgroup, transmission rate and/or scenario if there are no alternatives for each.

The Notes, Uncertainty and Strength of Evidence can optionally be used to provide additional points relevant to the data provided in that row. For example, the clinical impact of the hospitalizations (e.g., median days in ICU) and whether the events are reversible or predictable. These notes can reference the Statistical Methods section for relevant technical details.

While this module does not explicitly support the modelling and simulation needed for population-level B-R, information on population-level benefits and risks could be described below and supported with a supplemental report. These may include indirect benefits such as herd immunity, avoiding social and economic disruption (e.g., school closure, workday lost), isolation, reduced physical activity, weight gain, accrual of social disadvantages because of school closures, and poor outcomes for other diseases not treated because of the health system overload (e.g., delayed screening or surgeries).

This table should be completed for each combination of comparator, infection/transmission rate, subgroup, and scenario

**Table 1 Benefits for first set of comparator, subgroup, transmission rate and scenario**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Proportion or Rate (/1,000,000)** | | | | | |  |
| **Endpoint** | **Vaccine of interest** | **Comparator** | **Cases prevented** | **95% CI lower limit** | **95% CI upper limit** | **NNV\*** | **Notes, Uncertainty and Strength of Evidence** |
|  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |

\*NNV = number needed to vaccinate

Transmission rate definition, Scenario definition

**Table 2 Benefits for second set of comparator, subgroup, transmission rate and scenario**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Proportion or Rate (/1,000,000)** | | | | | |  |
| **Endpoint** | **Vaccine of interest** | **Comparator** | **Cases prevented** | **95% CI lower limit** | **95% CI upper limit** | **NNV\*** | **Notes, Uncertainty and Strength of Evidence** |
|  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |

\*NNV = number needed to vaccinate

Transmission rate definition, Scenario definition

**Table 3 Benefits for third set of comparator, subgroup, transmission rate and scenario**

…

|  |
| --- |
| **Section 6: Risk Data and mitigations**: |

**For each risk listed in the value tree (Section 2)**, provide the clinical or observational data to be used in the B-R assessment, including number of cases per 1,000,000 individuals vaccinated with vaccine of interest, number of cases per 1,000,000 individuals on the comparator, number of cases caused or prevented by the vaccine of interest vs. comparator per 1,000,000 individuals, and your assessment of strengths and uncertainties of evidence. If available and relevant to the B-R assessment, 95% confidence intervals for the number of cases caused or prevented can be included as a reflection of statistical uncertainty. Column headings can be changed as needed to reflect the type of data entered. Number needed to harm (NNH) can optionally be included.

As appropriate, and if possible, consider the impact of risk mitigations from the Risk Mitigation Plan and describe the impact of these mitigations on the harms. If mitigations can be described numerically, consider using scenarios to describe the risk data when including the impact of the mitigation.

Table titles or footnotes can be modified to include relevant information, such as the risk windows used.

For other details, see the instructions under Section 5: Benefits Data

**This table should be completed for each combination of comparator, infection/transmission rate, subgroup and scenario**

**Table 1 Risks for first set of comparator, subgroup, transmission rate and scenario**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Proportion or Rate (/1,000,000)** | | | | | |  |
| **Endpoint** | **Vaccine** | **Comparator** | **Cases caused** | **95% CI lower limit** | **95% CI upper limit** | **NNH\*** | **Notes, Uncertainty and Strength of Evidence** |
|  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |

\*NNH = number needed to harm

Transmission rate definition, Scenario definition

**Table 2 Risks for second set of comparator, subgroup, transmission rate and scenario**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Proportion or Rate (/1,000,000)** | | | | | |  |
| **Endpoint** | **Vaccine** | **Comparator** | **Cases caused** | **95% CI lower limit** | **95% CI upper limit** | **NNH\*** | **Notes, Uncertainty and Strength of Evidence** |
|  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |

\*NNH = number needed to harm

Transmission rate definition, Scenario definition

**Table 3 Risks for third set of comparator, subgroup, transmission rate and scenario**

**…**

|  |  |  |
| --- | --- | --- |
| **Mitigation** | **Endpoints Affected** | **Notes, Uncertainty and Strength of Evidence** |
|  |  |  |
|  |  |  |

**Mitigations for Risks**

|  |
| --- |
| **Section 7: Clinical impact / weighting**: **(optional)** |

Patient or general population preference data, if available and relevant, or other measures of the weight or clinical impact of each event. (e.g., relative importance of endpoints, maximum acceptable risk, choice share, preference subgroups). If preference data is used, a report on the assessment should be attached to this completed module.

Note that patient and population preferences in LMIC and HIC may differ substantially.

|  |  |
| --- | --- |
| **Question** | **Responses** |
| Is (or will) a preference study being used to support the B-R assessment | Yes / no |
| If yes: | |
| Whose preferences were assessed? (e.g., Subjects with acute onset of disease) |  |
| Research question addressed with study |  |
| What preference method was used? (e.g., qualitative interviews, discrete choice experiment) |  |
| Summary of key results used to support the B-R assessment |  |
| Publication or report on preference study, if any |  |

|  |
| --- |
| **Section 8: Integrated B-R Assessment** |

Using the information and evidence in all prior sections, provide a cogent, transparent, defensible assessment of whether benefits outweigh risks.

Typically, vaccine B-R uses tabular and graphical summaries of benefits and risks that show cases prevented and cases caused for all key benefits and risks. The summaries are then interpreted cumulatively using clinical judgment to assess the clinical impact of the various cases prevented and events caused. One simple example would be to present tables/figures comparing the number of disease-associated hospitalizations and deaths prevented by vaccinating a given population with the number of adverse events-associated hospitalizations and deaths caused by the vaccine in the same population during the pre-specified time period.

When this module is being used to plan for a B-R assessment, provide mock ups of the planned tables and figures. When this module is used to conduct a B-R assessment, these displays will be populated with the data in sections 5 and 6.

Account for strength of evidence, statistical and other uncertainties, and the context of the severity of the condition and the current unmet medical needs for patients. If the uncertainty is, for example, in the number of deaths caused by the disease that the vaccine is trying to prevent, then present alternative scenarios (sensitivity analyses) showing a best and worst-case scenario. For reporting a B-R assessment, provide a textual description of the user’s interpretation of the B-R data and whether the cumulative effects of benefits outweigh the cumulative effects of the risks. This description should be transparent and defensible to those not steeped in the B-R methodology and should account for strength of evidence, statistical and other uncertainties, and the context of the severity of the condition and the current unmet medical needs for patients.

Also include the acknowledged limitations of the B-R evaluation, specifying, as much as possible, which potential risks and benefits could not be considered and the reasons why. Note any limitations that may result is a mixture of clinical trial and on epidemiology data are used in the assessment, as trial data may not be representative of real-world use.

If appropriate, a regulatory benefit-risk framework (Appendix 2) can be used for the integrated B-R assessment (e.g. <https://www.fda.gov/media/152544/download>).

**Integrated B-R assessment**

|  |
| --- |
|  |

**Glossary**:

* **Benefit**: Benefits are the favourable effects of a medical product. Most commonly, a benefit is a clinical benefit, a positive clinically meaningful effect of an intervention such as preventing pathogen-induced death, hospitalizations or complications and reducing disease transmission. Benefits may also be patient-reported outcomes or other important characteristics of the medical product, such as the dosing regimen or route of administration that may impact patient compliance.7,19,21-26
* **Benefit-risk (B-R) Assessment**: Evaluation of the demonstrated benefits and risks of a vaccine or medical product and making a judgment as to whether the expected key benefits outweigh the potential key harms associated with its expected use.7,9,19,21,27-29
* **Benefit-risk Framework**: A structured approach to conducting a benefit-risk assessment. A framework itself is generic and can be applied to a wide range of assessment. There are several examples in current use, including COBRA (Consortium on Benefit-Risk Assessment), FDA BRF (US FDA Benefit-Risk Framework), SABRE (Southeast Asia Benefit-Risk Evaluation) and PhRMA BRAT/UMBRA (PhRMA Benefit-Risk Action Team / United Methodologies for Benefit-Risk Assessment).8,9,19,22,29,30
* **Benefit window**: For a specific benefit endpoint, the time after vaccination in which events are included in rate or risk calculations.
* **Decision context**: Defining the circumstances underlying the decision being made. For medical treatment benefit-risk assessment, the decision context typically includes the treatment/dose/regimen, comparators, indication, population, time horizon, decision maker and subgroups of interest.8,9,19,22,29
* **Identified (Benefit or Risk) Outcome**: Clinical outcomes for which there is sufficient scientific evidence that they are caused by the medicinal product. Evidence may be derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature.25,31
* **Individual level B-R assessment:** Assessments based primarily on the rates and severities of the benefits and risks that an individual experiences.26
* **Key (Benefit or Risk) Outcome**: Outcomes which are likely to have an impact on the Benefit-Risk balance of a therapy or vaccine. Key benefit outcomes are favourable effects generally assessed by primary and secondary endpoints across the studies in a development program. Key risk outcomes are unfavourable effects that are important from a clinical and/or public health perspective in terms of their frequency and/or severity and/or seriousness.19,21,31
* **Non-Key Outcome**: Low priority outcomes which do not contribute substantially to selection of therapy by stakeholder (patient, health care provider, Regulatory agency) versus other therapeutic options for the treatment of disease condition in a specific population
* **Number needed to harm (NNH)**: Number of individuals that must be vaccinated to see one additional harmful (risk) event25
* **Number needed to vaccinate (NNV)**: Number of individuals that must be vaccinated to prevent one additional case of disease25
* **Population level B-R assessment:** B-R models that account for transmission, herd immunity, hesitancy, distribution, storage, and other issues that are relevant to population-level models, in addition to rates and severities of the benefits and risks that the individual experiences.23,26
* **Potential (Benefit or Risk) Outcome**: Clinical outcomes for which there is scientific evidence to suspect the possibility of a causal relationship with the medicinal product, but where there is currently insufficient evidence to conclude that this association is causal.25,21
* **Preference**: A statement of the relative desirability or acceptability to patients of specified alternatives or choice among outcomes or other attributes that differ among alternative health interventions. Preferences studies can yield qualitative information to support qualitative B-R assessment and quantitative weights that can support quantitative B-R assessment.7,8,28,32,33
* **Risk**: Risks are adverse events and other unfavourable effects associated with a medical product. Risks for vaccines most typically include injection site reactions, serious adverse events shortly after vaccination such as anaphylaxis, and adverse events that occur in the days or weeks following vaccination that may result in hospitalization or death. Risks may also include interactions with drugs or other vaccines. Factors such as potential misuse, abuse, or diversion of the product may also be considered risks.7,20,21,25,26,30,31,34,35
* **Risk window**: For a specific risk endpoint, the time after vaccination in which events are included in rate or risk calculations.
* **Scenario**: A set of assumptions for key properties (assumptions) that span a range of interest. Assessing B-R for different scenarios provides a sensitivity analysis to baseline assumptions. Any set of properties can be used to define a scenario. For example, three scenarios spanning a range of vaccine efficacy and reporting rates can include:

**Table

Description automatically generated**

* **Subgroup**: A subset of the study population or study sample defined by specific baseline characteristics. For example, demographic subgroups are commonly defined by subject’s sex, race, and age.
* **Time horizon**: Time period during which events are included in the B-R assessment.9 The horizon should be no smaller than the largest of the benefit windows and risk windows.
* **Uncertainties**: Limitations in strength and/or quality of the evidence with respect to aspects of disease and/or patient population, treatment options, benefits, risks, and data sources.19,25,31 Examples include:
  + Frequency of rare serious adverse events
  + Longevity of vaccine efficacy beyond that studied to date
  + Statistical uncertainty on rates and on cases caused/prevented.
  + Limits on scientific understanding of the patient population and natural history of the condition
  + Aspects of the program or study design, such as the population, choice of controls, endpoints, duration, and data sources, as well differences between the clinical study and real-world use
  + Reliability of the estimates of benefit or risk based upon variability in estimated effects due to trial conduct such as missing data, poor protocol compliance, etc.
  + Limited understanding of the effects of the drug that may be used in combination with existing therapies (e.g., beneficial adjunctive effect, adverse drug-drug interactions, etc.).
  + Proposed risk management strategies (e.g., patient monitoring) not studied in clinical trials, or that have been studied in clinical trials but would be difficult to implement in practice.
  + Limited patient input on disease burden and unmet medical needs, meaningfulness of potential benefits, and acceptability of risk trade-offs and uncertainty
  + Introduction of a novel technology or control strategy in the manufacturing process, or other potential issues regarding vaccine formulation or manufacturing
* **Vaccine of interest**:The vaccine for which benefit-risk is being assessed, relative to one or more comparators.
* **Value tree**:A hierarchical depiction of the endpoints used in a B-R assessment, typically organized in functional or anatomic groups 14,26,27 (e.g., Appendix 1).

Figure 1: Categorizing Benefit Outcomes for Structured Benefit Risk Assessment

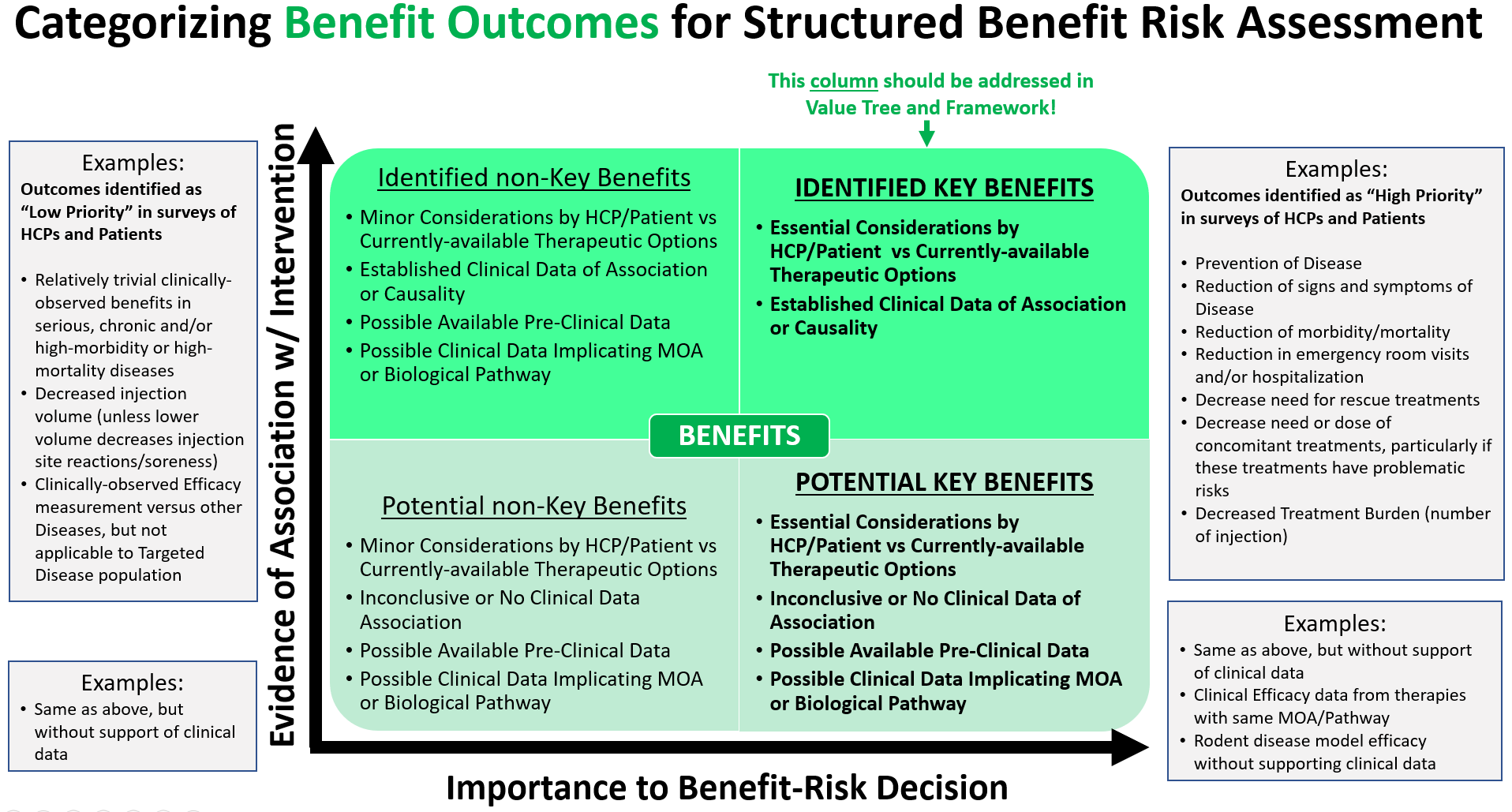
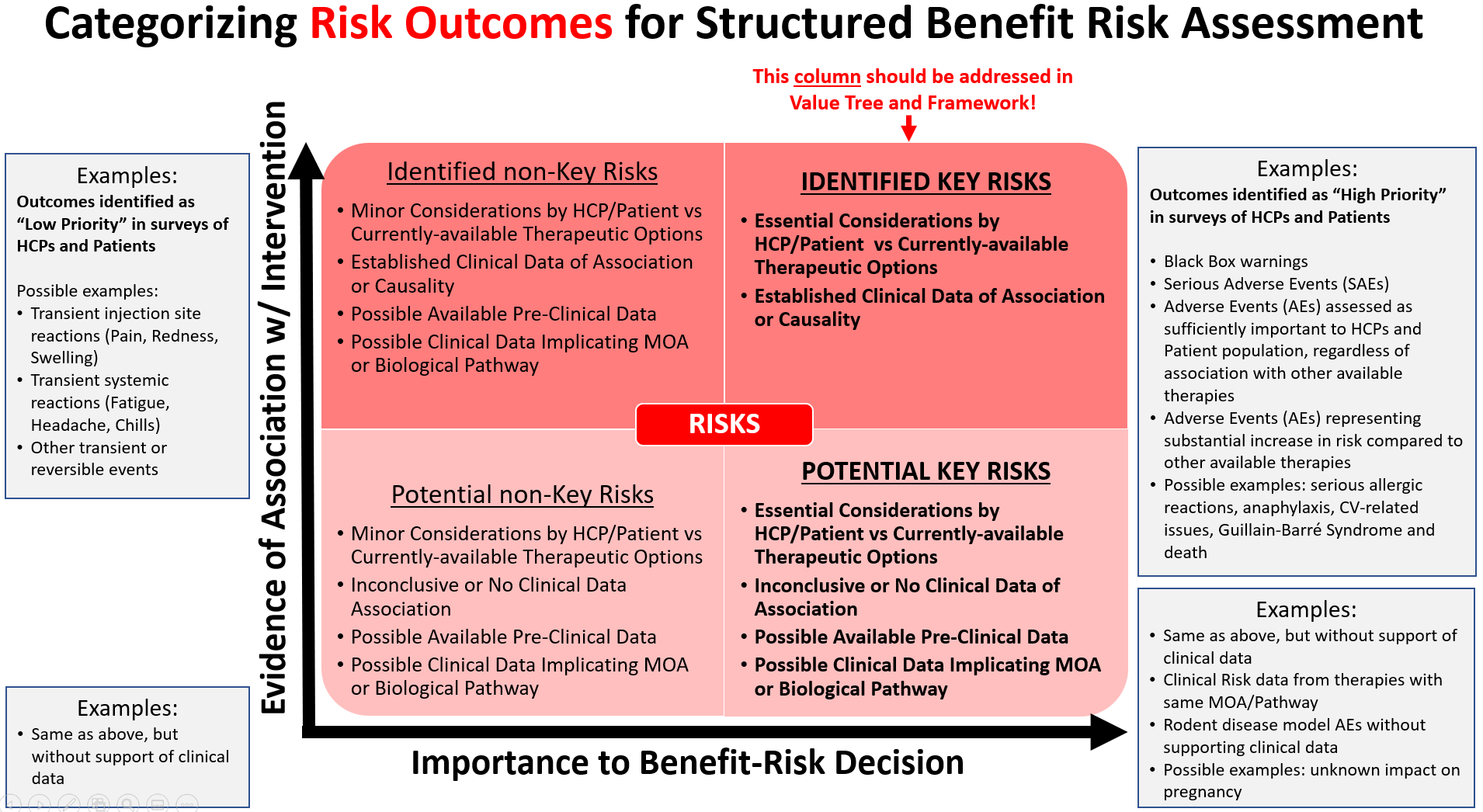


Figure 2: Categorizing Risk Outcomes for Structured Benefit Risk Assessment



**Appendix 1: Value Tree (optional)**

**Example value tree for pertussis vaccine36**

Diagram

Description automatically generated

Initial and final [pertussis](about:blank) vaccination value trees. The outcomes that were not retained for the final outcome tree are shaded in grey. (aP: [acellular pertussis vaccines](about:blank), wP: whole-cell pertussis vaccines, [HHE](about:blank): hypotonic-hyporesponsive episodes).

**Appendix 2: Regulatory Benefit-Risk Framework table (optional)**

|  |  |  |
| --- | --- | --- |
| **Dimension** | **Evidence & Uncertainties** | **Conclusions & Reasons** |
| **Analysis of Condition** |  |  |
| **Current Treatment Options** |  |  |
| **Benefits** |  |  |
| **Risks & Risk Management** |  |  |
| **Conclusions Regarding Benefit-Risk** | | |

**References**

|  |  |  |
| --- | --- | --- |
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1. A completed module may have blanks for unknown or missing data. [↑](#footnote-ref-1)
2. Note: Scenarios are an advanced topic that will not be used by most users. [↑](#footnote-ref-2)