



Innovative Medicines Initiative



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**Accelerated Development of VAccine beNefit-risk  
Collaboration in Europe**

Grant Agreement n°115557

**D4.3 Report on appraisal of vaccine  
benefit-risk methods**

**WP4**

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 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
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## TABLE OF CONTENTS

<b>DOCUMENT INFORMATION .....</b>	<b>5</b>
<b>DOCUMENT HISTORY .....</b>	<b>5</b>
<b>DEFINITIONS.....</b>	<b>6</b>
<b>EXECUTIVE SUMMARY .....</b>	<b>9</b>
<b>1. INTRODUCTION.....</b>	<b>10</b>
1.1 ADVANCE PROJECT .....	10
1.2 OBJECTIVES AND SCOPE OF THE REPORT .....	11
1.3 STRUCTURE OF THE REPORT .....	11
<b>2. ARE VACCINES DIFFERENT FROM DRUGS FOR BENEFIT-RISK ASSESSMENT?.....</b>	<b>13</b>
<b>3. BENEFIT-RISK METHODOLOGY .....</b>	<b>18</b>
3.1 DESCRIPTIVE OR SEMI-QUANTITATIVE FRAMEWORKS.....	18
3.1.1 <i>Summary tools</i> .....	19
3.1.2 <i>BRAT framework</i> .....	22
3.1.3 <i>ProACT-URL framework</i> .....	26
3.1.4 <i>Other frameworks</i> .....	29
3.1.5 <i>Concluding remarks</i> .....	30
3.2 BENEFIT-RISK MEASURES.....	31
3.2.1 <i>Numbers needed to treat and variants thereof</i> .....	31
3.2.2 <i>Differences in benefits and risks</i> .....	34
3.2.3 <i>Ratios in benefits and risks</i> .....	35
3.2.4 <i>Impact numbers</i> .....	37
3.2.5 <i>Concluding remarks</i> .....	40
3.3 COMPOSITE HEALTH MEASURES.....	41
3.3.1 <i>QALY</i> .....	42
3.3.2 <i>DALY</i> .....	43
3.3.2 <i>HALE</i> .....	43
3.3.4 <i>Concluding remarks</i> .....	44
3.4 QUANTITATIVE BENEFIT-RISK FRAMEWORKS.....	44
3.4.1 <i>'Principles of Threes', TURBO and Beckmann</i> .....	45
3.4.2 <i>Benefit-less risk analysis</i> .....	46
3.4.3 <i>Multi-criteria decision analysis and extensions</i> .....	47
3.4.4 <i>Data-driven benefit-risk assessment (Sarac et al.)</i> .....	50
3.4.5 <i>Clinical utility index</i> .....	50
3.4.6 <i>Concluding remarks</i> .....	51
3.5 MODELLING APPROACHES .....	51
3.5.1 <i>Decision trees and influence diagrams</i> .....	52

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	4/97

3.5.2 State transition models.....	54
3.5.3 Discrete event simulation .....	55
3.5.4 Dynamic transmission models.....	57
3.5.4 Meta-analytic approaches.....	57
3.5.5 Parameter estimation and uncertainty .....	58
3.5.6 Concluding remarks .....	61
3.6 PREFERENCE ELICITATION.....	63
4.6.1 Focus groups .....	66
4.6.2 Conjoint analysis overview .....	68
4.6.3 Choice Based Conjoint methods.....	70
<b>4. DISCUSSION AND RECOMMENDATIONS.....</b>	<b>83</b>
<b>ANNEXES.....</b>	<b>87</b>
ANNEX I. XXX.....	88

 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

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	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b> 6/97

		1.4	Review and comments
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## DEFINITIONS

- Participants of the ADVANCE Consortium are referred to herein according to the following codes:
  - **EMC.** Erasmus Universitair Medisch Centrum Rotterdam (Netherlands) - Coordinator
  - **UNIBAS.** Universitaet Basel (Switzerland) - **Managing entity of the IMI JU funding**
  - **EMA.** European Medicines Agency (United Kingdom)
  - **ECDC.** European Centre for Disease Prevention and Control (Sweden)
  - **SURREY.** The University of Surrey (United Kingdom)
  - **P95.** P95 (Belgium)
  - **SYNAPSE.** Synapse Research Management Partners, S.L. (Spain)
  - **OU.** The Open University (United Kingdom)
  - **LSHTM.** London School of Hygiene and Tropical Medicine (United Kingdom)
  - **PEDIANET.** Società Servizi Telematici SRL (Italy)
  - **KI.** Karolinska Institutet (Sweden)
  - **ASLCR.** Azienda Sanitaria Locale della Provincia di Cremona (Italy)
  - **AEMPS.** Agencia Española de Medicamentos y Productos Sanitarios (Spain)
  - **AUH.** Aarhus Universitetshospital (Denmark)
  - **UTA.** Tampereen Yliopisto (Finland)
  - **WIV-ISP.** Institut Scientifique de Santé Publique (Belgium)
  - **MHRA.** Medicines and Healthcare products Regulatory Agency (United Kingdom)
  - **SSI.** Statens Serum Institut (Denmark)
  - **RCGP.** Royal College of General Practitioners (United Kingdom)
  - **RIVM.** Rijksinstituut voor Volksgezondheid en Milieu \* National Institute for Public Health and the Environment (Netherlands)
  - **GSK.** GlaxoSmithKline Biologicals, S.A. (Belgium) – EFPIA Coordinator
  - **SP.** Sanofi Pasteur (France)
  - **NOVARTIS.** Novartis Pharma AG (Switzerland)
  - **SP MSD.** Sanofi Pasteur MSD (France)
  - **CRX.** Crucell Holland BV (Netherlands)
  - **PFIZER.** Pfizer Limited (United Kingdom)
  - **TAKEDA.** Takeda Pharmaceuticals International GmbH (Switzerland)
- **Grant Agreement.** The agreement signed between the beneficiaries and the IMI JU for the undertaking of the ADVANCE project (115557).
- **Project.** The sum of all activities carried out in the framework of the Grant Agreement.
- **Work plan.** Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in Annex I to the Grant Agreement.
- **Consortium.** The ADVANCE Consortium, comprising the above-mentioned legal entities.


 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

- **Project Agreement.** Agreement concluded amongst ADVANCE participants for the implementation of the Grant Agreement. Such an agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.
- **List of abbreviations:**

<b>ACBC</b>	Adaptive choice based conjoint
<b>ADVANCE</b>	Accelerated development of vaccine benefit-risk collaboration in Europe
<b>AF</b>	Aetiological fraction
<b>B-R</b>	Benefit-Risk
<b>BCoDE</b>	Burden of Communicable Diseases in Europe
<b>BLRA</b>	Benefit-less risk analysis
<b>BRAT</b>	Benefit-Risk Action team
<b>BRR</b>	Benefit-Risk ratio
<b>CBC</b>	Choice based conjoint
<b>CIN</b>	Case impact number
<b>CIRS</b>	Centre for Innovation in Regulatory Science
<b>COBRA</b>	Consortium on Benefit-Risk assessment
<b>CPM</b>	Confidence profile method
<b>CUI</b>	Clinical utility index
<b>DALY</b>	Disability adjusted life years
<b>DCE</b>	Discrete choice experiment
<b>DES</b>	Discrete event simulation
<b>DIN</b>	Disease impact number
<b>ECIN</b>	Exposed case impact number
<b>EIN</b>	Exposure impact number
<b>GBR</b>	Global benefit-risk
<b>GRADE</b>	Grading of Recommendations Assessment, Development and Evaluation
<b>HALE</b>	Healthy life expectancy
<b>HTA</b>	Health Technology Assessment
<b>IMI</b>	Innovative Medicines Initiative
<b>INHB</b>	incremental net health benefit
<b>IRBR</b>	Incremental benefit-risk ratio
<b>ISPOR</b>	
<b>MCDA</b>	Multi-criteria decision analysis
<b>MCE</b>	minimum clinical efficacy
<b>MPES</b>	Multi-parameter evidence synthesis
<b>MTC</b>	Mixed treatment comparison
<b>NEAR</b>	Net Efficacy Adjusted for Risk
<b>NEPP</b>	Numbers of events prevented in your population
<b>NHB</b>	net health benefit
<b>NITAG</b>	National Immunization Technical Advisory Group
<b>NNH</b>	number needed to harm
<b>NNT</b>	number needed to treat
<b>NNTB</b>	number needed to treat for one person to benefit

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b> 8/97

<b>NNTH</b>	number needed to treat for one person to harm
<b>NNV</b>	number needed to vaccinate
<b>PAF</b>	Population attributable fraction
<b>PAR</b>	Population attributable risk
<b>PBRER</b>	Periodic benefit-risk evaluation reports
<b>PhRMA</b>	Pharmaceutical Research Manufacturers of America
<b>PICO</b>	Population, Intervention, Comparison, Outcome
<b>PIN</b>	Population impact number
<b>PIN-ER-t</b>	Population impact number of eliminating a risk factor
<b>ProACT-URL</b>	Problem, Objectives, Alternatives, Consequences, Trade-offs, Uncertainty, Risk and Linked decisions framework
<b>PROTECT</b>	Pharmacoepidemiological Research on Outcomes of Therapeutics
<b>PSA</b>	Probabilistic sensitivity analysis
<b>PSM</b>	Probabilistic simulation method
<b>QALY</b>	Quality-adjusted life years
<b>QoL</b>	Quality of life
<b>QTwist</b>	Quality adjusted time without symptoms and toxicity
<b>RBAT</b>	Risk-benefit acceptability threshold
<b>RRM</b>	Random regret minimization
<b>RUM</b>	Random utility maximization
<b>RV</b>	relative utility value
<b>SABRE</b>	Southeast Asia Benefit Risk Evaluation initiative
<b>SMAA</b>	Stochastic multi-criteria acceptability analysis
<b>STIKO</b>	Standing Committee on Vaccination
<b>STM</b>	State transition model
<b>TURBO</b>	Transparent Uniform Risk/Benefit Overview
<b>UMBRA</b>	Unified Methodologies for Benefit-Risk Assessment


 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

## EXECUTIVE SUMMARY

Most of the benefit-risk methodology has been developed to assess the benefit-risk balance of (therapeutic) drugs. Several recent reviews of existing benefit-risk methodology exist. Therefore, we did not perform a formal systematic review of the literature on benefit-risk methodology. Instead, we revisited all methods described in the systematic reviews by the ISPOR Risk-Benefit Management Working Group and by PROTECT and appraised their suitability for the benefit-risk assessment of vaccines, with the exception of the estimation techniques described in the PROTECT review. Instead, we evaluated the modelling techniques and evidence-synthesis techniques most commonly used in Health Technology Assessment.

In this report, we first describe the vaccine specificities. Then, an extensive literature review of benefit-risk methods was performed, evaluating (1) descriptive or semi-quantitative frameworks, (2) benefit-risk measures, (3) composite health measures, (4) quantitative benefit-risk frameworks, (5) modelling approaches and (6) preference elicitation techniques. In total, xx different methods were evaluated.

In the final section, we recommend the use (or development of a vaccine-specific) qualitative or semi-quantitative framework, the use of a toolbox of selected quantitative methods, the quantification of various sources of uncertainty and the investigation of how to adapt common preference elicitation techniques to the field of vaccination. Ideas for Proof-of-Concept studies are formulated as well.


 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

## 1. INTRODUCTION

### 1.1 ADVANCE project

Benefit-risk (BR) assessments are indispensable to govern decision-making regarding pharmaceutical products, whether it is the manufacturer's decision for further pharmaceutical research and development<sup>1</sup>, the regulator's decision for approval, restriction or withdrawal of the product<sup>2, 3</sup> or the recipient's decision to take the product<sup>4</sup>. Balancing benefits and risks is however a complex exercise. It involves the integration of data and information from different sources, typically associated with different levels of uncertainty. In addition, measuring the benefit-risk balance is to a certain extent subjective as it involves value judgements of gaining certain benefits versus avoiding certain risks.

To allow more transparent, consistent, reproducible and communicable benefit-risk assessments of pharmaceutical products, the need for more structured approaches is generally acknowledged<sup>5</sup>. Following this need, the *Benefit-Risk Methodology Project* by the *European Medicines Agency (EMA)*<sup>2</sup> and the "*Pharmacoepidemiological Research on Outcomes of Therapeutics*" (PROTECT)<sup>6</sup> project funded by the *Innovative Medicines Initiative (IMI)* were both launched in 2009. Recognizing that vaccines are different from therapeutics for monitoring the benefit-risk balance, the IMI funded the "*Accelerated development of vaccine benefit-risk collaboration in Europe*" (ADVANCE) project. The ADVANCE project was launched in October 2013 and brings together 200 researchers from more than 30 institutions, including the *European Centre for Disease Prevention and Control (ECDC)*, the EMA, vaccine manufacturers, academics, regulators, public health authorities and *small and medium enterprises (SMEs)*. The overall objective of the ADVANCE consortium is to review, develop and test methods, data sources and procedures that should feed into a blueprint of an efficient and sustainable European framework that can rapidly deliver quantitative data to support manufacturers, regulators, public health authorities, health professionals and the general public to

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	11/97


make informed decisions regarding vaccines. The activities of the project have been grouped in seven work packages, amongst which *work package 4* (WP4) on the appraisal, development and testing of methods for burden of disease, vaccination coverage, vaccine safety, vaccine effectiveness/impact and benefit-risk methodology. This report is on the appraisal of benefit-risk methodology.


## ***1.2 Objectives and scope of the report***

Most of the benefit-risk methodology has been developed to assess the benefit-risk balance of (therapeutic) drugs. In this report, we describe the existing benefit-risk methodology and evaluate whether the methods are suited (or extendible) to conduct benefit-risk assessments of vaccines, with an emphasis on the post-licensure setting and specific ADVANCE objectives (such as timeliness and integration). The ultimate objective of this review is to identify suited methods as well as knowledge gaps and recommend further methodological developments to support the overall ADVANCE objective of developing a framework for rapid delivering of quantitative data to support vaccine decisions.

## ***1.3 Structure of the report***

In this report, we evaluate methods for their suitability for benefit-risk assessments of vaccines. Therefore, the vaccine specificities are described first (Section 2). Then, an extensive literature review of benefit-risk methods was performed, evaluating (1) descriptive or semi-quantitative frameworks, (2) benefit-risk measures, (3) composite health measures, (4) quantitative benefit-risk frameworks, (5) modelling approaches and (6) preference elicitation techniques (Section 3). Finally, some concluding remarks and recommendations are formulated (Section 4).

 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/ <del>Final</del>	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	12/97

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	13/97


## 2. ARE VACCINES DIFFERENT FROM DRUGS for BENEFIT-RISK ASSESSMENT?

Benefit-risk methodology aims to provide transparency to the process of balancing benefits and risks by structuring this process and making a clear distinction between data and value judgements. Most of the previous work on methods for benefit-risk assessments was related to drugs (e.g. see reviews<sup>7-10</sup>). In this section, we contrast prototypical therapeutic drugs (such as cancer treatment) with vaccines in general to identify the vaccine specificities that warrant special consideration when assessing the vaccine’s benefit-risk balance. The identified vaccine specificities will guide the appraisal of the benefit-risk methods originally developed for drugs for their use (or extendibility) to vaccines. The identified vaccine specificities do not apply to all vaccines and all vaccination usage.

First, most vaccines are different from therapeutic drugs because they can provide both individual-level and population-level protection, making them a public health matter. Further vaccine specificities include the potential long-term benefits contrasted to the immediate risks, the large levels of data uncertainty, the low risk tolerance, the challenging preference elicitation from vaccine candidates and the strong reliance on post-licensure observational studies.

### ***Population-level impact of vaccination***

Vaccines are different from pharmaceutical drugs because they might induce indirect effects in addition to the direct effects<sup>11</sup>. The direct effects concern the benefits and risks the vaccine is having on the vaccine recipient. The indirect effects refer to the effects of vaccination that can be measured on those not receiving the vaccine. Unvaccinated individuals might benefit from vaccination as a result of reduced disease transmission through herd immunity. Indirect effects are typically beneficial but may in some cases be detrimental. Examples of indirect effects that are not beneficial are: increased risk of


 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

varicella complications through an increased average age at infection as a result of herd immunity and risks to immuno-compromised people that come into close contact with a person vaccinated with some live vaccines. The population-level impact of vaccination refers to the effect vaccination is having on the entire population, including vaccinated and unvaccinated persons, and is a combination of direct and indirect effects<sup>11, 12</sup>. The impact further depends on the vaccine uptake within that population and other population characteristics (such as the prevalence of the vaccine-preventable disease and population density) as well as on the infectious disease dynamics. Therefore, to assess the benefit-risk balance at population-level, additional information is needed regarding the vaccine uptake and potentially other population characteristics.

### ***Different stakeholders and different perspectives***

Vaccine manufacturers, regulatory authorities, health care authorities, health care providers and vaccine recipients or their parents/tutors are all stakeholders involved in decision-making concerning vaccines. Public health authorities play a much more prominent role in decision-making for vaccines than they do for pharmaceutical drugs. Indeed, public health authorities recommend or even mandate vaccination in order to protect the entire population, evoking ethical issues regarding individual autonomy versus population protection. The different stakeholders might have different value judgements of the various vaccine effects (e.g. public health attaching more importance to the indirect effects than the regulators)


Regarding vaccine perspectives, the distinction is often made between the patient perspective (including only benefits and risks to the vaccine candidate) and the societal perspective (including all benefits and risks to the society). For therapeutic drugs (with the exception of antibiotics), only the patient perspective is relevant and benefits and risks are always borne by the same individual. This is not so for vaccines. Depending on the vaccine and how it is used, the patient perspective (e.g. travellers vaccines) or the societal perspective (e.g. measles, influenza) might be more or less important. In

 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

addition, there might be instances where the societal perspective renders a different benefit-risk decision than the patient perspective.

### ***Immediate (certain) risks and long-term (uncertain) benefits***

Vaccines are approved only when the highest standards for safety are met. Nevertheless, rare adverse events occur, often shortly after vaccination. For some vaccines, a large number of vaccine recipients are required in order to optimally prevent disease. This large number of vaccine recipients increases the power to detect very rare adverse events. For an intervention targeting a smaller population however, those rare adverse effects would remain undetected. Oftentimes, the risk profile of a vaccine is dominated by a single rare serious adverse event, detected in the post-licensure era, whereas the risk profile of therapeutic drugs typically consists of a multitude of adverse events, many of which already known at the time of approval. Vaccines are also different from therapeutic drugs because they are a primary preventive measure, potentially having long-term benefits preventing future morbidity and mortality. Furthermore, vaccines are often licenced based on surrogate endpoints like immunogenicity due to the lack of immediate endpoints and/or low disease incidence. This implies substantial uncertainty regarding the expected benefits at the time of licensure, even for the direct effects. The uncertainty around the population-level impact of vaccination is yet larger, because impact depends on the actual implementation of the vaccination programme and is influenced by changes in the transmission dynamics of the disease targeted by vaccination. Even long after licensure, establishing the vaccine benefits remains challenging due to factors such as heterogeneity in immune responses, waning of protection and lack of a comparable unvaccinated population. Finally, the potential of global eradication is another feature unique to some vaccines.


	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	16/97

### ***Challenging preference elicitation***

The elicitation of preferences or value judgements is challenging for various reasons. The first difficulty is to knowing who to ask. For therapeutic drugs, both benefits and risks are borne by the same patient. Hence, patient preferences are appropriate. Some vaccines however, are a public health matter and benefits and risks are not borne by the same individuals. Therefore, one might argue that public health policy might play an important role in generating the value judgements for such vaccines. These preferences might further depend on whether the vaccine is recommended or mandated. Also eliciting patient preferences is complicated for vaccines (or for primary preventive measures in general). First, there are no patient organisations to ask. Second, the perception of the vaccines benefits is often distorted because the candidates for vaccination and/or the vaccinated are only very rarely confronted with the disease they are protected against. On the other hand, a very low risk tolerance exists because vaccines are given to healthy people, typically young children, often as part of a vaccination recommendation or mandate. The risk perception is further influenced by the public concerns about vaccines and the enhanced media attention for vaccine-related issues<sup>13</sup>. Additionally, there is a difference between making decisions for oneself or on behalf of others (i.e. surrogate decision making), such as parents deciding on vaccination for their child<sup>14</sup>

### ***Importance of observational studies***


The rare adverse events and long-term benefits typical to vaccines cannot be fully investigated using pre-licensure studies, which are relatively small and limited in time. Therefore, there is a strong emphasis on post-licensure studies for vaccines. However, post-licensure studies are mainly observational, making them much more vulnerable to bias and confounding compared to well-controlled pre-licensure studies. In particular,

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	17/97

vaccine post-licensure studies might be sensitive to confounding by age- and seasonal effects because vaccines are often administered following recommended age-dependent immunization schedules (e.g. childhood vaccinations) or during specific seasons (e.g. influenza). Nevertheless, information collected post-licensure often complements the pre-licensure, clinical information already available.

### ***Concluding remarks***

The benefit-risk assessment of vaccines is challenging for reasons outlined above. Generally, for the benefit-risk assessment of vaccines, both the individual and the societal perspective are relevant. In that respect, vaccines are more comparable to therapeutic drugs when the patient perspective is adopted. In case the societal perspective is adopted, the benefit-risk methodology might need to be adjusted in order to account for e.g. the indirect vaccine effects. Furthermore, the uncertainty in the benefit-risk assessments of vaccines is substantial and therefore, appropriate benefit-risk methodology should be able to account for uncertainty. Because post-licensure studies often provide important information regarding the benefits and risks of vaccines, the benefit-risk methodology should be able to integrate both pre- and post-licensure information. Finally, because various stakeholders with potentially different value judgements are involved, appropriate benefit-risk methodology should provide a clear distinction between data and preferences.

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	18/97


### 3. BENEFIT-RISK METHODOLOGY

Several recent reviews of existing benefit-risk methodology exist, all focussing on the use of benefit-risk methodology for pharmaceutical drugs<sup>7-10</sup>; of which the reviews by the ISPOR Risk-Benefit Management Working Group (2010)<sup>8</sup> and by PROTECT (2014)<sup>9</sup> were systematic. Therefore, we did not perform a formal systematic review of the literature on benefit-risk methodology. Instead, we revisited all methods described in the two systematic reviews<sup>8, 9</sup> and appraised their suitability for the benefit-risk assessment of vaccines, with the exception of the estimation techniques described in the PROTECT review<sup>9</sup>. These estimation techniques include generic statistical techniques that are not unique to benefit-risk assessments, but were used in combination with other benefit-risk measures. Instead, we evaluated the modelling techniques and evidence-synthesis techniques most commonly used in Health Technology Assessment (HTA), some of which were also described by PROTECT. We did this because it has been recognised earlier that cost-effectiveness analyses and benefit-risk assessments share a lot of commonalities<sup>15</sup> and notwithstanding this, the applications of (adjusted) cost-effectiveness techniques to the field of benefit-risk assessment are sparse<sup>16</sup>.

In this section, we subsequently describe and appraise (1) descriptive or semi-quantitative frameworks, (2) benefit-risk measures, (3) composite health measures, (4) quantitative benefit-risk frameworks, (5) modelling approaches, and (6) preference elicitation techniques.

#### 3.1 Descriptive or semi-quantitative frameworks

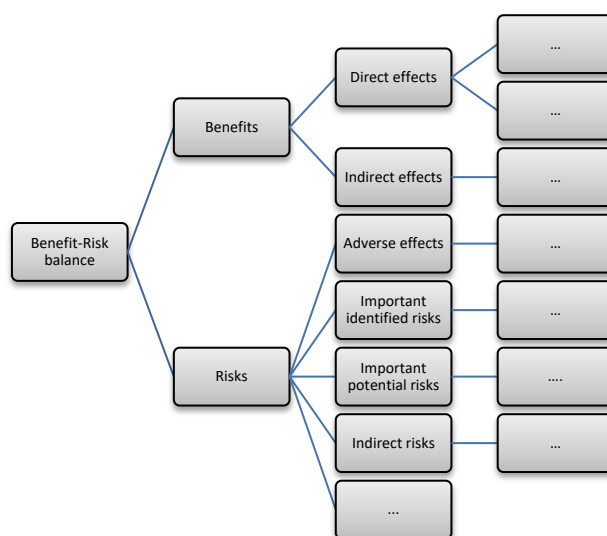
It has been recognised that structured qualitative processes must precede quantification<sup>17</sup>. Such processes or frameworks ensure that all elements of the benefit-risk balance have been considered and rendered explicit and this to improve transparency and communication in decision-making<sup>9</sup>. Descriptive or semi-quantitative frameworks are structured stepwise processes that might include graphical and/or

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b> 19/97

tabular summaries of the metrics associated with the key benefits and risks. The descriptive and semi-quantitative frameworks are to be distinguished from the quantitative frameworks, in which an overall benefit-risk score is calculated<sup>18</sup> (Section 3.4). In this section, we will first discuss common summary tools (Section 3.1.1) and the most commonly used frameworks in benefit-risk assessment, i.e. the BRAT and ProACT-URL frameworks (Section 3.1.2-3.1.3). Other frameworks are touched upon as well (Section 3.1.4).


### 3.1.1 Summary tools

Attribute trees, tabular summaries and forest plots are primary benefit-risk summary and visualisation tools. An **attribute tree** (or value tree) is a visual, hierarchic display of the key attributes or criteria relevant to the decision. A generic example of an attribute tree for vaccines is given in Figure 3.1. Attribute trees are useful to clarify the different benefits and risks, to facilitate communication and to enhance common understanding<sup>19</sup>.



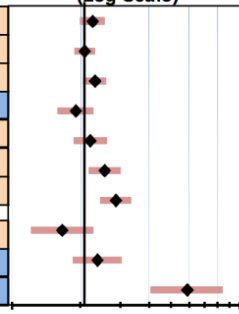
**Figure 3.1.** Generic example of an attribute tree for vaccines.

The **key benefit-risk summary table** (Table 3.1) and **effects table** (Table 3.2) are tabular presentations of all key benefits and risks relevant to the benefit-risk decision.


	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b> 20/97

The table rows match the branches of the attribute tree and minimally include a description of the benefits/risks and their reported values (and possibly units of measurements, ranges, uncertainties, comments). The key benefit-risk summary table is used within the BRAT framework (Section 3.1.2) whereas the effects table is used within the ProACT-URL framework (Section 3.1.3). The effects table is one of the four benefit-risk tools recommended within the scope of the EMA benefit-risk project (in addition to the ProACT-URL framework, MCDA and graphical displays)<sup>2</sup>.

**Table 3.1.** Example of key benefit-risk summary table, for CABG, coronary artery bypass graft (from <sup>20</sup>).

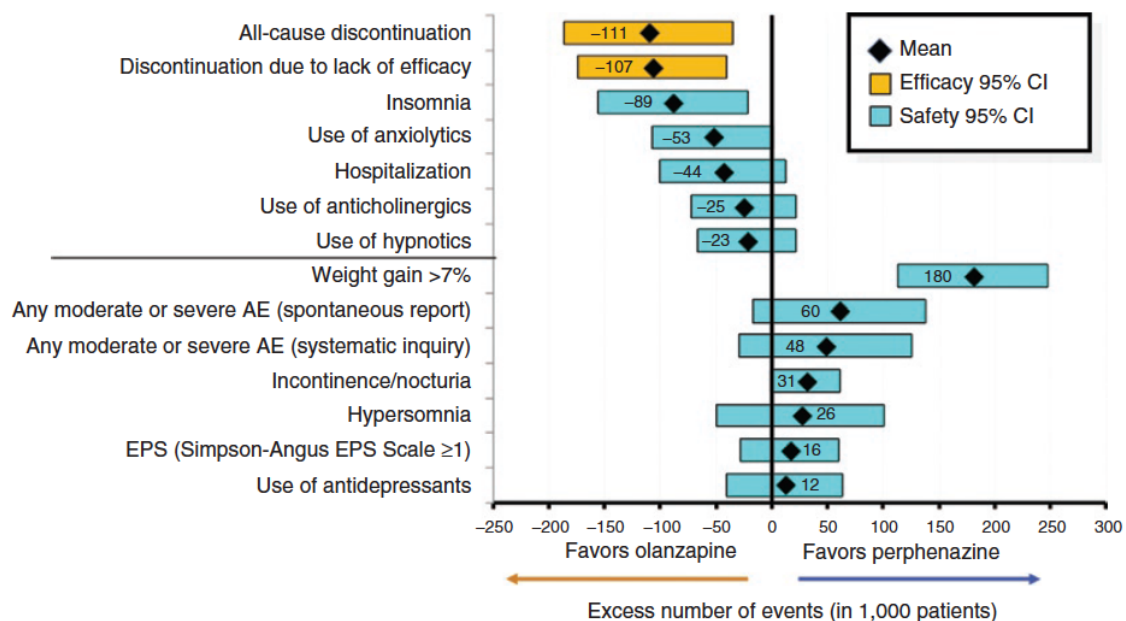
		Outcome	Study Drug Risk (/1,000 pts)	Comparator Risk (/1,000 pts)	Odds Ratio (95% CI)	Odds Ratio (Log Scale)
Benefits	↓ Pain	Rapid onset	271	248	1.13 (1.00,1.27)	
		Headache relief	643	633	1.04 (0.94,1.15)	
		Pain free response	383	349	1.16 (1.03,1.30)	
		Sustained response	285	295	0.95 (0.80,1.14)	
	↓ Sensitivity	Reduced sensitivity to sound and light	530	505	1.10 (0.94,1.30)	
	↓ Other	Reduction in functional disability	540	480	1.28 (1.09,1.49)	
		Reduction in nausea or vomiting	604	517	1.43 (1.22,1.67)	
Risks	↑ Individual Risks	Transient triptans sensations	43	52	0.83 (0.61,1.14)	
		CNS AEs	53	45	1.18 (0.92,1.51)	
		"Chest-related" AEs	58	21	2.93 (2.04,4.20)	


**Table 3.2.** Example of effects table, for Caprelsa, a drug for treatment of inoperable thyroid cancer (from <sup>21</sup>).

 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b> 21/97

		Effect	Description	Best	Worst	Units	Placebo	300 mg
Favourable effects	Primary endpoint	Progression-free survival Hazard Ratio	Date of randomisation to the date of objective progression or death (blinded independent review)	0	1	unitless	1	0.46
	Secondary endpoints	Progression-free survival (median)	Date of randomisation to the date of objective progression or death (Weibull model)	60	0	months	19.3	30.5
		Objective Response (RECIST)	Proportion of complete or partial responders (at least a 30% decrease in the sum of the longest diameter of target lesions compared to baseline)	100	0	%	13	45
Unfavourable effects		Diarrhoea, Grade 3-4	Increase of $\geq 7$ stools per day over baseline; incontinence; IV fluids $\geq 24$ hrs; hospitalisation; severe increase in ostomy output compared to baseline; interfering with activities of daily living; Life-threatening consequences	0	100	%	2.0	10.8
		QTc related events, Grade 3-4	QTc $> 0.50$ second; life-threatening signs or symptoms (eg, arrhythmia, CHF, hypotension, shock syncope); Torsade de pointes	0	100	%	1.0	13.4
		Infections, Grade 3-4	IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or operative intervention indicated; life-threatening consequences.	0	100	%	36.4	49.8

A **forest plot** (Figure 3.2) is a simple graphical representation that complements the effects table<sup>22</sup>. It provides a graphical representation of the risk differences (between treatment and comparator/baseline) for multiple dichotomous endpoints and their associated uncertainty, with different colours for the efficacy and safety endpoints.



	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	22/97


**Figure 3.2.** Forest plot representing risk differences for a variety of endpoints, comparing two treatments of schizophrenia. The x-axis represents the excess number of cases for a hypothetical population of 1000 patients (from <sup>22</sup>).

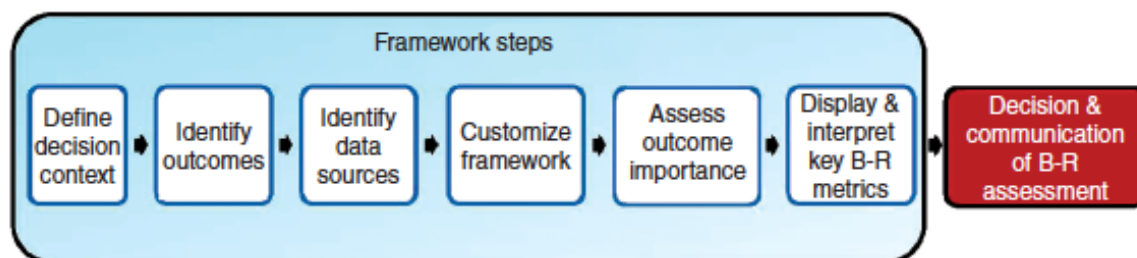
### 3.1.2 BRAT framework<sup>1</sup>

The Benefit-Risk Action Team (BRAT) framework is a general platform for benefit-risk assessment that facilitates the selection, organization, summarization, and interpretation of evidence relevant to benefit-risk decisions. The BRAT framework originated in 2005, when the Pharmaceutical Research Manufacturers of America (PhRMA) implemented a 5-year project to develop a transparent, systematic approach for pharmaceutical benefit-risk assessment. It has been iteratively developed and tested, first using hypothetical scenarios that incorporated the complexities found in real-work benefit-risk assessment<sup>20, 23</sup> and subsequently in a pilot program with PhRMA companies<sup>24</sup>. Since the pilot, the BRAT framework has been used by various companies and has appeared in FDA Advisory Committee Meetings and periodic benefit-risk evaluation reports (PBRERs)<sup>25-27</sup>. It has also been tested in five case studies in the IMI PROTECT project where it was considered valuable in facilitating benefit-risk assessments.

The BRAT framework formally consists of the six steps (see Figure 3.3), though it has been modified and extended by individual companies that have implemented custom versions of BRAT. One highlight of the BRAT framework is its use of tabular and graphic displays to clearly depict difference between treatments in all benefits and harms included, such as key benefit-risk summary tables (Table 3.1) and risk difference forest plots (Figure 3.2).

<sup>1</sup> This section is written by Bennett Levitan


	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	23/97



**Figure 3.3.** Steps in using the Benefit Risk Action Team (BRAT) benefit-risk assessment framework (from <sup>20</sup>).

From the patient perspective, the BRAT framework is an appropriate tool for the structuring the benefit-risk assessment. The rationale is well covered in<sup>20, 23, 24, 28-31</sup> and will not be discussed here. From the policy maker perspective, we will consider each step of the framework:

- Decision context: With some modifications of the typical elements included within, the BRAT decision context can easily apply to vaccines. In particular, the time horizon would be based on the nature of the illness (e.g. seasonal for influenza, lifetime for rubella), and some aspects of policies by which the vaccine is administered may be included (e.g., age for vaccination). The time horizon includes the duration of the exposure to the product (i.e. time frame) and the time period over which the benefit-risk events are measured (i.e. analytic horizon).
- Identifying outcomes: Identifying outcomes can differ considerably for vaccines than for drugs. Other than rare adverse events, the risks for a drug or device are generally known (either observed throughout the development program or predicted through the pharmacological mechanism) at the time of approval, while those for vaccines are often not clear. Vaccine benefit-risk assessment, at least for novel vaccines, will more often rely on post marketing data to identify the risks, and potentially effectiveness when administered in a real-world setting. This hampers the use of any framework at the time of vaccine approval. Post-


	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	24/97

approval, or for vaccines similar to those used before, it should generally be possible to identify the key risks to patients. If indirect risks such as mutation to more virulent, infectious or resistant forms of the disease are a consideration, such endpoints can be added as risks to the framework. Alternatively, some of these endpoints could instead be included in an analytical model (see Section 3.5).

- Identify and extract source data: Registry and observational data may play a critical role in the application of the BRAT and other frameworks to vaccines. However, unlike drug or device benefit-risk, vaccines assessments will generally require an analytical model. These models, particularly dynamic transmission models, require a large number of parameters and assumptions regarding transmission dynamics, heterogeneity in contact patterns, policy parameters for the vaccination program, etc. Accordingly, reviewers of such assessments will have many more questions about the data and its implications than in a typical drug benefit-risk assessment.

The incorporation of an analytical model has several other consequences on the use of BRAT:

- The number of alternative treatments typically considered in drug benefit-risk frameworks is small – typically two or three. Because vaccine programs can be implemented in so many ways, just comparing the alternative vaccines themselves may be insufficient. The assessment may need to consider many alternative policies for implementation. The BRAT framework currently lends itself to comparing only a small number of treatments and may need modification to more easily accommodate a wide variety of vaccine programs.
- Uncertainty manifests in several aspects of drug benefit-risk assessment – statistical uncertainty, whether the right endpoints were used, applicability of clinical trial data to real-world use, conduct and quality of the trials,


	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	25/97

implications of missing data, etc. In addition to these challenges, the transmission factor itself and well as the uncertainties related to vaccine policy and acceptance by patients introduce a new dimension of complexity for vaccine B-R evaluation. For vaccine problems, there are a host of new uncertainties related to vaccine policy, use, training, and acceptance by patients, etc. Therefore, BRAT analyses and displays may need to be extended to accommodate some additional factors.

- To date, the BRAT framework has assumed that the attributes are independent. This is not necessary, but the analyses and displays for BRAT have not been developed for cases where there is dependence between benefits and risks. Vaccine benefit-risk may need advancement of BRAT to account for such dependencies.

- Customize the framework: This step is important when accounting for differences between the ideal set of endpoints and those for which data is available or for which the audience will be receptive. Framework customization applies to vaccine benefit-risk with no complications.
- Assess outcome importance: This step in BRAT is the assessment of the relative clinical impact, or weight, for the outcomes included in the assessment. It is not always required and clinical judgment is often sufficient to make a drug or device benefit-risk assessment. The assessment of weights for vaccine benefit-risk problems can be done with the same methods as for drug benefit-risk.

The question of whose weights to use for vaccines is challenging. Since the decision is intended to affect public policy, the preferences of decision-makers may be appropriate. Government policies may dictate some of the weights or at least specify some preference trade-offs amongst the benefits and harms. For a non-communicable disease, it is ultimately the patient who is taking the risks, so conceivably patient preferences are appropriate. However, for a transmittable disease with a major implication on community, regional, and global public

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	26/97


health, one could argue that public health policy may play a significant role. There may be cases where the public health perspective renders different decisions than a patient level perspective.

- Display and interpret key benefit-risk metrics: The key benefit-risk summary table in BRAT lends itself well to vaccine benefit-risk assessment (Table 3.1); though the display may need modification to account for the potentially larger number of vaccine alternative scenarios that may need to be considered. The forest plot often used in BRAT (Figure 3.2) is limited to dichotomous endpoints. If several endpoints in a vaccine assessment are continuous, this display will be of limited use.

In summary, the BRAT framework is generally appropriate for vaccine benefit-risk assessment, but may need extensions to reliably account for the larger number of alternatives (e.g. different vaccines and different implementations of the vaccination program), the dynamic nature of the infectious disease model (e.g. the indirect effects that depend on the vaccine uptake and other population characteristics), and correlation in endpoints.


### 3.1.3 ProACT-URL framework

The ProACT-URL framework is conceptually similar to the BRAT framework. After having been used in other fields, especially operations research<sup>32</sup>, the ProACT-URL has only recently been applied to pharmaceutical B-R assessment. ProACT-URL structures the process of B-R assessment and contains the following eight steps: (1) ‘Problem’, (2) ‘Objectives’, (3) ‘Alternative(s)’, (4) ‘Consequences’ (5) ‘Trade-off’ between benefits and risks, (6) ‘Uncertainty’, (7) ‘Risk attitude’ of the decision maker and (8) ‘Linked decisions’. A more detailed description of the 8-step ProACT-URL framework is given in Table 3.3 along with a description of its suitability for vaccines. Step 4 of the framework suggests creating an effects table. The ProACT-URL framework is one of the four methods recommended within the scope of the EMA benefit-risk project<sup>2</sup> and was evaluated

 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>


positively by the PROTECT consortium<sup>9</sup>. Compared to the BRAT framework, the ProACT-URL framework contains the additional step ‘Uncertainty’ and ‘Linked decisions’, but does not require customizing the framework as the BRAT framework does.

Similar as the BRAT framework, the ProACT-URL framework is generally appropriate for vaccine benefit-risk assessments given that special consideration is being paid to vaccine specificities such as the time window, low risk tolerance and the high levels of uncertainty. Multiple effects table (commonly used within ProACT-URL) might be needed to summarize the evidence for vaccines with a substantial public health impact (e.g one for vaccine uptake of 30%, one for an uptake of 50%, etc).

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b> 28/97

**Table 3.3.** Description of the ProACT-URL framework (adjusted from <sup>17</sup>).


1. Problem	<p>Determine the nature of the problem, its context and frame the problem. This includes a description of the vaccine preventable disease epidemiology, the product, the indication(s) for use and the unmet medical need.</p> <p><i>For vaccines, it will be important to mention the time horizon, which includes the duration of the vaccine exposure (i.e. time frame) as well as the time period over which the benefit-risk events are measured (i.e. analytic horizon).</i></p>
2. Objective	<p>Establish the objectives that indicate the overall purposes to be achieved (e.g. approval, restriction, update after safety signal) and identify criteria of benefits (favourable effects) and risks (unfavourable effects), that is build the attribute tree.</p> <p><i>For vaccines, the identification of the criteria might be challenging because the vaccine-associated risks are generally little known at the time of approval. The same holds true for some indirect effects (e.g. strain replacement).</i></p>
3. Alternatives	<p>Identify the options to be evaluated against the criteria.</p> <p><i>For vaccines, there are many alternatives possible. These alternatives include no vaccination, the use of an alternative vaccine, the use of other preventive measures and other vaccination implementations.</i></p>
4. Consequences	<p>Describe how the options perform on the different criteria (i.e. the magnitudes of all effects, their desirability or severity, their incidence). Create the effects table.</p> <p><i>For vaccines, it is particularly challenging to assess the magnitude of the indirect effects as they depend on the vaccine uptake and other population characteristics (e.g. baseline prevalence, population density) as well as on the infectious disease dynamics. In addition, due to the lack of immediate endpoints, vaccines are often licensed on the basis of immunogenicity rather than efficacy, resulting in substantial uncertainty regarding the expected magnitude of the benefits at the time of approval. Different modes of protection (all-or-nothing versus leaky) and different protective effects (infection, illness, hospitalisation, death, infectivity) further add to the complexity of assessing the vaccine benefits. Also the risks are often unclear at time of approval.</i></p>
5. Trade-offs	<p>Assess the balance between favourable (benefits) and unfavourable (risks) effects (i.e. clinical judgement and rationale).</p> <p><i>For therapeutics, it is the same patient taking the benefits and the risks. This is not so for vaccines that have a major public health impact through herd immunity. This societal perspective sets (some) vaccines apart.</i></p>
6. Uncertainty	<p>Assess the uncertainty associated with the effects (e.g. statistical uncertainty, bias and representativeness of the studies, correlates of protection). Consider how uncertainty affects the balance by conducting sensitivity analyses and scenario analyses on the model.</p> <p><i>Some vaccine effects are highly uncertain, such as the long-term indirect effects.</i></p>
7. Risk tolerance	<p>Judge the relative importance of the decision maker's risk attitude for this product and indicate how this affects the balance reported in 5.</p> <p><i>A very low risk tolerance towards vaccines exists because they are typically given to young, healthy children. Risk tolerance is even lower for recommended or mandated vaccination.</i></p>
8. Linked decisions	<p>Consider the consistency of this decision with similar past decisions, and assess whether making this decision could have an impact on future decisions.</p>

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

### 3.1.4 Other frameworks

Currently, ProACT-URL and BRAT are the frameworks most commonly used in pharmaceutical and regulatory science. Other frameworks have been developed, which we will only briefly refer to. For a more in depth discussion of the frameworks developed by regulatory and industry, we refer to Noel<sup>17</sup>. The Centre for Innovation in Regulatory Science (CIRS) engaged a consortium of regulators from four countries (i.e. Health Canada, Australia’s Therapeutic Goods Administration, Swissmedic and the Singapore Health Science authority – the **CASS** group) to develop a common framework, referred to as the **COBRA** framework (Consortium on Benefit-Risk assessment). A similar initiative to harmonize regulatory activity was taken by the regulatory agencies of China, Indonesia, Malaysia, Philippines, Singapore, South Korea & Taiwan (the Southeast Asia Benefit Risk Evaluation initiative - **SABRE**). Also the **US FDA** developed a framework of its own, including the following steps: analysis of condition, current treatment options, benefits, risks and risk management. In addition, CIRS established the Unified Methodologies for Benefit-Risk Assessment (**UMBRA**) to provide a platform for the coordinated development of benefit-risk methodologies that can be used internationally during drug development and regulatory review<sup>33</sup>.


Apart from the pharmaceutical research and regulatory oriented frameworks, the German National Immunization Technical Advisory Group (NITAG), called the Standing Committee on Vaccination (**STIKO**), developed a decision framework or Standard Operation Procedure (SOP) to guide decisions related to vaccine recommendations<sup>34</sup>. The key questions addressed in this SOP fall within five categories: (1) pathogen characteristics, (2) characteristics of the target disease, (3) vaccination characteristics, (4) vaccination strategy and (5) implementation of the recommendation. Based on these questions, a benefit-risk assessment is conducted. The frameworks further utilizes existing tools: formulation of questions following the PICO method (Population, Intervention, Comparison and Outcome); assessment of the quality of individual studies following the Cochrane risk of bias tool<sup>35</sup>; assessment of the quality of body of evidence

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

following the GRADE system (Grading of Recommendations Assessment, Development and Evaluation)<sup>36</sup> and assessment of the quality of systematic reviews following the AMSTAR methodology<sup>37</sup>. The **framework of population impact analysis** have been proposed to assess the impact of an intervention or risk factor on a local population based on systematic reviews of public health literature<sup>38</sup>. The framework involves the following steps: (1) ask the right question (using PICO-T with T for type of evidence required), (2) collect the evidence, (3) understand, synthesise and appraise the information and (4) use the information in policy making. The authors suggest using Population Impact Numbers (Section 3.2.4) to collect the evidence. The latter two frameworks are developed to support vaccine implementation decisions and therefore, contain cost-effectiveness related elements. Finally, Ashby & Smith argue that a natural framework for medical decision-making is a Bayesian approach<sup>39</sup>. They described the following general structure for medical decision-making: (1) who is the decision-maker, (2) possible actions, (3) uncertain consequences, (4) sources of evidence and (5) utility assessments.

### 3.1.5 Concluding remarks

Currently, BRAT and ProACT-URL are the frameworks most commonly used in pharmaceutical and regulatory science, with the FDA favouring the BRAT framework<sup>25-27</sup> and EMA favouring the ProACT-URL framework<sup>21</sup>. Both frameworks are generally appropriate for vaccine benefit-risk assessments given that special consideration is paid to the vaccine specificities (Sections 3.1.2-3.1.3). The use of tabular and graphic displays to summarize the benefits and risks (e.g. forest plot, effects table, key benefit-risk summary table) might need to be adjusted to account for the dynamic nature of vaccine-preventable infectious diseases (e.g. increasing indirect benefits with increasing vaccine uptake). Finally, although cost-effectiveness analyses are out of the scope of the ADVANCE project, frameworks to support the vaccine implementation decisions (in particular, the STIKO framework<sup>34</sup>) contain elements that are worth considering for

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	31/97

benefit-risk assessments of vaccines. Particularly, because (post-marketing) benefit-risk assessment of vaccines relies on heterogeneous sources of data (including registries and observational data), it might be interesting to take into account the strength of the evidence in a structured way (e.g. using the GRADE system<sup>36</sup> as done within the STIKO framework<sup>34</sup>).

## 3.2 Benefit-risk measures

Benefit-risk measures are systems of measurements or metrics that are used for benefit-risk assessment. They encompass a broad range of metrics, some of them explicitly calculating a benefit-risk score and hence, requiring preferences (Section 3.6) to put benefits and risks on the same scale. We subsequently describe (1) numbers needed to treat, (2) differences in benefits and risks, (3) ratios of benefits and risks and (4) impact numbers.

### 3.2.1 Numbers needed to treat and variants thereof

A measure with an intuitive clinical interpretation is the '**number-needed-to-treat**' (NNT), which is to be interpreted as 'the average number of patients who need to be treated to prevent one additional unfavourable event compared to a control treatment'<sup>40</sup>. The NNT applies to dichotomous outcomes and is defined as the reciprocal of the absolute risk reduction (ARR) or


$$\text{NNT} = 1/\text{ARR} = 1/(P_C - P_T) = 1/\Delta P,$$

where  $P_C$  is the control group event rate (%) and  $P_T$  is the treatment group event rate (%).

When an adverse event is the health outcome of interest, this measure is called '**number-needed-to-harm**' (NNH), or

$$\text{NNH} = 1/\text{ARR} = 1/(Q_T - Q_C) = 1/\Delta Q,$$

where  $Q_C$  is the rate of adverse events (%) in the control group and  $Q_T$  is the rate of adverse events (%) in the treatment group. However, taking the reciprocal of a difference in probabilities results in undesirable statistical and mathematical

 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

properties<sup>41,42</sup>. In addition, the understanding of the confidence interval for the NNT is not straightforward in case the ARR is not significant<sup>43</sup>. Then the confidence interval (CI) of the ARR includes zero, implying that the corresponding CI for the NNT must include infinity ( $\infty$ ). In this case, Altman<sup>43</sup> suggest a (NNH to  $\infty$  to NNT) representation of the CI. To illustrate this, assume that the 95% CI for the ARR equals [-5%, 25%]. Then, the CI of the corresponding NNT-NNH is represented as [NNH 20 to  $\infty$  to NNT 4], which emphasizes that  $\infty$  is included in the CI. Furthermore, to avoid the awkward term ‘number-needed-to-harm’, Altman<sup>43</sup> proposed to use the terms NNTB (number needed to treat for one person to benefit) and NNTH (number needed to treat for one person to be harmed). To evaluate the benefit-risk balance of a product, NNT and NNH are compared with  $NNT < NNH$  indicating a positive benefit-risk balance and  $NNT > NNH$  a negative benefit-risk balance. However, this comparison implies that equal importance is attached to benefit and harm. Furthermore, the NNT-NNH comparison lacks the ability to account for multiple benefits and risks.

Several extensions to NNT have been proposed to address these limitations. To allow differential weighting of benefit and risk, Guyatt<sup>44, 45</sup> proposed to add the **relative utility value** (RV) to the NNH calculation, with RV given by


$$RV = (1 - \text{utility of AE}) / (1 - \text{utility of disease of interest}).$$

Utility  $u$  is defined as the numeric representation of the patients’ preference for a specific outcome, with  $u = 0$  representing ‘death’ and  $u = 1$  representing ‘perfect health’. RV is then interpreted as the value of avoiding an adverse event relative to avoiding the disease of interest. NNH adjusted for the relative utility values is

$$RV\text{-NNH} = 1 / (RV * \Delta Q) = (1/RV) * NNH.$$

Then, to evaluate the benefit-risk balance of product accounting for the preferences of avoiding an adverse event relative to avoiding the disease of interest, NNT and RV-NNH are compared. To account for multiple ( $k$ ) adverse events, the RV-NNH approach is readily extended as

$$RV\text{-NNH} = 1 / [\sum_{i=1}^k RV_i (Q_{ti} - Q_{ci})] = 1 / [\sum_{i=1}^k RV_i (\Delta Q_i)]$$

 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>


where  $Q_{Ci}$  is the rate of adverse event  $i$  ( $i = 1, 2, \dots, k$ ) in the control group (%) and  $Q_{Ti}$  is the corresponding rate (%) in the treatment group<sup>45, 46</sup>. Again, the benefit-risk balance is assessed through comparing NNT with RV-NNH, where RV-NNH is now the reciprocal of a weighted sum of absolute risk reductions. The bad statistical properties associated with NNT carry forward to the RV-NNH. Furthermore, and unlike NNT-NNH, the RV-NNH does not have an easy clinical interpretation.

Further modifications to NNT have been proposed. Riegelman<sup>47</sup> introduced the **utility and time adjusted NNT** to adjust for differences in timing of the health outcomes. The modified NNT uses life expectancy and time-discounting and measures the number needed to treat in order to produce one additional year of quality-adjusted life at present value. Schulzer and Mancini<sup>48</sup> introduced the concept of NNT for an ‘unqualified success’ (treatment success without treatment-induced adverse event,  $NNT_{us}$ ) and NNH for an ‘unmitigated failure’ (treatment failure with treatment-induced side effects,  $NNH_{uf}$ ) to use for therapies that are associated with severe treatment-related adverse events. These numbers are typically calculated under the assumption of independence between treatment success and induction of an adverse event, although they can be adjusted for use when treatment success and induction of an adverse event are correlated, which is particularly relevant when the therapeutic window of the treatment is narrow<sup>48, 49</sup>. Similar to NNT, these modified measures can only accommodate one beneficial and one adverse endpoint (or combined endpoints) and they have bad statistical properties.

The **number needed to vaccinate**<sup>50, 51</sup> is defined as ‘the number of people needed to vaccinate in order to prevent one event of disease per year’ and is obtained as

$$NNV = 1/(inc \times VE),$$

with *inc* being the annual incidence among the unvaccinated and VE being the vaccine effectiveness. This is equivalent to the reciprocal of the annual absolute risk reduction, since VE measures the relative risk reduction. Additional measures have been proposed, including ‘numbers needed to target for vaccination’, ‘the number of vaccine doses needed’ and ‘vaccine cost’, clearly having a more economical interpretation<sup>50</sup>. The NNV has been criticized because they only take into account the direct protective effects of

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

vaccination and ignore the indirect effects generated through herd immunity<sup>51</sup>. NNT-like concepts that allow the assessment of the wider impact of a treatment on a particular population have been proposed as well. They are discussed as impact numbers (Section 3.2.4).

### 3.2.2 Differences in benefits and risks

The **minimum clinical efficacy** (MCE) determines the minimal therapeutic benefit for a treatment at which the treatment is worth administering<sup>52</sup>. The minimal clinical efficacy of a new treatment compared to a standard treatment (control) is

$$E_t \geq E_c + (Q_t - Q_c)/P_0,$$

where  $Q_t$  and  $Q_c$  represent the adverse event rate (%) in the new treatment and control group,  $P_0$  represents the event rates(%) in the untreated population and  $E_t$  refers to the efficacy of the treatment  $i$  ( $i=1,2$ ) relative to no treatment or

$$E_i = (P_0 - P_i)/P_0,$$

where  $P_i$  represents the event rate in the population receiving treatment  $i$  (either new treatment  $t$  or control treatment  $c$ ). It is very easy to show that the MCE comes down to comparing absolute risk differences in benefits and risks. Indeed, from above two equations it follows that

$$(P_0 - P_t)/P_0 \geq (P_0 - P_c)/P_0 + (Q_t - Q_c)/P_0,$$


which readily simplifies as

$$P_c - P_t \geq Q_t - Q_c.$$

As such, MCE makes an analogous comparison as NNT-NNH without taking the reciprocal of the absolute risk differences. Analogous to RV-NNH, the MCE has been extended with **relative utility values** (RV) to account for multiple adverse events and the relative importance of the adverse events compared to the disease of interest or

$$E_t \geq E_c + ((Q_{C1}-Q_{T1}) \times RV_1 + \dots + (Q_{Ci}-Q_{Ti}) \times RV_i + \dots (Q_{Ck}-Q_{Tk}) \times xRV_k)/P_0.$$

**Net Health Benefit (NHB)** and **Incremental Net Health Benefits (INHB)** are commonly used in Health Technology Assessment<sup>53</sup>. NHB is the difference between the sum of the (weighted) benefits and the sum of the (weighted) risks of a treatment.

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

**Incremental Net Health Benefit (INHB)** is then the difference between the NHB of the treatment of interest and the control treatment or

$$INHB = \left[ \sum_{i=1}^k E_{ti} - \sum_{j=1}^l R_{tj} \right] - \left[ \sum_{i'=1}^{k'} E'_{t'i'} - \sum_{j'=1}^{l'} R'_{t'j'} \right] = NHB_t - NHB_c,$$

where E refers to the expected benefits and R to the expected risks and with all outcomes expressed using the same metric. This is done by quantifying benefits and risks using available clinical data or post-marketing surveillance data and attaching preferences to each outcome. A positive INHB indicates that the net benefits of the new treatment are positive compared to the control treatment and favours the new treatment. The use of INHB has been advocated for quantitative benefit-risk assessment of drugs<sup>54</sup>. Typically, the NHBs are expressed using QALY's (e.g.<sup>55 56</sup>), but other metrics can be used as well, such as Life Years (e.g.<sup>57</sup>).


### 3.2.3 Ratios in benefits and risks

The **Benefit-risk ratio** (BRR) is simply the ratio of a given benefit (with rate P) and a given risk (with rate Q), or

$$BRR = P/Q.$$

Similar as the simple NNT-NNH comparison, the BBR lacks the ability to account for multiple benefits and risks and implies that equal importance is attached to benefit and harm.

The **Net Efficacy Adjusted for Risk (NEAR)**, which is the relative risk (RR NEAR) or odds ratio (OR NEAR) of treatment success without adverse event of a new treatment compared to a control treatment<sup>58</sup>. It can be considered the 'ratio-variant' of the NNT for an 'unqualified success'<sup>48</sup>. The NEAR is derived from a 2x2 table of treatment success and treatment-induced side effects, typically assuming independence between treatment success and induction of adverse events. Just like NNT for 'unqualified success', the NEAR is mainly relevant for therapeutic drugs with more common and

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>


more serious adverse events. The NEAR compares a single risk with a single benefit and assumes equal weighting of benefit and risk.

Similar in spirit as the NEAR, Chuang-stein developed the **global benefit-risk** (GBR) methodology to describe the benefit-risk of an intervention by comparing differences in GBR scores using asymptotic statistical distributions. The method consists of creating benefit-risk outcome categories (e.g. individual experiencing (a) benefit without adverse events, (b) benefit with adverse events, (c) no benefit and no adverse events, (d) no benefit and no adverse event and (e) serious adverse event leading to withdrawal/death) and making statistical comparisons of treatment groups. Using probabilities of belonging to a certain category and weights assigned to each category, three measures were proposed; linear score, ratio score and composite ratio score. The basic principle is to discount benefits by the presence of untoward safety experiences according to pre-specified levels at the individual patient level. The method is mainly useful for clinical data. The method incorporates weights, but is still limited to comparing a single benefit with a single risk (or composite measures).

The **incremental risk-benefit ratio** (IRBR) is analogous to the incremental cost-effectiveness ratio (ICER) used in Health Technology Assessment. The IRBR is simply the ratio of the difference in risk to the difference in benefit comparing the new treatment with a standard treatment. In case of comparing a single benefit with a single risk, the IRBR is equal to the ratio of NNH to NNT or

$$\text{IRBR} = (Q_T - Q_C) / (P_C - P_T) = \text{NNH} / \text{NNT},$$

where  $Q_T$  and  $Q_C$  are the treatment and control group adverse event rates (%) and  $P_T$  and  $P_C$  the treatment and control group efficacy event rates (%). The interpretation of the IRBR is the number of serious adverse event incurred for every efficacy event. Similar as the INHB, the IRBR can be extended to account for multiple events.

 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

### 3.2.4 Impact numbers

Most measures discussed so far are limited to clinical (or regulatory) decision-making and lack a public health perspective. **Impact numbers** intend to fill that gap<sup>59-61</sup>. They are NNT-like concepts that allow the assessment of the wider impact of a treatment<sup>59, 60</sup> or risk factor<sup>61</sup> on the population (and not only on those actually treated or exposed).


The **disease impact number** (DIN) and the **population impact number** (PIN) can be used to assess the impact of an intervention in a population. The DIN is defined as ‘the number of those with the disease in question among whom one event will be prevented by the intervention’ and is given by

$$DIN = 1/((I_u - I_e) \times P_{e|d}),$$

where  $I_e$  and  $I_u$  are the event rates (%) among the exposed and unexposed and where  $P_{e|d}$  is the prevalence of exposure to intervention among the diseased<sup>60</sup>. The PIN is defined as ‘the number of those in the whole population among whom one case is prevented by the intervention’. It is calculated as

$$PIN_{interv} = 1/((I_u - I_e) \times P_{e|d} \times P_d) = 1/((I_u - I_e) \times P_e)$$

with  $P_d$  being the disease prevalence (%) and  $P_e$  the exposure prevalence (%) within the whole population. It is clear that for every intervention, disease and population impact numbers are higher than NNT. The DIN will be much higher than the NNT (and hence unfavourable) in case only a small proportion of the diseased population is having access to the intervention (e.g. because it is cost intensive, technically demanding, often contra-indicated). The PIN combines the probability of intervention success, the accessibility of the intervention and disease occurrence. Highly accessible and effective interventions for a common disease will have a favourable PIN. The DIN and PIN have a sound population impact interpretation, provided that the absolute risk difference, exposure prevalence and disease prevalence apply to the same population<sup>59, 60</sup>. The PIN and the DIN differ with respect to the population they are referring to: the PIN refers to the whole population, the DIN to the diseased population (Figure 3.4a).

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b> 38/97

The **population impact number** (PIN), the **case impact number** (CIN), the **exposure impact number** (EIN) and the **exposed case impact number** (ECIN) can be used to measure the impact of a risk factor on the population<sup>61</sup>. The PIN is ‘the number of those in the whole population amongst whom one case is attributable to the exposure to the risk factor’. The PIN is the reciprocal of the population attributable risk (PAR) or

$$PIN_{\text{risk}} = 1/[(I'_e - I'_u) \times P_e] = 1/PAR,$$

where  $I'_e$  and  $I'_u$  are the adverse event rates (%) among the exposed and unexposed and where  $P_e$  is the exposure prevalence. The CIN is the ‘the number of people with the disease among whom one case is attributable to the exposure or the risk factor’ and equals the reciprocal of the population attributable fraction (PAF) or

$$CIN = I'_{\text{pop}}/PAR = [P_e \times I'_e + (1 - P_e)I'_u]/[(I'_e - I'_u) \times P_e] = 1/PAF,$$


where  $I'_{\text{pop}}$  is the adverse event rate (%) within the population. The EIN ‘the number of exposed people among whom one excess case is attributable to the risk factor’ or

$$EIN = 1/[(I'_e - I'_u)] = 1/ARR,$$

and is called the NNH in the context of therapeutic interventions. The ECIN is ‘the number of exposed cases among whom one event is attributable to exposure’ and equals the reciprocal of the aetiological fraction (AF) or

$$ECIN = I'_e/[(I'_e - I'_u)] = 1/AF.$$

The risk-related PIN, CIN, EIN and ECIN also differ with respect to the population they are referring to: the PIN refers to the whole population, the CIN to the population of cases, the EIN to the population of exposed and the ECIN to the population of exposed cases (Figure 3.4b). The impact numbers discussed so far are all NNT-like measures and hence, suffer from the same statistical issues as the NNT. It is anticipated that their main use will be in communicating the population impact to public health professionals and policy makers<sup>61</sup>.

 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

An impact measure related to the PIN is the **Numbers of events prevented in your population** (NEPP), quantifying the population impact of an intervention<sup>62</sup>. Starting from the number of people in that population who are eligible for treatment (NTP), or  $NTP = \text{population size} \times P_{e|d} \times P_d$ .

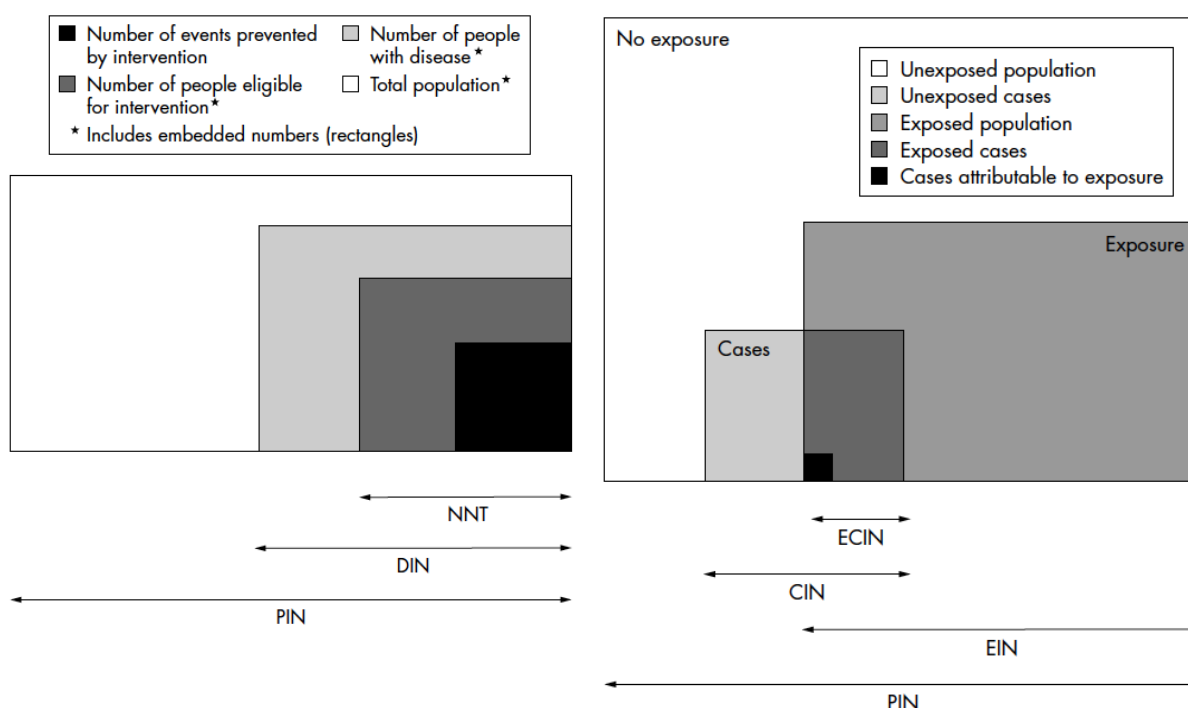
The NEPP is then obtained as


$$NEPP = NTP \times ARR = \text{population size} / PIN,$$

which is straightforwardly interpreted as ‘the numbers of events prevented in the population by the intervention’. Another measure related to the PIN is the **population impact number of eliminating a risk factor** (PIN-ER-t), which intends to measure ‘the potential number of disease events prevented in your population over the next  $t$  years by eliminating a risk factor’<sup>63</sup>. The PIN-ER-t is calculated as

$$PIN-ER-t = \text{population size} \times I_t \times PAR = \text{population size} \times I_t / PIN,$$

where  $I_t$  is the incidence of the outcome in the whole population over  $t$  years.



 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

(a) intervention-related


(b) risk-related

**Figure 3.4.** Visual representation of the population to which each the intervention-related impact numbers (left) and risk related impact numbers (right) relates; population-impact number (PIN) – total population, Disease impact number (DIN) – diseased population, Numbers needed to treat (NNT) – exposed population, Exposed impact number (EIN) – exposed population, Case impact number (CIN) – diseased population, Exposed case impact number (ECIN) – diseased population that is exposed (figures from <sup>59, 61</sup> ).

### 3.2.5 Concluding remarks

The benefit-risk measures were divided into (1) numbers-needed-to-treat (NNT) like measures, (2) differences in benefits and risk, (3) ratios of benefits and risks and (4) impact numbers. The NNT is the reciprocal of the absolute risk reduction. The NNT has been extended in order to allow integrating multiple outcomes and value judgements (RV-NNT), to allow a public health interpretation (i.e. impact numbers) and has been applied to vaccination as well (i.e. NNV). The NNT has been valued for its intuitive interpretation by clinicians and policy makers (i.e. ‘the effort that must be spent in order to accomplish a treatment target’). However, the variance estimation of the NNT (and all its variants) is problematic, implying that NNT is not a good measure to reflect uncertainty. The NNT-measures have their virtue in easy communication rather than in properly assessing the benefit-risk balance.

The undesirable statistical properties of the NNT-like measures are avoided by not taking the reciprocal of risk differences. Measures as (relative-value adjusted) minimum clinical efficacy (MCE and RV-MCE) and (incremental) net health benefit (NHB and INHB) are measures based on differences in benefits and risks. Particularly, the measures of (I)NHB are well suited for benefit-risk assessment, because they allow integrating multiple benefits and risks, as well as value judgements and are associated with proper measures of uncertainty.


 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

Ratios of benefits and risks have been proposed as well for benefit-risk assessment. They clearly have a relative interpretation. However, bad statistical properties result when comparing two treatment options using ratios (e.g. IRBR). Indeed, the division by a difference in probabilities implies that the confidence interval will be problematic whenever the difference in efficacy is non-significant.

Finally, impact measures were suggested as measures of benefit-risk<sup>9</sup>. The majority of impact measures (i.e. DIN, PIN, CIN, EIN, ECIN) are NNT-like concepts for which constructing confidence intervals is problematic. Impact measures are developed to support the implementation of a given health measure within a local population. They provide estimations of population impact, to which costs can be easily linked. As such impact measures are generally more suited for cost-effectiveness analysis than for benefit-risk assessments. Indeed, it is highly questionable whether e.g. the incidence of disease or the prevalence of exposure to the intervention should be taken into account for the benefit-risk assessment of a therapeutic drug.

For preventive measures, population impact matters. Indeed, the expected benefit of a preventive measure depends on the effectiveness of the prevention and on the incidence of the preventable disease, as properly reflected by number-needed-to-vaccinate<sup>50</sup>. For some vaccines, it is important to measure impact defined as the overall effect of the vaccination programme on the (partially) vaccinated population (including direct and indirect effects)<sup>12</sup>. Tuite and Fisman<sup>51</sup> proposed a measure that does reflect the impact of vaccination at population level. Their measure has a similar interpretation as number-needed-to-vaccinate. In particular, they calculated the number-needed-to-vaccinate as the ratio of the number of cases prevented through vaccination (directly and indirectly) to the number of individuals vaccinated. Their calculations were based on mathematical models simulating epidemic and endemic diseases.

### **3.3 Composite Health Measures**

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	42/97

Composite health measures combine different health outcomes (morbidity and mortality) into a single commensurable score. By far, the most common composite health measures are QALYs (typically used in health economics) and DALYs (typically used in public health)<sup>64, 65</sup>. They use validated methods to determine preferences and are used as metrics in some benefit-risk measures described earlier (i.e. IRBR, INHB).


### 3.3.1 QALY

**Quality-adjusted life years** (QALYs) represent the number of life years spent in discrete health states ( $i= 1, \dots, k$ )<sup>66</sup>. QALYs, in their most simple form, are calculated as

$$QALY = \sum_{i=1}^k q_i t_i,$$

where  $q_i$  represent the Quality of Life (QoL) associated with health state  $i$  and  $t_i$  the time spent in this state. The  $q_i$  's are also referred to as 'health utilities' and represent the quality of life (encompassing both physical and mental dimensions) enjoyed by individuals in health state  $i$ . They are elicited from the general population or from groups of patients, typically using elicitation techniques such as time-trade-off and standard gamble. The utilities produced represent the valuations attached to each health state with zero being equivalent to death and one representing perfect health state. Negative QALYs are possible as well. However, the utilities for short-term diseases in young children are virtually non-existent and the appropriate methodology for obtaining them among children is subject to debate<sup>67</sup>.

**QTwist** is an extension of QALY developed for the application to cancer treatments<sup>68</sup>. QTwist is obtained by dividing the survival time of a patient into discrete health states (time with toxicity effects, time without toxicity and disease and time from relapse to death), to which different utilities are attached.

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b> 43/97

### 3.3.2 DALY


**Disability-adjusted life years** (DALYs) represent the number of healthy life years lost due to a certain disease or condition<sup>69, 70</sup>. DALYs are calculated by adding the adjusted number of years lived with disability (YLDs) to the number of years of life lost due to premature death (YLLs). Basically, DALYs are calculated as

$$DALY = \sum_{i=1}^k d_i t_i + E_{(age\ at\ death)},$$

where  $d_i$  represents the disability associated with health state  $i$  and  $t_i$  the time spent in this state and where  $E$  is the residual life expectancy at age of death. The disability weights  $d_i$  indicate to which extent the health state  $i$  reduces the patient's physical capacity, ranging from zero (perfect health) to one (worst possible health state). The disability weights tend to be based on a universal set of standard weights based on expert opinion, with the Global Burden of Disease (GBD) disability weights being the most commonly used ones. DALYs are also used within the BCoDE (Burden of Communicable Diseases in Europe) study to calculate the burden of infectious diseases in the European member states<sup>71</sup>. There is a debate on the validity of the DALYs. It is argued that the DALY method is problematic because it uses the residual life expectancy at age of death<sup>72</sup>. This feature might cause a life extending intervention to increase the disease burden. Indeed, if the years of life gained (of low quality) due to the intervention are lower than the additional years of life lost due to the patient living longer (and hence having a higher residual life expectancy). This will only happen if older patients are treated with an intervention that extends life with a limited amount of time and of poor quality.

### 3.3.2 HALE

**Healthy life expectancy** (HALE) is a metric developed by the WHO that connects life expectancy and good health<sup>73</sup>. HALE is the average number of years that a person can

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	44/97

expect to live in full health by taking into account years lived in less than full health. This measure is less commonly used.

### 3.3.4 Concluding remarks


Vaccination programmes are typically evaluated by estimating the QALYs gained or DALYs averted. However, these evaluations typically do not take into account adverse events<sup>74</sup>. Both DALYs and QALYs are reasonable choices for benefit-risk assessment of vaccines, although not without issues. QALYs have already been used for benefit-risk assessment as the common metric for Incremental Net Health Benefits (e.g.<sup>55 56</sup>). The composite health measures could be further tailored to the specificities of benefit-risk assessment. A systematic overview of the differences between QALYs and DALYs is given in Table 3.4.

**Table 3.4.** Systematic overview of QALYs and DALYs.

QALYs	DALYs
Combines quantity of life with quantity of life.	Combines morbidity and mortality
Requires time spent in the different health states and the associated health utility.	Requires time spent in the different disabled health states, the associated disability weight and the residual life expectancy at age of death.
Utilities are derived from the general population or patient population using common elicitation techniques.	Disability weights are standard sets based on expert opinion.
Obtaining utilities from young children is subject to debate.	The validity of DALYs is questioned. DALYs are mainly problematic to evaluate life-extending interventions.
	DALYs are global and are used within the BCoDE project.
Cross-vaccine comparisons are possible.	Cross-vaccine comparisons are possible.

## 3.4 Quantitative benefit-risk frameworks

Quantitative frameworks are structured stepwise processes (like the descriptive and semi-quantitative frameworks), as part of which an overall benefit-risk score is calculated.


	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

### 3.4.1 ‘Principles of Threes’, TURBO and Beckmann

The ‘Principle of Threes’<sup>75</sup>, the TURBO model<sup>76</sup> and Beckmann model<sup>77</sup> can be considered as first attempts to develop a quantitative benefit-risk framework. The ‘**Principles of Threes**’<sup>75</sup> (1996) is a grading system to quickly assess the benefit-risk balance of a medicine by grading the (1) seriousness, (2) duration and (3) incidence of the (1) the treatment benefits, (2) the treatment induced adverse effects and (3) the target disease. Each parameter is rated as (1) low, (2) medium and (3) high. The methodology aims at visible weighting the benefits and risks. The third dimension (i.e. the seriousness, duration and incidence of the target disease) is used to determine how much the benefits should outweigh the risks.

The **TURBO** model<sup>76</sup> (1998) (Transparent Uniform Risk/Benefit Overview) is a quantitative and graphical approach to comparative benefit-risk analysis. Risk scores (R-scores) are assigned to the risks associated with the most serious adverse event (scores 1-5) and an additional risk (scores 1-2). Similarly, Benefit scores (B-scores) are assigned to the primary benefit (scores 1-5) and an ancillary benefit (scores 1-2). The R-scores are determined by severity of the risk or the impact on health status and socio-professional capabilities (minor, slight, moderate, severe, very severe) and the probability of the risk (very rare, rare, not uncommon, common, frequent). Similarly, the B-scores are determined by the degree of benefit (minor, slight, moderate, marked, major) and the probability of the benefit (rare, not uncommon, common, frequent, nearly always).

**Beckmann**<sup>77</sup> (1999) described a model in which the evidence-weighted benefit is balanced against the evidence-weighted risk. The benefit of a product is evaluated for each indication separately and is defined as ‘efficacy for a given indication x responder rate x the evidence of the benefit’. The evidence of the benefit is established using a hierarchy of evidence: randomized controlled intervention trials, non-randomized controlled intervention trials, controlled observational studies, case series, reported experience and no data. The risk of a specific adverse effect is defined as ‘seriousness x frequency x the evidence for the risk caused by the adverse effect’, with the seriousness

 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

based on the WHO Collaborating Centre for International Drug Monitoring. Then, in case of multiple adverse events, the sum of the evidence-based risks is taken, although difficult to accomplish.


For all models, various limitations have been identified<sup>78</sup>. One of the most important limitations of the models is that they essentially cover only one benefit and one risk criteria. Furthermore, these models (e.g. criteria, grading systems) have not been validated and their actual use seems to be very limited<sup>78</sup>. The models can be considered as predecessors of more structured benefit-risk assessment. A strong point of the Beckmann model is the importance attached to the strength of the evidence.

### 3.4.2 Benefit-less risk analysis

In line with the basic principle of GBR to discount benefits by the presence of untoward safety experiences, Chuang-Stein introduced **Benefit-less risk analysis** (BLRA)<sup>79</sup>. The same benefit-risk outcome categories are created as in GBR. Then, for each individual  $i$ , the risk-adjusted benefit measure is obtained by discounting the benefit by a multiple of the aggregated risk score (RS) or

$$E_i^* = E_i - f \times RS_i,$$

where  $f$  controls the amount of discounting. Then, if applied in a clinical trial comparing different treatments, statistical significance tests can be performed. The model provides a detailed methodology for assessing the safety data (organised following body functions), proposes to use sensitivity analysis and provides a structure for combining benefits and risks into a single measure. The model has been criticized because it requires weights that reflect the relative seriousness of groups of adverse events organised by body function<sup>78</sup>. Furthermore, the model is developed for clinical trial data and therefore not suited for post-marketing benefit-risk surveillance.

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b> 47/97


### 3.4.3 Multi-criteria decision analysis and extensions

Multi-criteria decision analysis (MCDA) is a methodology for integrating various benefits and risks, and consequently includes value judgements. The use of MCDA in the context of drug benefit-risk analysis was first proposed by Mussen et al<sup>78</sup> and has been extensively evaluated by the PROTECT consortium<sup>6</sup>. Both EMA<sup>2</sup> and PROTECT<sup>9</sup> recommend the use of MCDA for pharmaceutical benefit-risk assessment. Developing a MCDA model involves different steps, which are summarized in Table 3.5. For worked-out examples we refer to <sup>6, 80</sup>.


MCDA provides a highly structured approach based on the ProACT-URL framework<sup>9</sup>. It allows assessing and integrating multiple benefits and risk criteria and comparing multiple options. MCDA can be applied for benefit-risk assessment of vaccines given that special consideration is paid to the vaccine specificities as discussed when appraising the BRAT and ProACT-URL frameworks (see Sections 3.1.2 – 3.1.3).

Furthermore, MCDA assumes fixed values for the criteria measurements as well as for the weights reflecting the clinical relevance of the different criteria. The uncertainty in model inputs can be investigated using simple (deterministic) sensitivity analyses (i.e. change the input parameters and re-run the model)<sup>81</sup>. However, this might be cumbersome if many model parameters (both criteria measurements and weights) are subject to uncertainty. A straightforward extension is using **probabilistic sensitivity analysis** (PSA). In a PSA, the uncertain model inputs are represented by probability distributions and Monte Carlo simulation is used to evaluate the model. Wen et al. (2014)<sup>82</sup> recently introduced this Monte-Carlo approach to account for uncertainty in MCDA models, as well as the delta-method.

**Stochastic multi-criteria acceptability analysis** (SMAA) is very similar to a probabilistic simulation analysis of MCDA. SMAA is a family of probabilistic extensions of MCDA methods that allow defining preference information and criteria measurements with uncertain or missing values<sup>83</sup>. SMAA uses Monte Carlo simulation to evaluate the uncertain information. Missing preference information is now represented using


	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	48/97

uniformly distributed normalized weights (e.g. the feasible weight space in the 3-criterion case is a triangle with corners (1,0,0), (0,1,0) and (0,0,1)). Uncertain preference information can then be presented by weight intervals or importance ranking of the criteria that constrain the uniform weight space. Uncertain criteria measurements are represented by suited probability distributions (e.g. beta distributions for probabilities, Poisson distributions for counts). Clearly, SMAA is very similar to PSA. The only difference is that SMAA uses weight spaces based on uniformly distributed normalized weights to reflect uncertain preference information, whereas triangular or betapert distributions are typically used in PSA to reflect preference information.

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

**Table 3.5.** Steps in creating and exploring an MCDA model (from <sup>80</sup>).

<b>1. Context</b>		
	Establish the decision context	<ul style="list-style-type: none"> <li>Identify the medicinal product</li> <li>Identify the therapeutic area and the indication for use</li> <li>Recognise the unmet medical need, severity and morbidity of condition, affected population, patients' and physicians' concerns, time frame for health outcomes</li> <li>Define the decision problem (what is to be decided and by whom)</li> </ul>
<b>2. Alternatives</b>		
	Identify the options	<ul style="list-style-type: none"> <li>Describe the medicinal products</li> <li>Describe the comparators</li> </ul>
<b>3. Criteria</b>		<ul style="list-style-type: none"> <li></li> </ul>
	Identify and define the criteria for assessing the effects of each alternative. Represent these in an effects tree	<ul style="list-style-type: none"> <li>Select the favourable effects</li> <li>Select the unfavourable effects</li> </ul>
<b>4. Weighting</b>		<ul style="list-style-type: none"> <li></li> </ul>
	Establish a measurement scale for each criterion and assess the relative importance of the scales	<ul style="list-style-type: none"> <li>Define each effect's measurement scale and its units (e.g., mean, median scores, proportions) and determine upper and lower limits that encompass a plausible range for the data</li> <li>Assess swing weights to represent the clinical relevance of the swing from the lower to the upper limit of each scale</li> </ul>
<b>5. Scoring</b>		<ul style="list-style-type: none"> <li></li> </ul>
	Describe how the alternatives perform for each of the criteria and show how to convert input data into preference values (i.e. assess value functions).	<ul style="list-style-type: none"> <li>Gather available data, pooling or performing meta-analysis of multiple data sources, to give data summaries and confidence intervals</li> <li>Provide data summaries in effects table with alternatives in columns and criteria in rows</li> <li>Assess linear or nonlinear value functions using direct (more means better) for favourable effects, and inverse (more means worse) for unfavourable effects</li> </ul>
<b>6. Results</b>		
	Calculate results and provide graphical displays	<ul style="list-style-type: none"> <li>Multiply preference values and criterion weights and sum the products to obtain overall value (usually carried out by appropriate software)</li> <li>Construct preference value bar graphs for favourable and unfavourable effects, and for individual effects</li> <li>Calculate difference displays for pairs of alternatives</li> </ul>
<b>7. Sensitivity analyses</b>		
	Explore effects of uncertainty on the benefit-risk balance	<ul style="list-style-type: none"> <li>Vary individual weights over their entire range from 0 to 1; display the overall results graphically</li> <li>Change input data over ranges of uncertainty (e.g. pessimistic values for favourable effects and optimistic ones for unfavourable effects)</li> <li>Examine the overall BR-balance under possible future scenarios (e.g. adverse events) by changing input data and criteria weights</li> <li>Revise any of the above numbered steps and tasks as insights emerge</li> </ul>
<b>8. Recommendation</b>		<ul style="list-style-type: none"> <li></li> </ul>
	Formulate recommendations	<ul style="list-style-type: none"> <li>Judge the relative importance and effect of the decision maker's risk tolerance for this product</li> <li>Consider how this decision is consistent with similar past decisions in the future easier or more difficult</li> <li>Metabolize the results before making any decisions (newly constructed preferences can change with reflection and new insights surface)</li> </ul>

 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>


### 3.4.4 Data-driven benefit-risk assessment (Sarac et al.)

Sarac et al. proposed a data-driven benefit-risk assessment method, where two or more drugs can be compared<sup>84, 85</sup>. Their approach is similar to MCDA, but is tailored directly to drug development and approval. They proposed a structured 8-step process, involving: (1) defining the decision context, (2) defining the decision profile, (3) weighting the criteria, (4) scoring the performance of the drugs (and the comparator) for each of the selected criteria, (5) evaluating the uncertainty, (6) calculating the weighted scores, (7) presenting the results and (8) obtaining the overall conclusion. Their method is data-driven, based on the analysis of clinical data, and simple and transparent rules for weighting and scoring has been proposed. Indeed, each benefit and risk criterion is assigned a weight of 1 (low), 2 (medium) and 3 (high) and weighting is done independently of the data. Then, for each criterion, the drug is scored relative to the comparator using a simple and transparent scale: -1 (inferior), 0 (non-inferior or equivalent) and 1 (superior). The method of scoring may be different for different types of data (e.g. difference distribution scoring for continuous variables, confidence interval scoring for rare events). They further proposed to account for uncertainty through the use of bootstrapping and to visualize the results using tornado-like diagrams.

The method proposed by Sarac is specifically developed to provide structure and support to the benefit-risk interpretation of clinical trial data. Particular features of the analysis of clinical trial data (e.g. inferiority, non-inferiority, superiority) play a special role within Sarac’s approach, making it less suited for post-marketing surveillance. However, the simplicity and full transparency of this approach are extremely valuable.

### 3.4.5 Clinical utility index

The **clinical utility index** (CUI) quantifies the tradeoffs between different product attributes by providing a single metric for the multiple attributes (i.e. criteria) of the product profile<sup>86</sup>. The additive multivariate utility function is

 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

$$CUI = \sum_{i=1}^n w_i U_i(x_i),$$


with  $i$  indexed over  $n$  drug attributes, with weight  $w_i$  and utility function  $U_i(x_i)$  that transforms the attribute from its original scale into the (0,1) scale of utility. The attributes are typically limited to clinical attributes. Key steps in clinical utility analyses are: (1) identification of the key attributes, (2) normalization of the attributes, (3) assigning importance weights to the attributes and (4) sensitivity analysis and measurement of uncertainty. The CUI tool shows a lot of similarities with MCDA (multiple criteria, scaling, weighting, sensitivity analysis,...) and has been mainly used in early drug development.

### 3.4.6 Concluding remarks

All quantitative frameworks described are tailored towards (early) drug development, with the exception of MCDA. MCDA was originally developed within the field of operations research<sup>87</sup> and only recently introduced for medicinal benefit-risk assessment<sup>78</sup>. MCDA has been valued because it provides a highly structured approach in line with the ProACT-URL framework, allowing to assess and integrate multiple benefits and risks for multiple options<sup>9</sup>. Important choices are to be made when building and trimming the value tree, constructing the effects tables, defining the (scales of the) value functions and eliciting the weights. MCDA and its stochastic variants (SMAA) seem generally applicable to assess the benefit-risk balance of vaccines given that special consideration is paid to vaccine specificities such as time window, indirect effects and high levels of uncertainty.

## 3.5 Modelling approaches

(Decision) Analytical modelling techniques facilitate the estimation of the consequences of health care decisions and are commonly used in Health Technology Assessment (HTA)<sup>88</sup>. As also recognised by Lynd & O'Brien<sup>15</sup>, it is natural to apply techniques used for cost-effectiveness analysis to benefit-risk assessment as well. Indeed, the risks of a


 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

medicine can be considered a nonmonetary cost and benefits are synonymous with effectiveness. Therefore, we describe the most commonly used modelling techniques in HTA<sup>89</sup> (i.e. decision trees, state-transition models, discrete event simulation and dynamic transition models) as well as some meta-analytic approaches. We give examples of their application for benefit-risk assessment. Finally, we will discuss the different sources of model uncertainty and how they can be dealt with.

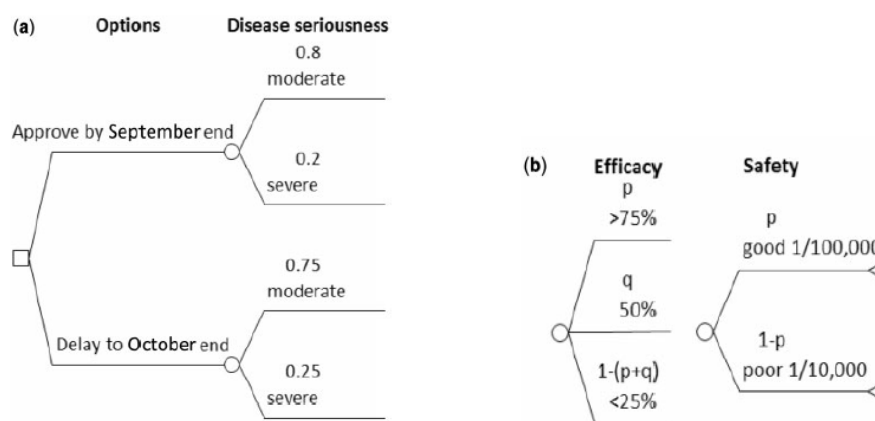
### 3.5.1 Decision trees and influence diagrams

A simple way to analytical modeling is the **decision tree** (Figure 3.5). There are three types of nodes on a decision tree: decision nodes, chance nodes and terminal nodes. The first branch in the tree is the decision node and represents the decision question. The pathways that follow each decision option are the logical consequences, possibly emanating from chance nodes. The options at a chance node should be exhaustive and mutually exclusive and their probabilities should sum to 1. The end points at each pathway are the terminal nodes, to which values (QALY's, utilities,...) are assigned. Then, the decision tree is averaged out or 'rolled back' to calculate the expected value of each option. Decision tree models may be more realistic if the branching probabilities (and possibly the values or utilities) are represented by distributions rather than point estimates. Monte Carlo simulation techniques<sup>90</sup> and Bayesian analyses<sup>91</sup> can then be used for modeling this uncertainty. **Influence diagrams** offer an alternative approach to graphically represent a decision problem (Figure 3.6). An influence diagram is a directed acyclic graph with three types of nodes (rectangle: decision node, oval: uncertainty node and diamond: value node) and three types of arrows (functional arcs ending in a value node, conditional arcs ending in uncertainty nodes and informational arcs ending in a decision node). Compared to decision trees, influence diagrams offer a more compact representation.


Decision trees and influence diagrams offer a nice graphical representation of the decision problem and are valued for their transparency. They aid structuring the

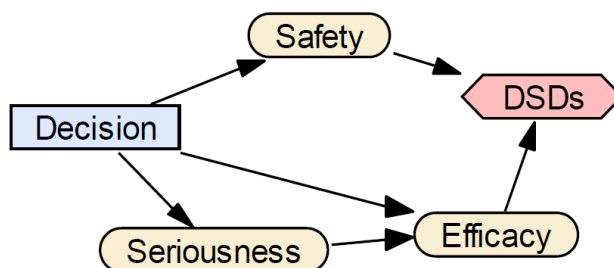
	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

decision problem and clarifying the options and their consequences). However, decision trees lack a time variable and do not allow for time-dependent variables (such as time-to-event) or recurrent events and interactions. As such, they are not suited for modeling complex, time-dependent and dynamic decision problems. Decision trees have already been used for benefit-risk analyses<sup>57</sup>, even for vaccines<sup>92, 93</sup>. Decision tree models have also been used for vaccine-related economic analysis<sup>93, 94</sup>



**Figure 3.5.** Decision tree on modelling the risk–benefit impact of H1N1 influenza vaccines (figure from <sup>92</sup>). (a) The initial part of the decision tree: a decision node (square) with two decisions followed by Disease seriousness nodes (circles) with two possible outcomes and their probabilities, which are conditional on the decision. (b) The subsequent events’ efficacy and safety, and their outcomes. The Safety node attaches at the end of each branch of the Efficacy node, which in turn attaches at the end of each Serious node’s outcome branch. The triangles at the end of each path receive the number of DSDs (deaths and serious disabilities) appropriate for the outcome of the uncertain events in that path.

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	54/97




**Figure 3.6.** Influence diagram representation of a decision tree on modelling the risk-benefit impact of H1N1 influenza vaccines<sup>92</sup>.

### 3.5.2 State transition models

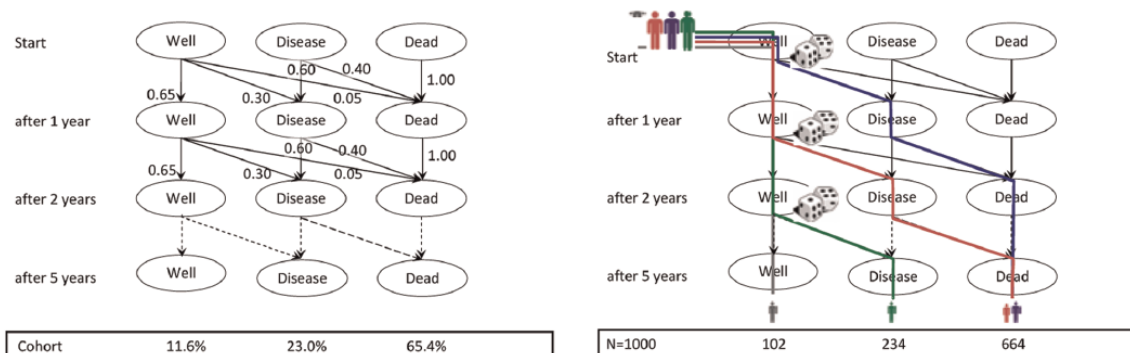
State transition models (STMs) assume that a patient is in one of a finite number of discrete health states (also called Markov states) at any point in time and make transitions between the health states. The probability of staying in a health state or moving towards another health state is determined by a set of transition probabilities. A STM is typically evaluated as a cohort simulation or Monte Carlo simulation. The constituent elements of a state-transition model are: the initial state vector, states, transitions with certain transition probabilities, cycle length and state values (e.g. life years, QALY's).

When cohort simulation is used, a hypothetical (closed) cohort of patients transitions to the model simultaneously at specified time intervals (Figure 3.7a). These models are also called **Markov models** or **cohort models**. These models are relatively simple to develop and communicate. Unlike decision trees, Markov models permit a flexible sequencing of outcomes, including time-dependent parameters such as recurring outcomes and time-to-event outcomes. An important limitation of the Markov model is the assumption that the transition probability only depends on the current health state and not on the previous ones (also called the Markovian property). Solutions have been proposed to this problem. However, they result in overly complex models.

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b> 55/97

**Individual-based state transition models** are a special case of micro-simulation models and are evaluated using first order Monte-Carlo simulation. In these models, patients are randomly selected from the hypothetical cohort and they transition to the model once at a time (Figure 3.7b). Unlike the Markov model, the individual-based STM is not characterized by the Markovian property because the state history of an individual can be traced and the state transition probabilities can be adjusted accordingly. Compared to Markov models, the individual-based STM is computationally much more intensive.


Consensus-based guidelines for the application of STMs in the context of health care (ISPOR) exist<sup>95</sup>. They are recommended when the decision problem can be framed in states, interactions between individuals are not relevant and the population is a closed cohort. STMs (Markov models) have already been successfully used for benefit-risk analyses<sup>96</sup>, also for vaccines<sup>97-100</sup>.



**Figure 3.7.** Example of a Markov model (left) and individual-based state transition model (right). In a Markov model, the entire cohort is redistributed across states after each cycle. In an individual-based model, first order Monte-Carlo simulation is used to move individuals across states (figure from <sup>95</sup>).

### 3.5.3 Discrete event simulation

Discrete event simulations (DES) describe the progress of individuals through health care processes or systems as a discrete sequence of events in time. The system is assumed to not change between consecutive events and therefore, the simulation model

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

can jump in time from one event to the next. DES is an operational research model, being originally developed for industrial planning. The constituent elements of a DES are: entities (e.g. patients), events (e.g. adverse events, hospitalization), attributes (e.g. age, sex, past events) and resources (e.g. number of beds). In addition, time is a fundamental component of a DES as well. An example of a graphical representation of a DES is given in Figure 3.8. Unlike decision trees and state-transition models, a DES allows entities (e.g. patients) within a system to interact or compete with each other. Unlike state-transition models, the timing of the events is not fixed by the cycle lengths, but can be stochastic. Compared to decision trees and state-transition models, a DES is more complex to build, to understand and to communicate.

Consensus-based guidelines for the application of DES in the context of health care (ISPOR) exist<sup>101</sup>. A DES is best used when the modeled system involves competition for resources, the timing of the event is stochastic and when there are interactions between events or entities. DES has been used for benefit-risk analysis as well<sup>55, 102</sup>.

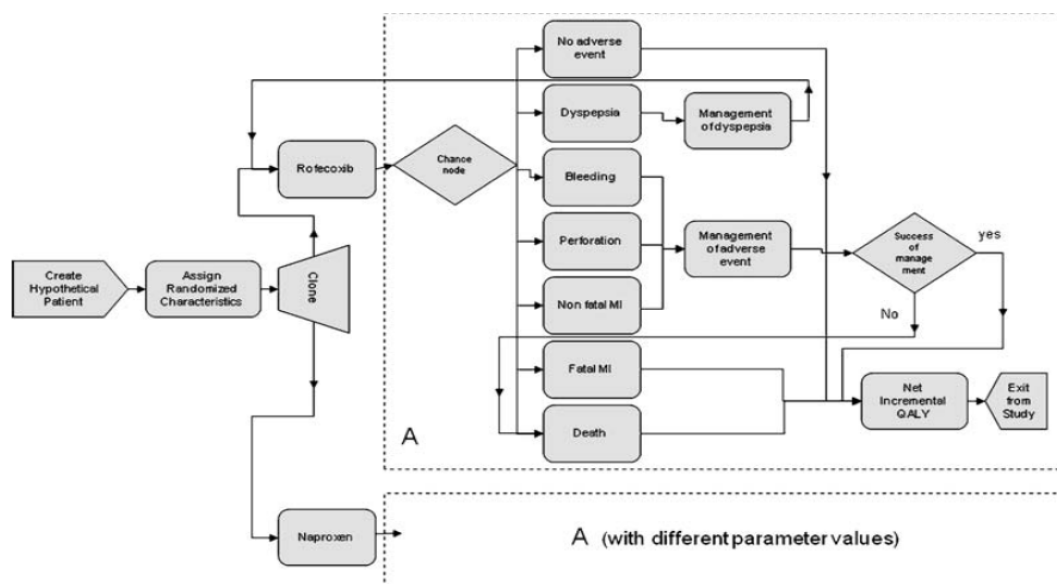



Figure 3.8. Example of a discrete event simulation model, used to calculate the incremental net benefit of rofecoxib relative to naproxen in arthritis patients over a 1-year time horizon (figure from <sup>55</sup>).

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	57/97

### 3.5.4 Dynamic transmission models


Dynamic transmission models are mathematical models used to model infectious diseases, explicitly modeling disease transmission. Static models (e.g. Markov models, discrete event simulation) assume a constant risk of infection (or force of infection) whereas dynamic models allow the force of infection to depend on the number of infectious agents within the population at a given point in time. There are two main groups of dynamic transmission models: compartmental models and individual-based models. Compartmental models divide the population according to infection status (e.g. SIR-model: susceptible-infectious-recovered) and assume homogeneous mixing of the population. Individual-based models are a collection of individuals (agents) and rules specifying how they behave within a specific environment. Compared to compartmental models, individual-based models are more flexible and more computer-intensive.

Consensus-based guidelines for the application of dynamic models in the context of health care (ISPOR) exist<sup>103</sup>. They are recommended when evaluating an intervention against an infectious agent when the intervention affects disease transmission and when the intervention affects a pathogen’s ecology (i.e. strain replacement). A static model is acceptable if target groups eligible for intervention are not epidemiologically important, when the effects of vaccination are expected to be entirely direct and when the static model suggests that the intervention is ‘cost-effective’, and that the indirect effects would enhance this.

### 3.5.4 Meta-analytic approaches

Meta-analysis is a well-established technique to combine multiple sources of quantitative evidence. It is common practice to use pair-wise meta-analysis methods to estimate the effectiveness of two specific interventions (A versus B comparisons).


Recently, more advanced evidence-synthesis methods were developed. **Mixed**

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	58/97


**treatment comparisons** (MTCs) (also called Multiple Treatment Comparisons or network meta-analysis) are a generalisation of pair-wise meta-analysis. MTC allows the simultaneous estimation of the effectiveness of multiple treatments using a network of trials that individually do not compare all treatment options (e.g. using A versus B, B versus C and A versus C comparisons)<sup>104</sup>. Pairwise meta-analysis and mixed treatment comparisons can both be formulated within a common Generalised Linear Model (GLM) framework, which can be applied in either frequentist or Bayesian contexts<sup>105</sup>. The **confidence profile method** (CPM) was developed in the late eighties as a Bayesian method to evaluate evidence from different types of empirical studies, adjust individual pieces of evidence for biases, combine evidence from different studies and incorporate subjective judgements to derive a probability distribution for the intervention effects<sup>106</sup>. Multiple pieces of evidence are incorporated by successive applications of Bayes' theorem. The **multi-parameter evidence synthesis** (MPES) approach builds on and extends the confidence profile method<sup>107</sup>. Within a MPES model, multiple sources of information on either model parameters and/or functions of several parameters are incorporated. An important feature of MPES is the ability to incorporate information on more functions of parameters than there are parameters in the model, allowing to validate the model and to check the consistency of the different sources of evidence. MPES has been used in epidemiology (to estimate disease impact<sup>108, 109</sup>) and health technology assessment. The MPES approach is a powerful technique to combine evidence from different sources and is gaining popularity. However, developing a MPES model is time-consuming and technically complex.

### 3.5.5 Parameter estimation and uncertainty

Different types of uncertainty in analytical modelling techniques exist, i.e. stochastic uncertainty, parameter uncertainty, heterogeneity and structural uncertainty. Stochastic uncertainty (or first order uncertainty) relates to the fact that 'identical' patients (i.e. patients having the same genetic predisposition and sharing the same environmental factors) will respond differently to disease or intervention due to chance. 'Identical'

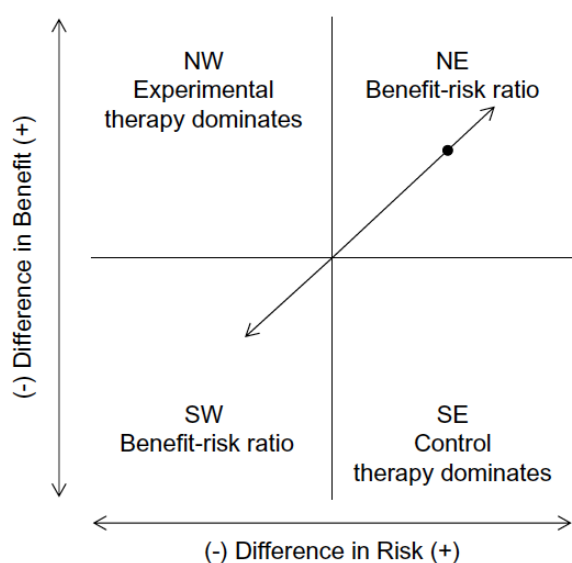
	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	59/97

patients have the same probability of developing a specific outcome, but the realisations of these outcomes might still be different. Some of the models described earlier do account for stochastic uncertainty (i.e. individual-based STM, DES, individual based dynamic models) whereas others not (i.e. decision tree, Markov models, compartmental models). Parameter uncertainty (or second order uncertainty) relates to the fact that the model parameters themselves (e.g. outcome probabilities) are subject to uncertainty because they have been estimated. Parameter uncertainty results from the finite sample size of the study used to inform the parameter, ‘conflicting’ multiple studies and might be further enhanced by bias and confounding in these studies. In a frequentist context, parameter uncertainty can be represented by deterministic sensitivity analysis or probabilistic sensitivity analysis. In a **deterministic sensitivity analysis**, parameter values are varied according to a predefined set of values and the impact on the model results is assessed. Such a deterministic sensitivity analysis can be easily improved upon by using (probabilistic) Monte Carlo simulation, randomly sampling parameter values from predefined probability distributions (i.e. second order Monte Carlo simulation). This is commonly called **probabilistic sensitivity analysis (PSA)** by health economic modellers and is used by Lynd & O’Brien, although they used the broad term **probabilistic simulation method**<sup>15</sup>. In a Bayesian context, parameter uncertainty is naturally incorporated as prior information<sup>91</sup>. Both types of sensitivity analyses (deterministic and probabilistic) as well as Bayesian analysis can be used to account for potential sources of bias and confounding that might have affected the studies used to inform the model parameters<sup>110</sup>. A third type of variability is heterogeneity, which refers to differences in parameters across patients, patient populations. In contrast to parameter uncertainty, heterogeneity cannot be reduced through performing additional or better studies, but should be acknowledged using e.g. stratified analyses. Finally structural uncertainty (or model uncertainty) relates to the assumptions inherent to the model. Structural uncertainty can be addressed by specifying several (plausible) assumptions about the model structure. For guidelines on accounting for several

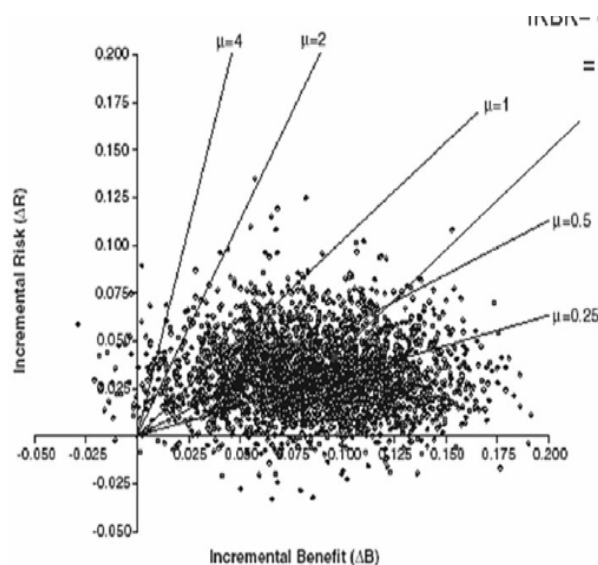
 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

sources of uncertainty in analytical modeling techniques, we refer to Bilcke et al<sup>111</sup> and Briggs et al<sup>112</sup>.


Uncertainty can be graphically represented. An example of such a graphical representation is the **risk-benefit plane**<sup>15, 113</sup>, which is a two-dimensional plot with the differences in risk on the x-axis and the differences in benefit on the y-axis (Figure 3.9). The plane is divided in four quadrants (NE, SE, NW and SW). In the SE quadrant, the new therapy dominates the old therapy (more benefit and less risk), and vice versa in the NW quadrant (less benefit and more risk). In the NE and SW quadrants, the decision to prefer the new treatment over the old one, depends on the **risk-benefit acceptability threshold** (RBAT), which is the maximum number of additional adverse events the decision maker is willing to accept to realize one additional beneficial outcome. The risk-benefit acceptability threshold is represented as the slope of the line passing through the origin and crossing the NE and SW quadrants (Figure 3.9). A risk-benefit plan with RBAT can be used to graphically display both statistical uncertainty in risk-benefit ratio (scatterplot of risk-benefit pairs generated through Monte-Carlo simulation) and uncertainty in preferences (varying RBAT slopes).



(a) risk-benefit plane

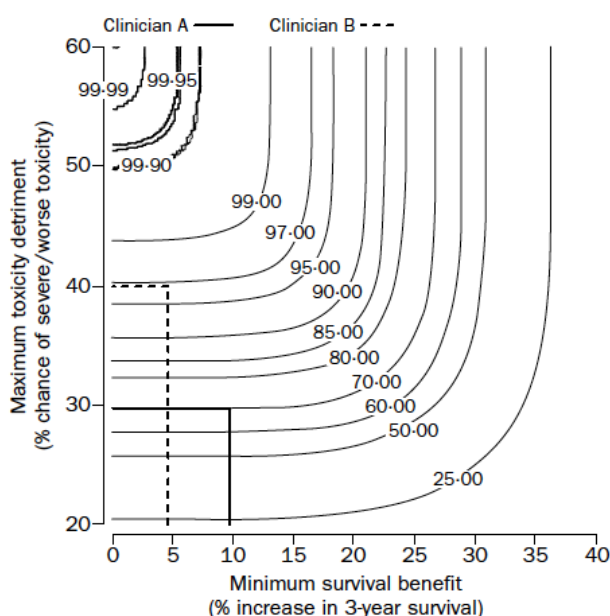


(b) joint distribution of risk and benefit

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b> 61/97

**Figure 3.9.** (a) Risk-benefit plane with the line through the origin representing the risk-benefit acceptability threshold (figure from<sup>113</sup>). (b) Results of a Monte Carlo simulation presented as a scatter plot of benefit-risk pairs within a risk-benefit plane (figure from<sup>15</sup>).


The **risk-benefit contour plot** is an alternative way to graphically represent the probability of benefit and risk and associated uncertainty<sup>114</sup>. The probabilities can be derived from the reported confidence intervals<sup>114</sup> or from simulation studies<sup>15</sup> and plotted as contour lines. The various contours provide degrees of probability of both benefit and risk. For example, a clinician might recommend the new treatment if there is at least 10% survival benefit compared with another treatment and if the probability of severe harm is not increased by more than 30% compared with the other treatment. The contour plot given in Figure 3.10 shows a 70% probability that these two conditions will be met (clinician A).



**Figure 3.10.** Example of a benefit-risk contour plot (figure from<sup>114</sup>).

### 3.5.6 Concluding remarks


Decision analytical modelling techniques are at the core of health technology assessment (HTA), but are sparsely used for benefit-risk assessment, although their use has been advocated<sup>15, 16</sup>. Their merits lie in their capability of synthesising evidence from

 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

different sources while being able to account for different sources of uncertainty (e.g. through using first and second-order Monte Carlo simulation or adopting a Bayesian approach). The modelling techniques as they are commonly applied in HTA do not reflect stakeholders’ preferences, though they can be modified to do so. Lynd et al.<sup>102</sup> gave a nice example of the modifiability of the techniques used in HTA for the purpose of benefit-risk assessment. The authors used discrete event simulation in combination with QALY’s with preference weights derived using conjoint analysis (see Section 3.6) to quantify the incremental net health benefit (INHB) of alosetron<sup>102</sup>.

When assessing the benefit-risk of a vaccine adopting a patient perspective, decision trees, state-transition models and discrete event simulations might be appropriate. When assessing the benefit-risk balance of vaccination adopting the societal perspective, dynamic transition models are suited, at least insofar as the indirect effects are judged to be important. Multi-parameter evidence synthesis is very powerful to combine different sources of evidence. This method is particularly relevant if direct evidence to inform the model parameters is unavailable, but the model parameters can be ‘indirectly’ informed based on evidence of functions of parameters.

Adhering to the fundamental modelling principle of keeping a model as simple as possible (but not too simple), static models might be acceptable in some cases. It is reasonable to accept a static model if target groups eligible for intervention are not epidemiologically important, when the effects of vaccination are expected to be entirely direct or when the static model suggests that the benefit-risk balance of vaccination is positive and that the indirect effects would enhance this (ISPOR guidelines<sup>103</sup> adjusted to the context of benefit-risk assessment). Two other modelling principles are a prerequisite for their use, being transparency and validation<sup>115</sup>. Transparency involves clearly describing the model structure, equations, parameter values and assumptions to enable both technical and non-technical readers to understand the model. Validation implies subjecting the model to tests, such as comparing the model results with external data.

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	63/97

### 3.6 Preference elicitation<sup>2</sup>

The section below assumes the reader is acquainted with Appendix 11 of the IMI-PROTECT WP5 report<sup>16</sup>.

#### 1. What is aimed at with utility stakeholder surveys

Surveys were used in marketing and transportation domain for many years to inform decision-makers on what matters really to customers. Likewise, utility surveys applied to benefit-risk assessment aim at improving the decision quality by decision makers. Opinion and preferences of “users” or “consumers” are collected (or “elicited”) through some kind of methodology (qualitative or quantitative) and accounted in a quantitative model for decision-making.


#### 2. Qualitative and Quantitative approaches

Thoroughly quantitative survey methods like conjoint analysis often initiates with qualitative preference assessment that narrows down the problem considered and focus on the most important information to clarify for the decision-making. Among others, focus groups, individual and group interviews, or open questionnaires are those sorts of qualitative approaches that may be very informative for decision-making although not immediately covered in PROTECT. We suggest covering some aspects on the quantitative analysis of those qualitative assessments of preferences and opinion.

#### 3. Revealed and stated preference survey

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<sup>2</sup> This section is written by Edouard Ledent, GSK

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	64/97

Retrospective survey may include database search reflecting on subject’s actual behaviour when purchasing or selecting a health care alternative. The conclusions driven from these analyses are identified as “Revealed Preferences”. That strategy for preference assessment and benefit-risk evaluation is uncommon and out of the scope of this section.


The alternative pathway involves asking the same individuals to state their preferences in hypothetical (or virtual) settings (or markets). The conclusions that follow that strategy are collectively known as “Stated Preferences” techniques and are the focus of the following paragraphs<sup>117</sup>.

#### 4. Groups of respondents to consider for the survey

Collecting preferences from various group representatives presents technical challenges. It also involves a broader issue on how those opinions from different groups should be balanced and how trade-offs should be made. Although preferences from regulatory authorities, public health authorities, health care professionals, vaccine recipients from general populations and minorities would be collected, no clear framework exists on how those preferences from different groups interact to form recommendations and how the decision is communicated and articulated. Prior to collecting those feedbacks, we would benefit from more clarity on how to use that information for decision-making.

#### 5. Communication of utility survey results

PROTECT WP5 report<sup>116</sup> mentioned the absence of standard visualization from utility survey techniques which seems a limitation in communicating the results to a broader audience, and enhance trust and transparency to the public. A proposal for visualizations was made by Sur D & al<sup>118</sup> in the context of policy makers.

 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

Statistical technology allows that survey results are communicated as predictions (i.e. prospectively rather than retrospectively) for a specific subject profile, accounting for his/her individual parameters. That sort of communication channel may improve the impact of such survey results to the public. Utility survey methodologies allowing such improved communications to a large audience might present additional advantages as compared to other methodologies.


## 6. Innovative perspectives

Since the PROTECT systematic review<sup>116</sup>, a few improvements or innovative proposals were made that may ease quantitative benefit-risk using a mixed level of qualitative or quantitative information. No recommendations identifying the most critical innovations for utility survey in the vaccine field is available. Instead, retrospective analysis of what might be pertinent for those surveys is performed through publication reviews and a couple of those are described below.

(a) Proposals were made to adapt the questionnaires of ongoing surveys based on the results of information already collected aiming at focusing on attributes that requires more data to support better the decision-making process. General software (Sawtooth Software ACBC<sup>119</sup>) and academic proposals<sup>120, 121</sup>, for adaptive survey are available but have rarely been used in health care.

(b) Theoretical considerations that underneath better the collection and analysis of preferences for benefit-risk in vaccines might not follow the utility-maximization approach that is mostly used for conjoint analysis methods (see definition below)<sup>122</sup>

(c) Improved probabilistic simulation methods can make better use of qualitative or semi-quantitative information from respondents to proceed with quantitative benefit-risk assessment<sup>123</sup>. Qualitative or semi-quantitative survey information is faster and easier to collect and probably less prone to large or uncertain bias. The outcome of benefit-risk evaluation might account for larger uncertainty but maybe not to an extend

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	66/97

that decision-making cannot be made. If such situation would apply, further (fully) quantitative survey would then focus on the value of information regarding to what is most critical for the decision.

Defining an ideal strategy for an efficient and effective collection of information pertaining to benefit-risk assessment would provide better guidance to researchers on what innovations would have the highest impact.


#### 4.6.1 Focus groups

##### Definition and context

Focus groups are defined as "carefully planned series of discussions designed to obtain perceptions on a defined area of interest in a permissive, non-threatening environment."<sup>124</sup>. They consist of small groups of people who have been gathered together for a group discussion in order to gain insight on a particular topic<sup>124</sup>. Sullivan<sup>125</sup> provides a thorough review of focus groups for MCDA, involving swing-weighting, Analytic Hierarchy Process or MACBETH as simplified forms of preference elicitation for decision-making as compared to conjoint analysis.

Those structured group interviews are conducted by a trained facilitator and can provide useful qualitative information to feed initial selection of attributes and levels for surveys or key information for quantitative benefit-risk frameworks relying on qualitative data only<sup>123</sup>. Comparison between focus groups and other types of surveys or discussions were summarized by Grudens-Schuck & al<sup>126</sup> and reproduced in Table 3.6.

**Table 3.6.** Comparing and contrasting focus groups and other types of discussion groups (from <sup>126</sup>).

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b> 67/97

	<b>Focus Groups</b>	<b>Other Small Discussion Groups<sup>1</sup></b>	<b>Large Discussion Groups<sup>2</sup></b>
<b>Application</b>			
Identify problems	Recommended	Recommended	Limited use
Design programs	Limited use	Limited use	Not recommended
Evaluate programs	Limited use	Not recommended	Not recommended
Educate or inform participants	Not recommended	Recommended	Recommended
Build consensus	Not recommended	Recommended	Recommended
Purpose	Designed to encourage divergent thinking and disclosure of personal perceptions and behaviors	Designed to study and/or generate ideas and solutions	Designed to build consensus, educate, or persuade
Participant selection	Participants are selectively invited, based on similar characteristics	Participants invited or required to participate because of their organizational affiliation. Similarity between participants is not a qualifier and may be a limitation in some situations.	Open to everyone in an organization or community
Group size	Group size from 6 to 12 individuals	Group size from 6 to 20 individuals	Group size from 6 to 100 or more individuals, depending on the issue
Event environment	Open, trusting environment	Open, trusting environment	Open, trusting environment

<sup>1</sup> For example, Study circle, Delphi Technique, Search Conference


<sup>2</sup> For example town meeting

## Set-up and conduct

Focus groups scenarios are set up prior to the conduct of the group interviews by facilitators that will make sure that each group member can have the opportunity to express him/herself or acknowledge his/her agreement or disagreement with what was said by other attendees. Focus groups are usually taped or video-recorded after personal identifiable information is taken care of and transcripts are made available for further analysis. Each intervention should be related to a unique participant in a way to allow between-subjects analysis but also to follow how the opinion of each individual evolves along the interview depending on what ideas are mentioned.

## Quantitative Analysis

Content analysis of focus group data<sup>127</sup> provides vital and robust information that will be used to build the design of a conjoint experiment. The survey quality and biases may be

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	68/97

driven by poor preliminary review of expert opinions, interviews or focus group feedback.

No clear standard in analysing focus groups for health care purposes is available and the recommend process<sup>127</sup> is followed in various ways, possibly leading to poor surveys. Computer Aided Qualitative Data Analysis Software (CAQDAS) products are available to ease the process (e.g. ATLAS.ti, MAXQDA, NVivo, Hyperresearch and QDA Miner) although the structure of the group interview may allow formal identification of ideas, attributes or concepts by the participants themselves .

### **Publication search results**


A publication review through Scopus on abstract, titles & keywords, searching for focus groups and conjoint analysis in the vaccine field provided one reference only (i.e. <sup>128</sup>), although the use of focus groups together with conjoint analysis in any fields provided 112 hits mostly in medicine, agriculture, nursing social sciences and engineering. Focus groups may have been used to set-up surveys in the 48 references related to conjoint analysis in the vaccine field although not mentioned in the abstract (e.g. <sup>129</sup>).

## **4.6.2 Conjoint analysis overview**

### **Introduction and historical perspectives**

Louviere (2011)<sup>130</sup> presented to the Isaac Newton Institute an introduction to DCE and the several important challenges that researchers are facing when implementing such widely spread survey approach. Bryan Orme<sup>131</sup> provides a short summary and practical knowledge required to implement these techniques:

- Conjoint methods were based on work in the sixties by mathematical psychologists Luce and Tukey. Discrete choice methods come from econometrics, building upon the work of McFadden (1974)<sup>132</sup>, 2000 Nobel prize winner in economics.

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>


Marketers have thought that the word “conjoint” refers to respondents evaluating features of products or services “CONsidered JOINTly”. In reality, the adjective “conjoint” derives from the verb “to conjoin” meaning joined together. The key characteristic of conjoint analysis is that respondents evaluate product profiles composed of multiple conjoined elements (attributes or features). Based on how respondents evaluate the combined elements (the product concepts), we deduce the preference scores that they might have assigned to the individual components of the product that would have resulted in those overall evaluations. Essentially, it is a back-door, decompositional approach to estimating people’s preferences for features rather than an explicit, compositional approach of simply asking respondents to rate the various features.

The estimation procedure relies on a statistical model that is expected to provide (partial) insight into the respondent’s answers. What cannot be explained by the model, either due to variables not captured or simply respondent’s mistakes, is absorbed into “residuals” that are given a specific statistical distribution and potentially some correlation features.

PROTECT mentioned utility measures used in MCDA like Swing-weighting, Analytic Hierarchy Process, MACBETH, ELECTRE or PROMETHEE as “conjoint” approaches. For clarity, we will not refer those methods as “conjoint analysis” and reserve that wording to the methods that share the features described by Orme above.

### Types of Conjoint Analysis

Several type of conjoint analysis are available although the Choice-Based-Conjoint (CBC) also called Discrete Choice Conjoint (DCE) now represents ~80% of the conjoint experiments implemented<sup>131</sup>. A classification of conjoint experiments is provide in **Error! Reference source not found.** although the criteria interact heavily and consulting Orme’s guidance using consult Sawtooth Software’s “*Interactive Advisor*” for selecting the most appropriate conjoint method is recommended.

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b> 70/97

**Table 3.7.** Summary classification of conjoint analysis

	<b>CVA</b> Conjoint Value Analysis	<b>ACA</b> Adaptive Conjoint Analysis	<b>CBC</b> Choice- based- conjoint	<b>PPCBC</b> Partial-Profile Choice-based- conjoint	<b>ACBC</b> Adaptive Choice-Based- Conjoint	<b>Menu- based</b> (a)	<b>Best- worst scaling</b> (b)
<b># attributes</b>	≤6	(≥ 8)	≤4, 5-7	((5-7)), (≤12), ≥ 12	(5-7), ≥ 8		≥ 8
<b># levels/attri bute</b>			≤15	≤15, ≥ 15	≤15, ≥ 15		15 - 40
<b>Interview method</b>	Paper, (PC)	PC, (Phone)	Paper, PC	Paper, PC	PC only	PC	Paper, PC
<b>Sample size</b>	Small, (≤ 100), (high)	(≤ 100)	≥ 100	≥ 100	(≤ 100)		
<b>interview time</b>			≤8 min, average, (longer)	≥ 8 min, longer			
<b>Monetary research</b>			Yes	Yes			

(..)The preferred approach or feature for a method is presented without parenthesis that indicates that the methodology can be selected for the feature but another methodology may be more appropriate.

(a) More appropriate when the respondent may select the product's attributes using a menu-based approach.


(b) Where the goal is to estimate the relative importance or preferences for each of the items separately but NOT being able to estimate how multiple items taken together affect overall preference.

### 4.6.3 Choice Based Conjoint methods

The scope of current document will be limited to the choice-based conjoint methods (CBC, PPCBC and ACBC) as they represent the most prominent methodologies currently used for utility surveys although other approaches might reveal valuable to some specific vaccine applications.

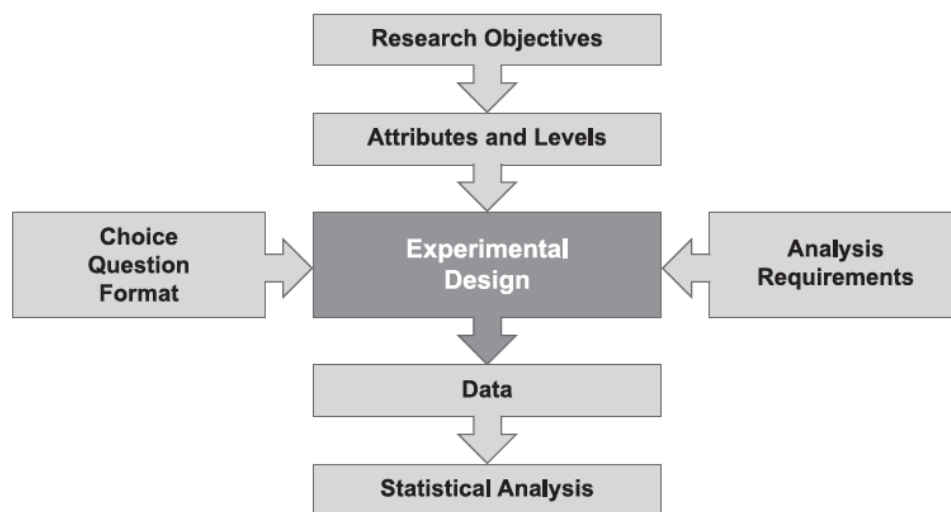
#### Introduction and general guidance

On the contrary to standard interview, CBC methods rely on a statistical model to get insights in respondent's preferences and choice motivations. The alternatives described to the respondents in the questionnaire rarely correspond to an existing alternative. Conversely, the researcher is focusing on how the characteristics that build those

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	71/97

alternatives influence the chance for the respondent to select the proposed alternatives. Guidance on how to build efficient and effective CBC experiments is provided by ISPOR<sup>133, 134</sup>. A convenient summary of the process by which to conduct CBC is illustrated in **Error! Reference source not found.**. Examples of CBC experiments for benefit-risk<sup>135</sup> and for health care decision-making<sup>136, 137</sup> exist.


Those methods rely heavily on behavioural and cognitive theories explaining how humans are making choices. The challenges are therefore not only of statistical optimization nature. The methods should also account for that part of irrational behind each of us. The researcher is facing both theoretical and practical issues when selecting a survey strategy that will provide the most effective understanding on respondent’s motivations. The sections below are aiming at providing some aspects of those challenges.



**Figure 3.11.** Key stage for developing a discrete-choice-experiment (from<sup>133</sup>)

### **Compensatory and non-compensatory behaviours**


The random utility theory that dominated the field assumes that respondents are prone to select an alternative presenting a less-than-desirable characteristic provided that alternative presents at least one characteristic that has more value to his/her preferences. The respondent is ready to compensate the lower value of the first characteristics with the higher value of the second.

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	72/97

Respondents are not always ready to compensate for all attributes. Some alternatives might be selected due to the presence of that characteristic that dominates all other characteristics. Conversely, an alternative may always be rejected due to the presence, or absence, of that characteristic, irrespective of the other constituents of that alternative. The respondent presents therefore a non-compensatory behaviour that may bias the data collection, corrupt the model parameters and obscure the real respondent’s motivations to the researcher.

Deviations from expected behaviour are usually absorbed by the model’s residuals and pose no major problems to the researcher when such behaviour does not dominate. When the alternative covers a critical domain of the respondent’s life, the researcher may anticipate that some questions may trigger an emotion aiming at some non-compensatory behaviour. The focus group’s objectives may include identifying those situations and avoiding them in the questionnaire. When such mitigation approach cannot be implemented, the researcher has other recent options; of which two, adaptive CBC<sup>131, 138</sup> and random-regret theory<sup>136, 139</sup> are presented below.

Asking healthy respondents about choices to be made with regards of their health or the health of their children may trigger some emotional reactions, different from what might happen with respondent suffering from a non-severe disease or when asking a customer about purchase preferences. Vaccination involves a broader scope of personal values, including e.g. social orientation and altruism<sup>140, 141</sup>, when selecting a prevention alternative. Exploring the extent to which the answers to CBC questions may be altered by deviations to random utility theory could help the researcher to anticipate such situations and select the appropriate strategy when building the questionnaire.

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	73/97


### Experimental design

In comparison to “Revealed Preferences” analyses, “Stated Preferences” methodologies control as much as possible the parameters (or attributes of alternatives) that determines stimulus administered to the respondents. The experimental design describes how many and which combinations of alternative characteristics (or attribute’s levels) must be evaluated by respondents to provide sufficient data for unambiguous analysis and decision-making.

No gold standard exists in selecting an efficient design and options vary depending on the analysis technique and the research objectives. Precise guidance on the questionnaire features and experimental design is beyond the scope of this document and can be found in a series of articles or books (i.e. <sup>117, 121, 142-145</sup>), from which some paragraphs below have been summarized.


Experimental design will account for the following topics:

- 1) Model identification that refers to the ability to obtain unbiased estimates from the data for every parameter in the conjoint model. Statistical criteria (e.g. D-optimality, D-efficient, S-optimality, Kullback–Leibler divergence, ...) for optimal design also determine how alternative characteristics should be combined together to form the questionnaires. Iterative algorithms are available that searches for such design. It is recommended to first focus on identification and then on efficiency of the design since the latter can be improved by increasing the sample size although the former cannot be changed once the design is constructed<sup>146</sup>

 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

2) Parameter interaction applies when the respondent's preference towards characteristic may change depending on the presence of other characteristics also present in the same alternative. The features are interacting and the experimental design and analysis model should account for those possible interactions when the researcher may anticipate their relevance. Including all interactions is not practical and would lead to implausible combinations. Focus groups and expert input may inform of the need to consider interaction parameters. The researcher can therefore select a design efficient to estimate the relevant fraction (i.e. fractional factorial design) of the design involving all possible combinations (full factorial design).


Statistical efficiency refers to minimizing the confidence intervals around parameter estimates for a given sample size. Perfectly efficient design presents each level equally often within an attribute (balanced design) and each pair of levels appears equally often across all pairs of attributes within the design (orthogonal design). Constraints on the combinations of parameters alter the efficiency but moderate reduction of orthogonality is preferred over generating implausible combinations of attribute levels. Eventually, balance & orthogonality are limited by the actual respondent's choices and the resulting dataset. Statistical efficiency can be improved by asking a large number of difficult trade-off questions, which however affects the response efficiency. The overall precision of the design results in the combination of both the response and the statistical efficiencies.

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b> 75/97

3) Response efficiency refers to measurement error resulting from respondent's inattention to the choice questions or other unobserved, contextual influences. Improvements can be made by asking a smaller number of easier trade-off questions. An attribute may present the same level for all alternatives in a choice set. Such overlaps improve the response efficiency but potentially limit the trade-off information collected. Sources of reduction in response efficiency include, but are not limited to:

- i) Short-cut by the respondent in making choices that are inconsistent with utility maximization or other error-model considered.
- ii) Respondent fatigue resulting from a large number of choice questions or respondent inattention resulting from a scenario much too different from respondent's reality.
- iii) Confusion, misunderstanding, assumptions made or heterogeneous interpretation by respondents, poorly constructed attributes or levels
- iv) Unobserved prognostic variable influencing respondent's choices

Some researchers implement logic tests in the questionnaire, identify those respondents that fail the test(s) and exclude them from the analysis. Ryan et al. (Chapter 9)<sup>117</sup> provides a thorough discussion on that topic. Respondents often have "reasonable" arguments to explain their "irrational" responses. A large fraction of those respondents may lack a consistent and coherent choice criterion across choice sets; some irrational responses were due to strict preferences and some others appeared to have reformulated the experiment in some way in their mental process. Practical considerations are given to reduce the proportion of irrational responses.


 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>

- 4) Labeled alternatives involve an external reference (e.g: a label, a name, a brand...) that provides meaning to the responder, in addition to the list of characteristics for that alternative. The attributes may involve different levels for each of the labels involved and therefore all levels for that attribute cannot exist for all alternatives; which would alter the efficiency of the design and for which recommendations were provided<sup>147</sup>, including the use of “L<sup>MA</sup> design” implemented by Lancsar<sup>130</sup>.
- 5) Constant alternative refers to the presence of the same alternative, with unchanging attribute levels in all choice sets, and describe a reference condition, a status-quo or an option to not participate. Specific considerations are made when such alteration to optimal design are necessary<sup>143, 144</sup>.
- 6) Block-assignment of respondents to the questionnaire refers to the need of several subjects to answer all questions required by design. The response efficiency may imply a lower number of questions per subjects as compared to the optimal number of questions according to statistical efficiency. The questionnaire is therefore split into several blocks of sub-questionnaires and the total number of subjects will be (ideally) a multiple of the number of blocks.

### Sample Size

Rose & Bliemer<sup>148</sup> provide detailed methods for sample size estimation based on asymptotic t-statistics using prior information. The focus is based on “statistical significance” (i.e. type-1 error), considering a maximum of 5% “false-positive risk” to identify a parameter as “relevant” although the utility that parameter is actually null.

A valid decision however can be made with a “false-positive risk” higher than 5% or the researcher maybe more concern about the “false-negative risk” associate with the failure of identifying an opportunity. A Bayesian statistician would potentially consider the distributions of gains (or losses) of the alternatives under considerations based on predictions made using the available information and recommend decisions based on


	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	77/97

maximizing the mean gain, minimizing the percentile of the distribution of gains below a gain-threshold (i.e. the value-at-risk), minimizing the mean gains below that threshold (i.e. expected value-at-risk); or even a combination of approaches.

Sample size considerations are therefore far from being only driven by a formula and depend very much on the questions under consideration and the resources being available. Studies aiming at estimating utilities over the whole population may be limited to a few hundreds of subjects but studies aiming at differentiating utilities between different sub-populations may require thousands of respondents. Models for which parameter-interactions are the topic of interest require more subjects than studies for which effects are constant whatever the level of other attributes.

Considering an adaptive approach to the sample size and the experimental design may be valuable to the decision-maker. Respondent recruitment can be stopped based on interim analysis of the data accumulated so far if the decision can be made. The experimental design can be altered to focus on critical attributes for which the precision should be improved. The researcher may use the predictive distributions of the model parameters at interim analysis to anticipate on the consequences of accumulating additional data on the decision to be made and compared them with the costs of increasing the sample size. A maximum sample size would probably be identified for operational reasons but theoretical considerations do not prevent from moving beyond that limit.

The sequential clinical trial design<sup>149</sup> and many other adaptive approaches<sup>150</sup> suggest various adjustments to researchers concerned by inflating the “false-positive risk” as a consequence of making several analyses, or by altering the design of the current study based on preliminary data. Interestingly, none of the ~6200 publications on conjoint

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	78/97

analysis in a Scopus search had mentioned “interim analysis” in title, abstract or keywords.

### **Selection of choice-based conjoint models**

A good understanding of the various models that can be used for the analysis of conjoint experiments allows the scientists to use efficient designs when generating the questionnaire. The model classification is made difficult by the absence of unique denomination across the whole conjoint literature<sup>3</sup>.


Considerations should be given to both the fixed effect model (i.e. the model for the means and slopes) and the variance-covariance models (i.e. parameters used to model the residual errors) when deciding on which model is a priori more relevant for an experiment (see figure below). Providing recommendations on which model to select for a specific application is beyond the scope of this document. More references on conjoint analysis models can be found in <sup>117, 142, 151-153</sup>

Decisions on the fixed effect model will account for the need of interactions between simple effects, but also the number of scenarios to be considered by the respondent, leading to a different set of parameters for each scenario. Alternatives for which the label has a specific meaning (like a brand name) lead also to a specific set of parameters.

Decisions on the variance-covariance structure should account, for instance, for the likelihood that the probability of selecting the best option from a set of alternatives does not change if a subset of those alternatives is considered instead (e.g. independence of irrelevant alternatives). Also, heterogeneity in tastes of the respondent may lead to

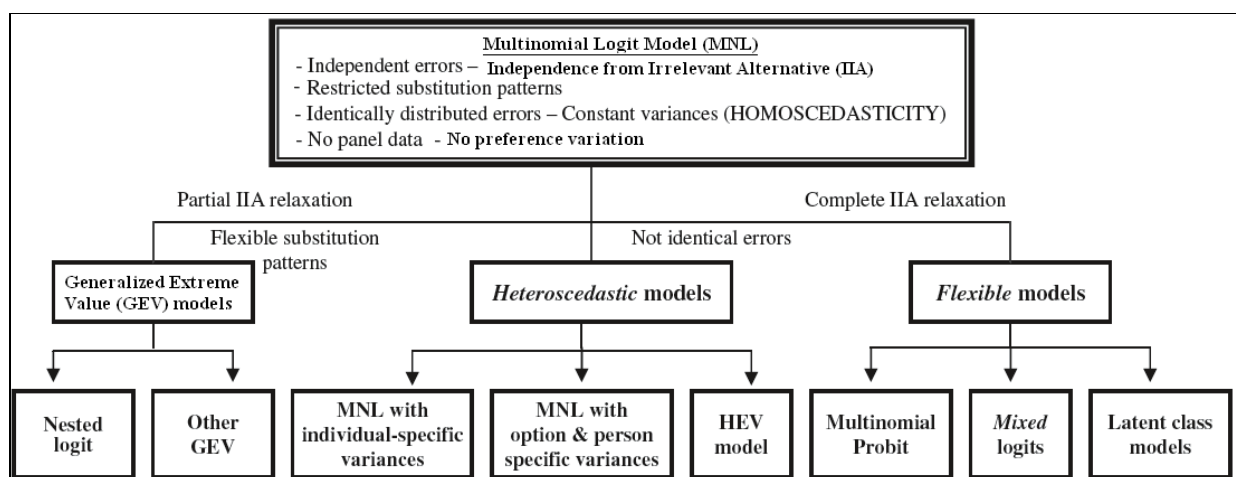
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<sup>3</sup> For instance, the wording “hybrid conjoint model” may refer to mixed logit models that address the covariance structure, but may also refer to fixed effect model that presents characteristics of both the conditional logit model, allowing for a same set of parameters for each alternative, and the standard multinomial logit model allowing for a different set of parameters for each alternatives.

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b> 79/97

considering random parameters and, therefore, mixed logits or hierarchical Bayesian models would be more appropriate.

Logit models used for choice-based conjoint experiments include therefore a large number of parameters and require enough data for an appropriate estimation. In addition, the scientist may be more interested in estimating the probability of selecting each alternative and compare them. For those reasons, sample size calculations are made difficult and usually require simulations<sup>117, 152, 153</sup>.




**Figure 3.12.** Families of choice-based-models and relaxations of assumptions (from<sup>117</sup>)

### Adaptive choice-based conjoint approaches

The use of web-interface allows the researcher to collect preliminary data on the previous and current respondents and build the questionnaire further accounting for the current data already accumulated. Various approaches to handling adaptive CBC<sup>4</sup> questionnaire have been proposed<sup>131, 138</sup>. In those applications, the heterogeneity in the respondent preferences is taken into account. The model assumes that the individual characteristic-values (i.e. path-worths) follow a statistical distribution that fits the between-subjects variability. The researcher is therefore not only interested in the average preferences among the population but also in the preferences of individual

<sup>4</sup> ACBC should not be confused with ACA, an older and much less efficient approach to conjoint experiment.


	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	80/97

respondents. Bayesian estimation procedures are usually applied to such models, which allow the design of future questionnaire in the ongoing study to account for the data already collected.

Other ACBC features include the ability to concentrate the questionnaires on those parameters that present lower precisions and adapt better to the respondent’s actual profile. That flexibility may alter the efficiency of the design on other aspects. The time needed to identify the most efficient design may take several minutes to a multi-core multi-threads computer, which cannot be achieved during an interview. Therefore, the researcher will adopt a pragmatic approach to questionnaire building rather than using the most efficient design.

In its commercial Adaptive-Choice-Based-Conjoint software, Johnson & Orme<sup>154</sup> first assess the respondent’s optimal choice. The questionnaire is then optimized around that optimal choice in order to improve the respondent’s experience, allowing for more attributes and levels per attribute to be included in the survey, as compared to standard CBC approach. The respondent will also be screened for any non-compensatory behaviour and the ACBC software will exclude those characteristics (i.e. attribute’s levels) from further questions. A near-to-optimal approach to questionnaire design is used to limit the time required between 2 choice sets. Health care applications were limited so far<sup>155-157</sup>.

Crabbe et al<sup>120</sup> presents major advances in identifying such design in switching the optimization criteria from (Bayesian) D-optimal to Kullback–Leibler divergence (also called the Kullback–Leibler information or the Kullback–Leibler distance between 2 statistical distributions), much easier to estimate but as efficient to identify effective designs. More specifically, and applied to the discrete choice setting: in order to select the next best choice set for a specific respondent, one maximizes the divergence between the current posterior of the coefficients (obtained with the choice data at hand) and the updated posterior one will obtain with the additional response information from the next choice set.

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	81/97


Finally, using the answers to early questions in a conjoint interview to select later questions may induce (endogeneity) biases in the estimated parameters (i.e. part-worths) when the researcher overlook the need to account for those answers to early questions in the final analysis. Liu & al. (2006)<sup>158</sup> has shown that including all data collected (i.e. early and later answers) for the analysis of such questionnaires ensures the validity of the results as it adheres to the likelihood principle. Such adaptive procedure however requires advance software that handles properly the variance components of earlier or later sections of the questionnaire. Such approach is implemented for instance by Otter<sup>159</sup> in Sawtooth's ACBC based on his original Matlab implementation, but renders very difficult the proper analysis of the same dataset with another software without appropriate coding of Otter's algorithm.

### Random Regret Theories

Chorus (2010) introduced recently a modelling approach based on the notion of regret minimization-driven choice behaviour for analysing data from conjoint experiments. The minimization of anticipated regret may be an important factor when choices are perceived by the individual as difficult and important to them or their relatives<sup>160</sup>.

The Random Regret Minimization (RRM) assumes that regret associated with an alternative depends on the performance of each attribute relative to other alternatives in the set of choices proposed to the respondent. In contrast, most of the standard Random-Utility-Maximization (RUM) theories postulate that the utility of an alternative only depends on its own performance<sup>139</sup>.

In standard RUM analysis of CBC experiments, effects are coded to represent the levels of categorical variables and (often) numerical are coded to represent the linear or non-linear effects of quantitative variables. In RRM, however, the variables code the differences between an attribute level in a given product profile and the total regret of


	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b> 82/97

not being able to choose the more attractive levels for that attribute in the choice set<sup>161</sup>. RRM will give equivalent results to RUM when categorical effects only are included. RRM's interest increases if the model includes quantitative attributes to model as (non-) linear functions.

RRM also has a compromise effect that can allow alternatives with attributes at intermediate levels of utility to perform better in some RRM simulations than in standard RUM CBC simulations. RRM also departs from RUM model in how the choice probability ratios can be greatly impacted by the introduction of new alternatives to the choice sets, although standard RUM exhibit independence towards irrelevant alternatives property.

The RRM approach is implemented in the NLOGIT software and can be coded into softwares likes SAS, Matlab or Gauss. Sawtooth Software users can estimate MNL, Latent Class MNL or hierarchical Bayesian (HB) MNL models for RRM by employing user-specified coding of the variables

Comparisons made between RRM and RUM<sup>162</sup> do not show definite superiority of RRM versus RUM. RRM seems more appropriate to predict choices between alternatives that are comparable in terms of their attributes. That scenario does not apply, for instance, when a no-choice option (i.e. opting-out the choice-set proposed for trade-off) is available to the respondent. Future applications using RRM may bring clarity on when RUM theory is outperformed. The foundations of regret theory may however be very useful to explain deviations to choice predictions and provide alternatives to RUM models.

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	83/97

## 4. DISCUSSION and RECOMMENDATIONS


It is essential to understand that pharmaceutical benefit-risk assessment involves both the accurate measurement of the benefits and risks and the value judgments about the relative importance of the various benefits and risks. Based on the current review, the following points for attention and areas for further research were identified.

### ***Qualitative or semi-quantitative framework***

It is recognised that the application of any quantitative method must be based on a qualitative framework<sup>1</sup>. The use of such a framework enhances communication and adds transparency and consistency to the process of benefit-risk assessment. Therefore, we recommend to develop a framework (or adjust existing frameworks) to support the conduct of benefit-risk assessments of vaccines. Such a framework should preferably support decisions throughout the life cycle of a vaccine and should be suited for use by all stakeholders. The preapproval benefit-risk assessment could then be used to inform which health outcomes to monitor during the post-launch benefit-risk monitoring. The BRAT and the ProACT-URL framework are currently the most commonly used ones. Evidence grading as done by the German standing Committee on Vaccination (STIKO) is advisable, particularly for post-launch benefit-risk assessments.

### ***Toolbox of quantitative methods***

For some benefit-risk assessments, a qualitative or semi-quantitative approach may not be sufficient and quantitative methods may be needed. We believe that the various quantitative methods described in this report are complementary and that no single approach can cover all issues related to the benefit-risk assessment of vaccines. We advocate the use of a toolbox containing methods (or combinations of methods) that can be applied depending on the perspective taken (individual or societal) and on the complexity of the benefit-risk profile (profile dominated by one benefit and one risk,

 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>


profile with multiple benefits and multiple risks, profile with indirect effects). Based on the current appraisal, we initially recommend to further investigate the following methods for post-launch benefit-risk assessments of vaccines: numbers-needed-to-vaccinate (NNV) including the extension proposed by Tuite & Fisman, QALYs and DALYs, multi-criteria decision analysis (MCDA), incremental net health benefit (INHB) and modelling techniques, particularly cohort models, dynamic transmission models and multi-parameter evidence synthesis (for argumentation, see sections ‘concluding remarks’ of the current report).

### ***Uncertainty***

Monte Carlo simulation and Bayesian statistical modelling are two commonly used techniques to quantify uncertainty. Monte Carlo simulation is a method for propagating uncertainties in model inputs to uncertainties in model outputs. It relies on repeated random sampling from input distributions to obtain the output distribution. Bayesian modelling combines the evidence from the data with uncertain prior probabilities. Depending on the quantitative method, it is more common to use either Monte Carlo simulation or Bayesian modelling to quantify uncertainty. For example, (second order) Monte Carlo simulation is typically used to evaluate uncertainty in cohort models whereas Bayesian modelling was used to develop multi-parameter evidence synthesis.

### ***Preference elicitation***

Utility surveys applied to Benefit-Risk assessment aim at improving the decision quality by decision makers. Opinion and preferences of “users” or “consumers” are elicited using qualitative or quantitative approaches that both can be used in quantitative decision models. Discrete-choice conjoint experiments rely on both a statistical theory and behavioral models that, together, render the approach particularly interesting in those situations where the decision-making involves a trade-off between favorable and unfavorable aspects.


	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b> 85/97

Conjoint experiments involve an integrated process that includes preliminary interviews and discussion or “focus” groups with various actors of decision-making, from which the topics for the questionnaires are identified. The design and analysis of those questionnaires are conducted according to evolving statistical theories. Adaptive questionnaire for instance modifies the questionnaire based on preliminary answers from the respondent although random regret theory provides an alternative approach to describe how individuals can make difficult decisions.

Asking healthy subjects about their preferences on favorable and unfavorable aspects of vaccination is much different than asking a patient about aspects of a disease or side effects of a drug. Accepting vaccinations with the promise of also protecting your peers more sensitive to the disease at the expenses of some burden, involve more than just expressing preferences for a purchase. It is unclear how conjoint experiments, used standardly to inform about economic, marketing or transportation purposes, are adapted to the vaccine field or how to account for the various parties involved in decisions-making. Behavioral attitude, aspects of communication about vaccination to the public and the type of societal values conveyed in the population may have drastic influence on how respondents make their choices and how conjoint experiments capture them.


Sample sizes and model selections are particularly difficult with conjoint experiment as they determine the design of the questionnaires and, therefore, the limitations of the study itself. Adaptive features, both in terms of the effects to consider or the number of respondents to involve may improve the benefits that policy makers and vaccine manufacturer can retrieve from the technique.

Overall, the use of conjoint experiments to inform on preferences and utilities of health care interventions has increased significantly over the last 5 or 10 years. The implementation to the vaccine field poses additional challenges, in addition to its already rather technical features. The technique brings however some unique advantages that render clearer the choices made by a population with regard to an

	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	86/97


intervention that matters to a large number of individuals. It may also be used ahead of vaccine development to improve how those interventions are evaluated and accepted by the populations.

***Proof-of-Concept studies***

 <b>ADVANCE</b> IMI - 115557	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b>


## ANNEXES

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	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b> 88/97

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	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b> 89/97


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	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b> 90/97


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	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b> 91/97


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	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods	<b>Version:</b> v0.1 – Draft/Final	
	<b>Author(s):</b> Advance Benefit-Risk Working Group	<b>Security:</b>	92/97


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	<b>D4.3</b> Appraisal of vaccine benefit-risk methods		
	<b>WP4.</b> Methods		<b>Version:</b> v0.1 – Draft/Final
	<b>Author(s):</b> Advance Benefit-Risk Working Group		<b>Security:</b> 93/97


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