Vaccine Safety Monitoring and Pharmacovigilance Tools
Advanced Pharmacovigilance Mini E-Workshop
16-18 March 2020

dcvmn
Developing Countries Vaccine Manufacturers Network

Aggregate Reporting
PSURs / DSURs
Best Practices

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Why aggregate reporting?

Changes in the Benefit-Risk (B/R) balance of medicinal products may occur.

The B/R balance is valid at a given point in time – but may change later on.

New in formation on the benefits and risks may emerge once the vaccine is on the market and is widely used, also in vaccination campaigns.

Periodic safety reports (e.g., PSURs / PBRERs / annual reports) are intended to provide an evaluation of the benefit – risk balance for submission by pharmaceutical companies to the regulators at defined time points during post-authorization phase.

- ✓Greater number of exposed to the vaccine as compared to exposed in clinical trials.
- ✓Rare AEFIs may not have been discovered in clinical trials.
- ✓Vaccines administered in the “real world” in vaccinees with underlying diseases
- ✓Post-marketing studies may be ongoing to demonstrate vaccine effectiveness and / or to measure risks

Purpose and Content of PBRERs / PSURs

Continuous reporting on safety

Implementation of a periodic benefit risk evaluation and surveillance program

Important tool to identify safety problems

MAH must analyze safety data from all possible sources. Appraisal of overall benefit/risk

Continuous surveillance of the benefit-risk of the product

- Comprehensive and critical analysis of new or emerging information on the risks and new evidence of benefit
- Evaluation of new relevant information becoming available during the reporting interval
- Examination if new information is in accord with previous knowledge of the benefit risk profile
- Summary of relevant new safety information that may impact the benefit risk profile
- Summary of any important new efficacy / effectiveness information
- Integrated Benefit / Risk Evaluation where new important safety information has emerged.

Main content of the PSUR

Actions taken for safety reasons

- e.g. clinical trial suspension, communications to healthcare professionals

Significant findings

- Clinical trials, spontaneous adverse reactions reports, patient support programs, literature…

Risks

- New risks identified and new information about already known risks

Benefit- Risk analysis

- Reassessment of the benefit-risk balance

Patient exposure

- Volume of prescriptions
- Actual use including use outside the authorised conditions

Signals

- New signals analysed

Benefits

- New benefits identified and new information about already known benefits

Conclusions and actions

- e.g. update of the product information with the new identified risk and risk communication as appropriate

EMA 2013

Aggregate Reporting Requirements
Periodic reporting to regulatory authorities

Pre-licensure from clinical trials: ICH E2F Development Safety Update Report DSUR

- DSURs to replace existing annual reporting requirements

Post-licensure from authorized products: ICH E2C (R2) Periodic Benefit-Risk Evaluation Report PBRER

- EU: GVP Module VII Periodic Safety Update Report PSUR
- US: Guidance for Industry: Providing Post-marketing Periodic Safety Reports in the ICH E2C(R2) Format (Periodic Benefit-Risk Evaluation Report)
  - ✓ FDA grants waivers to allow applicants to substitute PBRER for PADER / PAER and existing PSUR (ICH E2C R1) waivers
- National requirements

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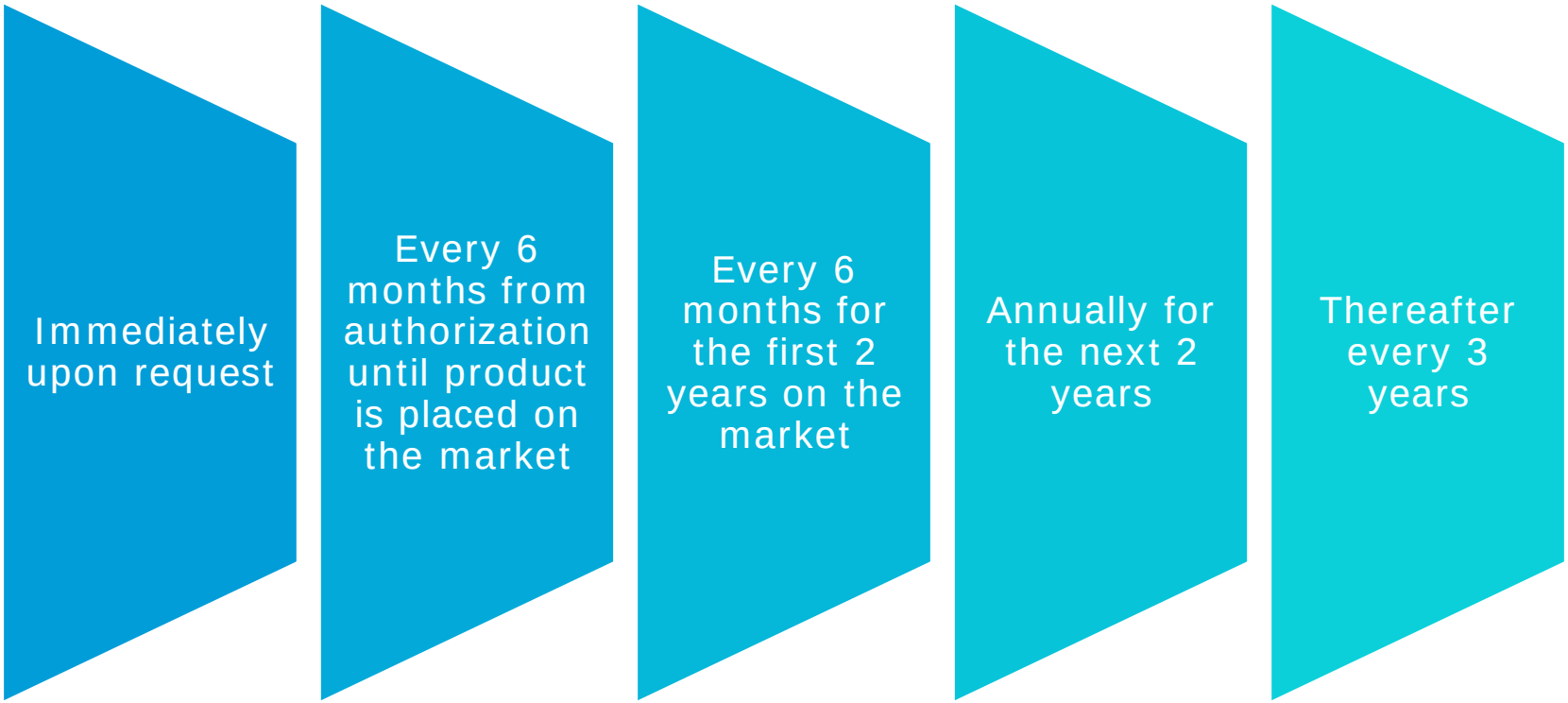
Reporting Requirements
Periodic reporting to regulatory authorities

Pre-licensure	Post-licensure
ICH E2F Developmental Safety Update DSUR Starting from the International Birth Date (IBD) In various national legislation: Annual Reports	ICH E2C (R2) Periodic Benefit Risk Evaluation Report PBRER / PSUR Starting from date of authorization In the European Union: GVP Module VII In various national legislation: Annual Reports

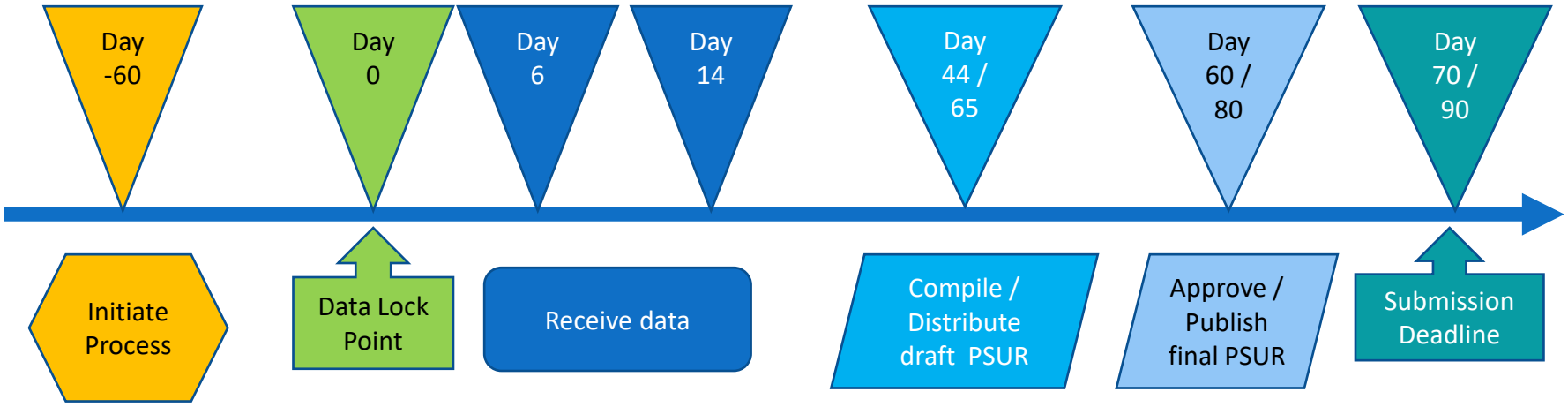
Differences in periodicity / submission schedules and regional content requirements according to national legislation or as agreed with NRA at the time of authorization.

Periodicity of PSURs (ICH E2C)



Exception in the EU: Frequency and dates are laid down as a condition of the MA or determined in the list of European Union Reference Dates (EURD List)

PSUR Preparation Planning



Submission of PSUR:

- By day 70 after data lock point (DLP) for intervals up to 12 months
- By day 90 after DLP for intervals > 12 months

Format - ICH E2C PBRER / GVP Module VII PSUR

Part I Title page
Part II Executive Summary
Part III Table of contents
1. Introduction
2. Worldwide marketing approval status
3. Actions taken in the reporting interval for safety reasons
4. Changes to the reference safety information
5. Estimated exposure and use patterns 5.1. Cumulative subject exposure in clinical trials 5.2. Cumulative and interval patient exposure from marketing experience
6. Data in summary tabulations 6.1. Reference information 6.2. Cumulative summary tabulations of serious adverse events from clinical trials 6.3.Cumulative and interval summary tabulations from post-marketing data sources
7. Summaries of significant findings from clinical trials during the reporting period 7.1. Completed clinical trials 7.2. Ongoing clinical trials 7.3. Long-term follow-up 7.4. Other therapeutic use of medicinal product 7.5. New safety data related to fixed combination
8. Findings from non-interventional studies Cont.

Format - ICH E2C PBRER / GVP Module VII PSUR

9. Information from other clinical trials and sources

10. Non-clinical data

11. Literature

12. Other periodic reports

13. Lack of efficacy in controlled clinical trials

14. Late-breaking information

15. Overview on signals: New, ongoing or closed

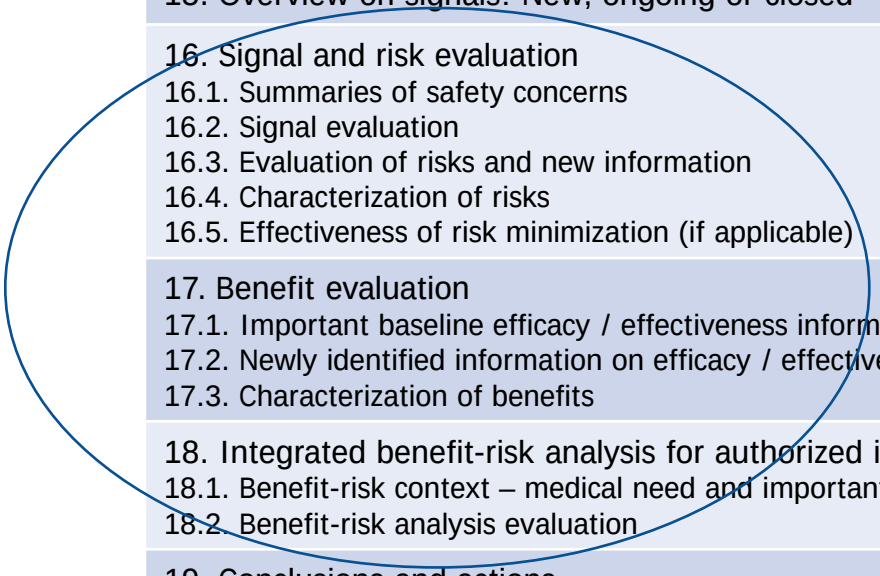
16. Signal and risk evaluation
16.1. Summaries of safety concerns
16.2. Signal evaluation
16.3. Evaluation of risks and new information
16.4. Characterization of risks
16.5. Effectiveness of risk minimization (if applicable)

17. Benefit evaluation
17.1. Important baseline efficacy / effectiveness information
17.2. Newly identified information on efficacy / effectiveness
17.3. Characterization of benefits

18. Integrated benefit-risk analysis for authorized indications
18.1. Benefit-risk context – medical need and important alternatives
18.2. Benefit-risk analysis evaluation

19. Conclusions and actions

20. Appendices to the periodic safety update report



Section 16 – 18
NEW in PBRER

Additional analyses for “Vaccine PSURs”

- Consideration to any potential impact on safety of changes in the manufacturing process
- Batch and age-related adverse reactions must be evaluated
- Analysis of adverse reactions for different doses and across different vaccination schedules
- Reports on vaccine failure, lack of efficacy / effectiveness
- Vaccination errors
- Vaccination-anxiety-related reactions such as syncope
- Literature data relevant to similar vaccine / vaccine components (e.g., stabilizers, preservatives, adjuvants)
- Integrated benefit–risk analysis using all available data:
  - ✓Prevention of target disease
  - ✓Severity of symptoms
  - ✓Hospitalisation
  - ✓Complications
  - ✓Effect of target disease on offspring in case of vaccination of pregnant women

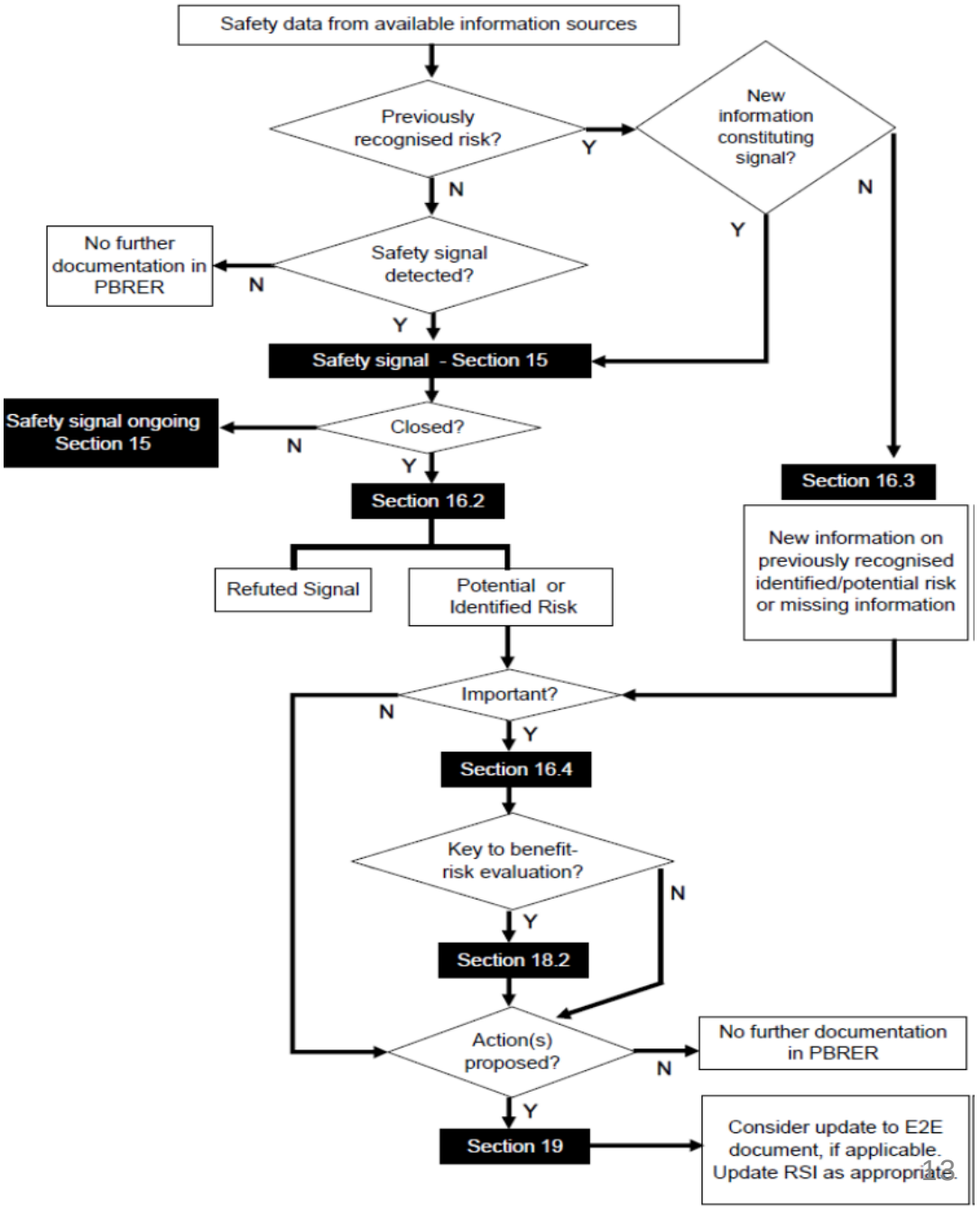
Evaluation of the Benefit-Risk Balance within PBRERs / PSURs

ICH E2C (R2): Appendix C – Example of a Tabular Summary of Safety Signals, ongoing or closed during Reporting Interval

Signal term	Date detected	Status (ongoing or closed)	Date closed (for closed signals)	Source of signal	Reason for evaluation & summary of key data	Method of signal evaluation	Action(s) taken or planned
Stroke	month/ year	ongoing	month/year	meta-analysis (published trials)	statistically significant increase in frequency	review meta-analysis and available data	pending
SJS	month/ year	closed	month/year	spontaneous case reports & one case report in Phase IV trial	Rash already an identified risk SJS not reported in pre authorisation CTs. 4 apparently unconfounded reports within 6 months of approval; plausible time to onset.	targeted follow up of reports with site visit to one hospital. Full review of cases by MAH dermatologist and literature searches	RSI updated with a Warning and Precaution DHPC sent to oncologists Effectiveness survey planned 6 months post DHPC. RMP updated.

ICH E2C (R2) Periodic Benefit-Risk Evaluation Report (PBRER)

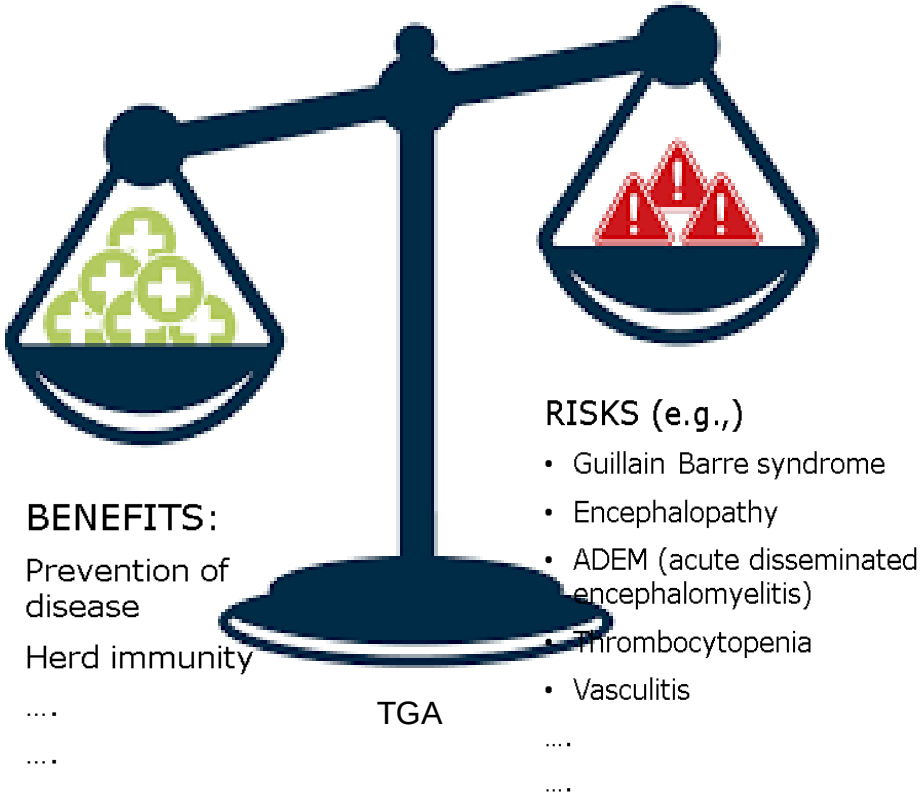
Flowchart mapping signal and risks in different sections



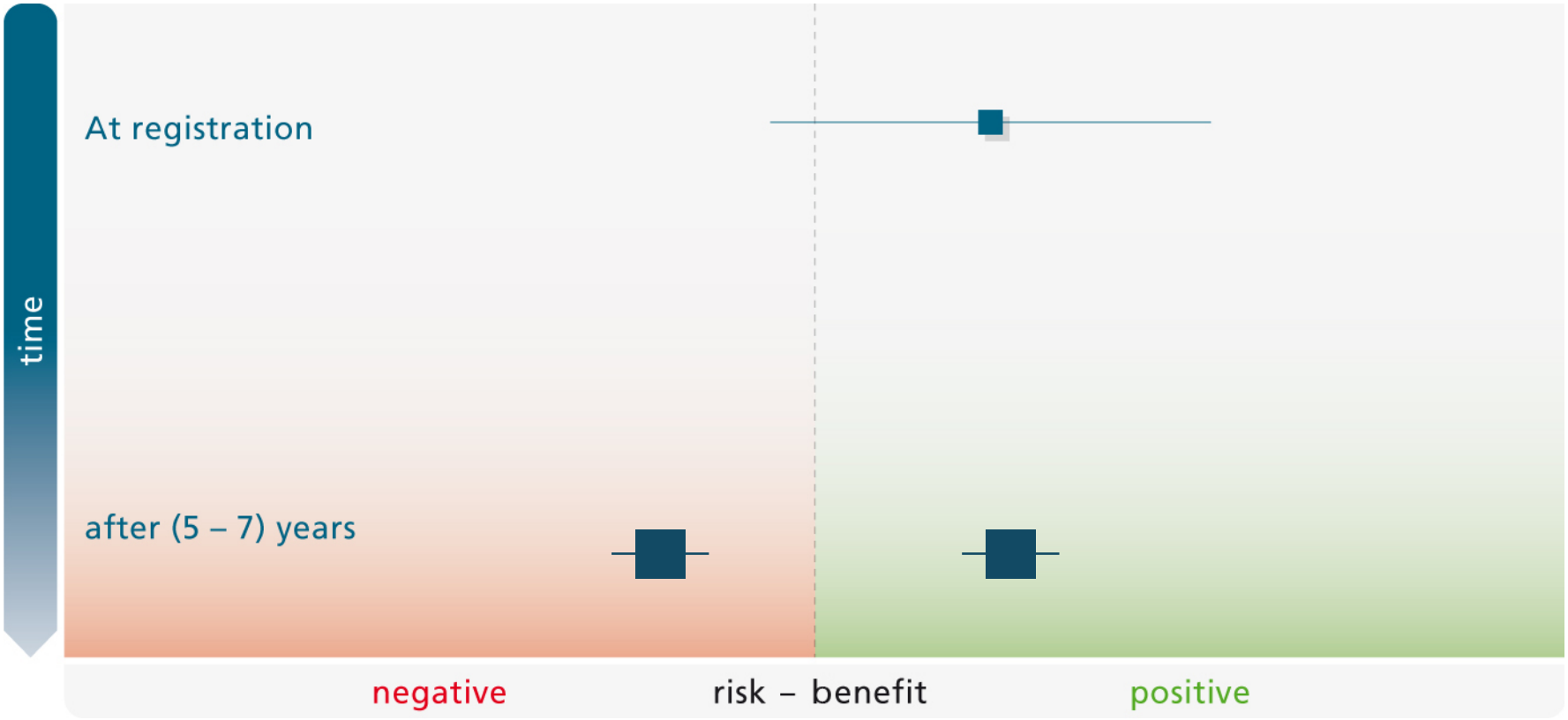
Benefit – Risk Balance

Benefit - Risk Balance:

An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks, i.e. any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health (EU definition).



Benefit – Risk Evaluation
Generic forest plot



A forest plot is a graphical display of estimated results from a number of scientific studies addressing the same question, along with the overall results. It is used in medical research as a means of graphically representing the analysis of the results of randomized controlled trials.

Concepts in Benefit - Risk Assessment

All available data should be considered in benefit – risk assessment

The nature of the disease to be taken into account for benefit – risk balance

e.g., self-limiting diseases versus diseases with high mortality

Absolute versus relative benefit – risk balance

e.g., alternative therapies to be considered, interpretation of the B / R to involve comparisons (consideration of alternative sources of risk)

Benefit – risk balance is dynamic and evolves over time

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Benefit-Risk assessment

Many initiatives and tools to standardize and improve consistency, transparency and communication of B/R assessment

Benefits

- ✓Beneficial effects (e.g., prevention of disease, lowering mortality etc.)
- ✓Uncertainty in the knowledge about beneficial effects

Risks

- ✓Unfavorable effects (e.g., AEFIs, lack of effectiveness etc.)
- ✓Uncertainty in the knowledge about unfavorable effects

Assessment of Benefit / Risk balance

- ✓Should be performed in a structured approach (qualitative / quantitative?)
- ✓Focus on the individual and population benefits and risks
- ✓Assess frequency of benefits (e.g., vaccine efficacy) and risks (e.g., frequency of serious AEFIs, vaccination failures)
- ✓Weigh frequency and importance of favorable and unfavorable effects appropriately
- ✓Benefit – risk balance
- ✓Discussion on the benefit-risk assessment
- ✓Conclusions

Methodologies for assessing Benefit - Risk of vaccines

Qualitative and semi-quantitative benefit-risk frameworks:

- CIOMS WG Report IV (1998): Benefit-Risk Balance for Marketed Drugs
- Relies on expert clinical / medical judgement

Quantitative benefit-risk frameworks:

- Various quantitative methods involving modelling, based on pharmaco-epidemiological principles
- No single agreed upon formal method for vaccine B/R assessment.
- A number of initiatives under way that involve regulators, industry and academia to harmonize evaluations at a global level:

✓IMI-PROTECT to harmonize project : Assessing available methodologies and developing tools for visualization of B/R; development of recommendation roadmap

✓ADVANCE (Accelerated Development of Vaccine B/R Collaboration in Europe) project: To establish a prototype of a sustainable system to provide best available scientific evidence on vaccination B/R

✓Benefit-risk action team (BRAT) framework: Standardization and communication of B/R assessments between pharmaceutical companies and regulators

✓Multi-criteria decision analysis framework (MCDA) integrates multiple benefits and risk criteria

Qualitative / descriptive analysis method*

AEFIs / risks characterized by

- Seriousness
- Duration
- Incidence

Benefits evaluated / described for a target disease in the light of

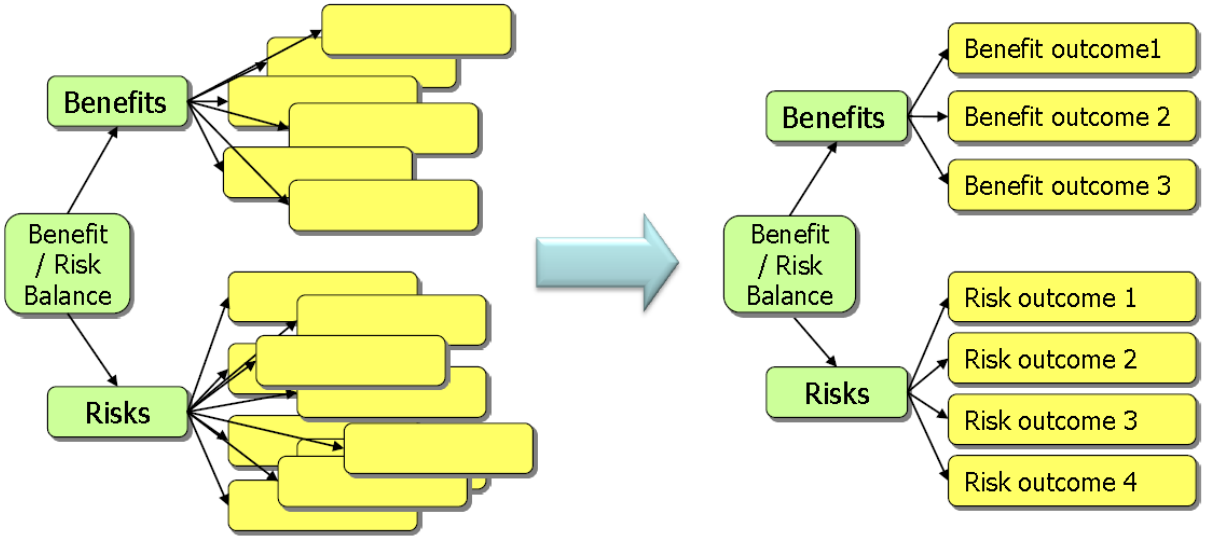
- Seriousness
- Chronicity (e.g., acute, chronic, or duration of disease,)
- Extent of control or cure - Vaccines: Disease incidence reduction / eradication

Property	High	Medium	Low
Seriousness	Fatal	Disabling	Inconvenient
Chronicity / Duration	Permanent	Persistent	Temporary
Extent of control/cure Incidence	Common	Infrequent	Rare

*CIOMS WG IV; Benefit-Risk Balance

Qualitative Benefit-Risk Framework
Value Tree

Establish a preliminary scope for the benefit-risk assessment by identifying and paring down potential benefit/risk outcomes



Framework can serve as basis for discussion with health authorities to prospectively frame the benefit-risk assessment

Requires expert clinical / medical judgement – to be operationalized by cross-functional teams (Safety Management Team SMT)

Structured Benefit Risk Assessment Regulatory activities

EMA Benefit-Risk Methodology Project:

EMAs four-fold qualitative model	
favourable effects	uncetainty of favourable effects
unfavourable effects	uncetainty of un-favourable effects

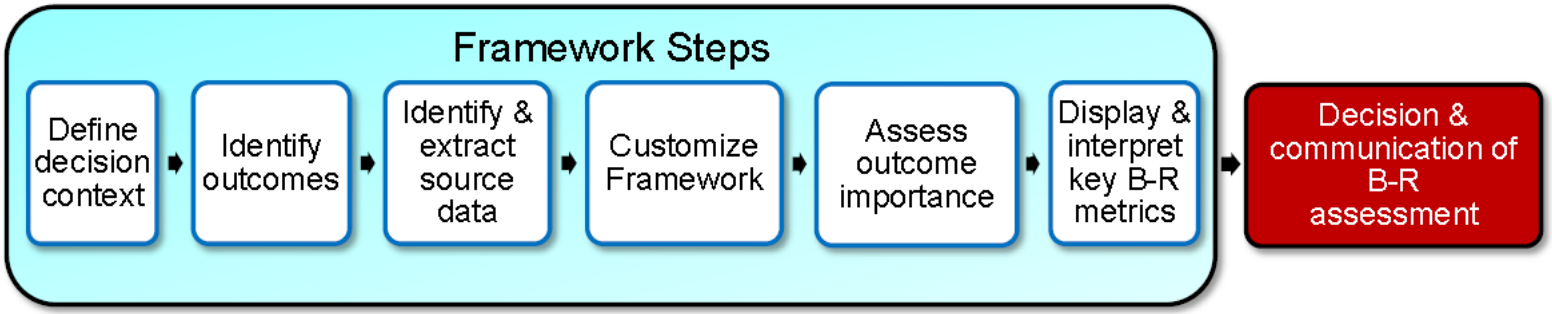
FDA Benefit-Risk Grid:

Figure 1: FDA Benefit-Risk Framework

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

Basis:
ICH E2C(R2)– Periodic Benefit-Risk Evaluation Report (PBRER)

Structured Benefit Risk Assessment Industry activities

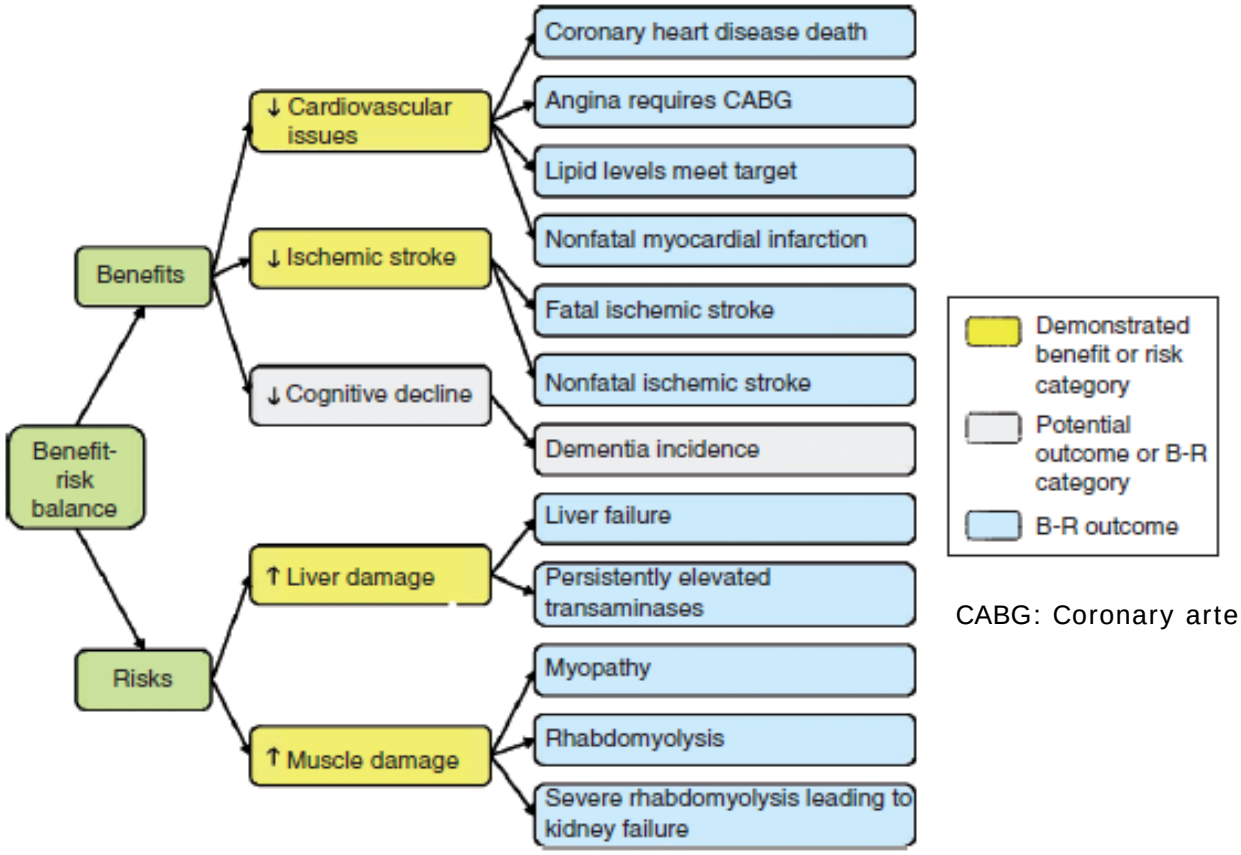


The Benefit Risk Action Team (BRAT) is a framework well suited to benefit-risk analysis

- Benefit-risk analysis is conceptually easy but hard to operationalize – in particular:
  - To define consistent criteria across decision options, find data matching these criteria, and elicit value judgments
  - Squash the messy complexity of real life into a simple model
- A Benefit-risk assessment does not necessarily give the answer:
  - It is a framework for decomposing and understanding a problem
  - Assesses the main value drivers of a decision
  - Communicates issues in a transparent, rational and consistent way
  - Allows sensitivity analysis around different perspectives (industry, regulator, patient, payer, prescriber)

Coplan et al 2010
Levitan et al 2012

Value Tree
Benefit-Risk outcomes for inclusion in a comparative B/R assessment

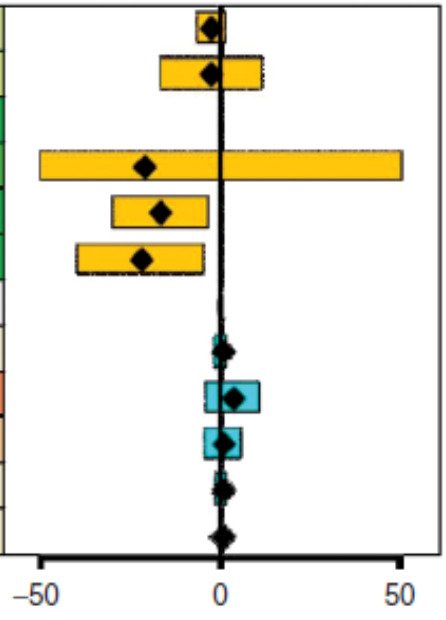


CABG: Coronary artery bypass graft

Coplan et al 2010
Levitan et al 2012

Key Benefit-Risk Summary Table
Presentation from Value Tree Example

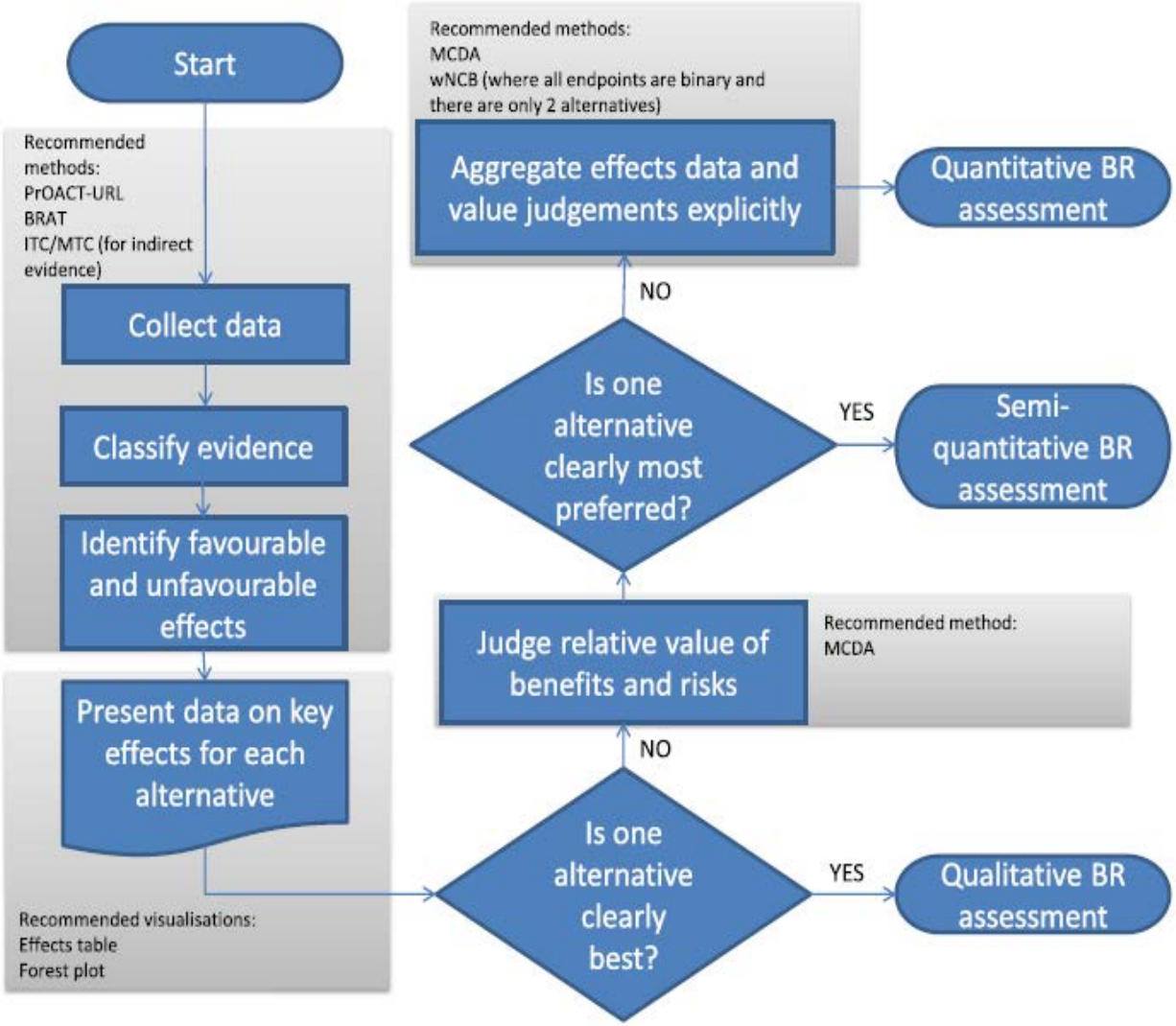
		Outcome	Study drug risk[a]	Placebo risk[a]	Risk difference per 10,000 person-years		Risk difference forest plot[a]
Benefits	Cardio-vascular issues	Angina requiring CABG	3.7	6.4	–2.6	(–6.4, 1.2)	
		Coronary heart disease death	31.0	33.6	–2.7	(–16.9, 11.6)	
		Lipid levels meet target	6700	2900	3800	(2,691, 4,909)	
		Nonfatal myocardial infarction	22.1	43.3	–21.2	(–95.2, 52.8)	
	Ischemic stroke	Fatal ischemic stroke	18.6	35.4	–16.8	(–29.9, –3.6)	
		Nonfatal ischemic stroke	97.5	119.8	–22.3	(–39.8, –4.8)	
Risks	Liver damage	Liver failure	0.6	0.6	0.0	(–1.6, 1.6)	
		Persistently elevated transminases	13.6	10.1	13.5	(–3.8, 10.9)	
	Muscle damage	Myopathy	5.9	5.3	0.6	(–4.5, 5.6)	
		Rhabdomyolysis	0.6	0.5	0.1	(–1.5, 1.6)	
		Severe rhabdomyolysis → kidney failure	0.029	0.026	0.003	(–0.07, 0.08)	



[a]Risk per 10,000 person-years strong risk strong benefit

Coplan et al 2010
Levitan et al 2012

Flowchart indicating the differences between qualitative and quantitative benefit-risk assessment with recommended methods



Hughes 2016

Summary

- Benefit-risk balance of a vaccine can change over time and there could be a need for re-adjustment
- PSURs permit the periodic re-assessment of the benefit-risk balance
- Legal actions can be taken from the PSUR assessment
- Minimizing risks and optimizing benefits throughout the lifecycle of a vaccine will promote and protect public health and enhance patient safety by avoiding unnecessary risks to vaccinees.

Main focus of the PSUR:

- ✓ Integrated post-authorization benefit-risk assessment
- ✓ Ensuring benefit-risk balance remains favorable
- ✓ Signal detection and evaluation
- ✓ Establishing and documenting "core safety profile"
- ✓ Ensuring up-to-date product information