Emerging methodological standards: overview of current international benefit-risk initiatives

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Disclosure

The views and opinions expressed in this presentation are those of the presenter, and should not be attributed to the Dutch Medicines Evaluation Board or the Eurpean Medicines Agency.

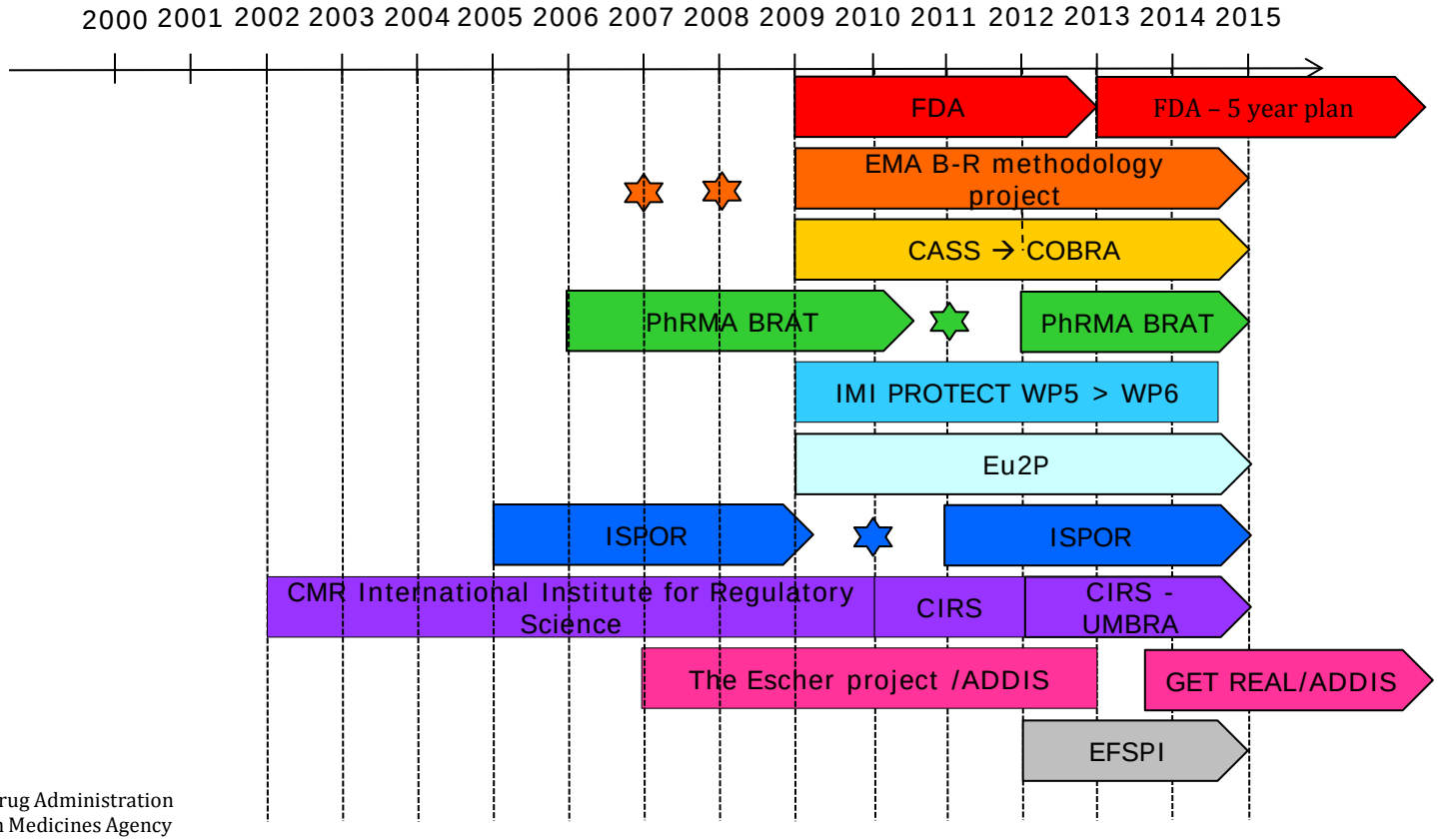
Sources / contributors

- *Framework for Benefit Risk Assessment of Medicines for a Structured Approach to Decision-Making in Drug Development & the Regulatory Review. Dr Neil McAuslane Prof Stuart Walker Centre for Innovation in Regulatory Science, EMA february 17th, 2014 London.*
- *Can the benefit-risk landscape converge? Isabelle Stöckert Annual European Medicines Agency Review of the Year and Outlook for 2014 28th – 29th November 2013 De Vere Venues, Westferry Circus, London*
- *ESFPI/PSI Benefit-Risk Special Interest Group meeting February 2013*
- *Francesco Pignatti, EMA Benefit-Risk project Current status, CIRS Workshop 20-21 June 2013*
- *Patrick Frey FDA Benefit-Risk Framework: Current and Future Efforts in FY2013—2014, CIRS Workshop 20-21 June 2013*
- *Deborah Ashby, President's Invited Lecture, ISCB-33: A Benefit-Risk Analysis of using Formal Benefit-Risk Approaches for Decision-Making in Drug Regulation Bergen, 22nd August 2012*

Benefit Risk assessment

- The challenging task of a decision maker is to make more ***transparent, reproducible*** **and** ***defensible*** decisions
- The ***justification*** of these decisions to e.g. ***patients*** and other stakeholders is increasing
- Can more formal approaches of decision-making, and especially ***more modern methods*** help clinical decision makers do these better ?

Overview of the initiatives since 2000



- *FDA*: Federal Drug Administration
- *EMA*: European Medicines Agency
- *CASS*: Taskforce of representatives from Health Canada, Australia's Therapeutic Goods Administration, Swissmedic and the Singapore Health Science Authority
- → *COBRA*: Consortium on Benefit-Risk Assessment
- *PhRMA BRAT*: Pharmaceutical Research and Manufacturers of America Benefit-Risk Action Team
- *IMI PROTECT*: Innovative Medicine Initiative Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium
- *Eu2P*: European programme in Pharmacovigilance and Pharmacoepidemiology
- *ISPOR*: International Society for Pharmacoeconomics and Outcomes Research
- *CMR*: Centre Medical Research
- *CIRS*: Centre for Innovation in Regulatory Science
- *UMBRA*: Unified Methodologies for Benefit-Risk Assessment
- *EFSPI*: European Federation of Statisticians in the Pharmaceutical Industry

FDA

- The best presentation of benefit-risk considerations involves focusing on the individual benefits and risks, their frequency, and weighing them appropriately
- FDA has adopted a structured qualitative approach that is designed to support the identification and communication of the key considerations in FDA's benefit-risk assessment and how that information led to the regulatory decision.

FDA Benefit Risk Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Summary of evidence	Conclusions (implications for decisions)
Current Treatment Options	Summary of evidence	Conclusions (implications for decisions)
Benefit	Summary of evidence	Conclusions (implications for decisions)
Risk	Summary of evidence	Conclusions (implications for decisions)
Risk Management	Summary of evidence	Conclusions (implications for decisions)
Benefit Risk Summary and Assessment		

FDA PDUFA V / FDASIA implementation

- BR Framework to be integrated in review processes
- Road Testing in “Live Reviews” 6 ongoing reviews in CDER’s Office of New Drugs
- Gain patient perspective on 20 disease areas in public meetings (2012-2017)

EMA Benefit Risk Assessment

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Guidance document on the content of the <Co->
Rapporteur day 80 critical assessment report

Overview and list of questions

EMA Benefit Risk Assessment

- 5. Benefit risk assessment
  - Benefits
    - Beneficial effects
    - Uncertainty in the knowledge about the beneficial effects
  - Risks
    - Unfavourable effects
    - Uncertainty in the knowledge about the unfavourable effects
  - Balance
    - Importance of favourable and unfavourable effects
    - Benefit-risk balance
    - Discussion on the benefit-risk assessment
    - Conclusions

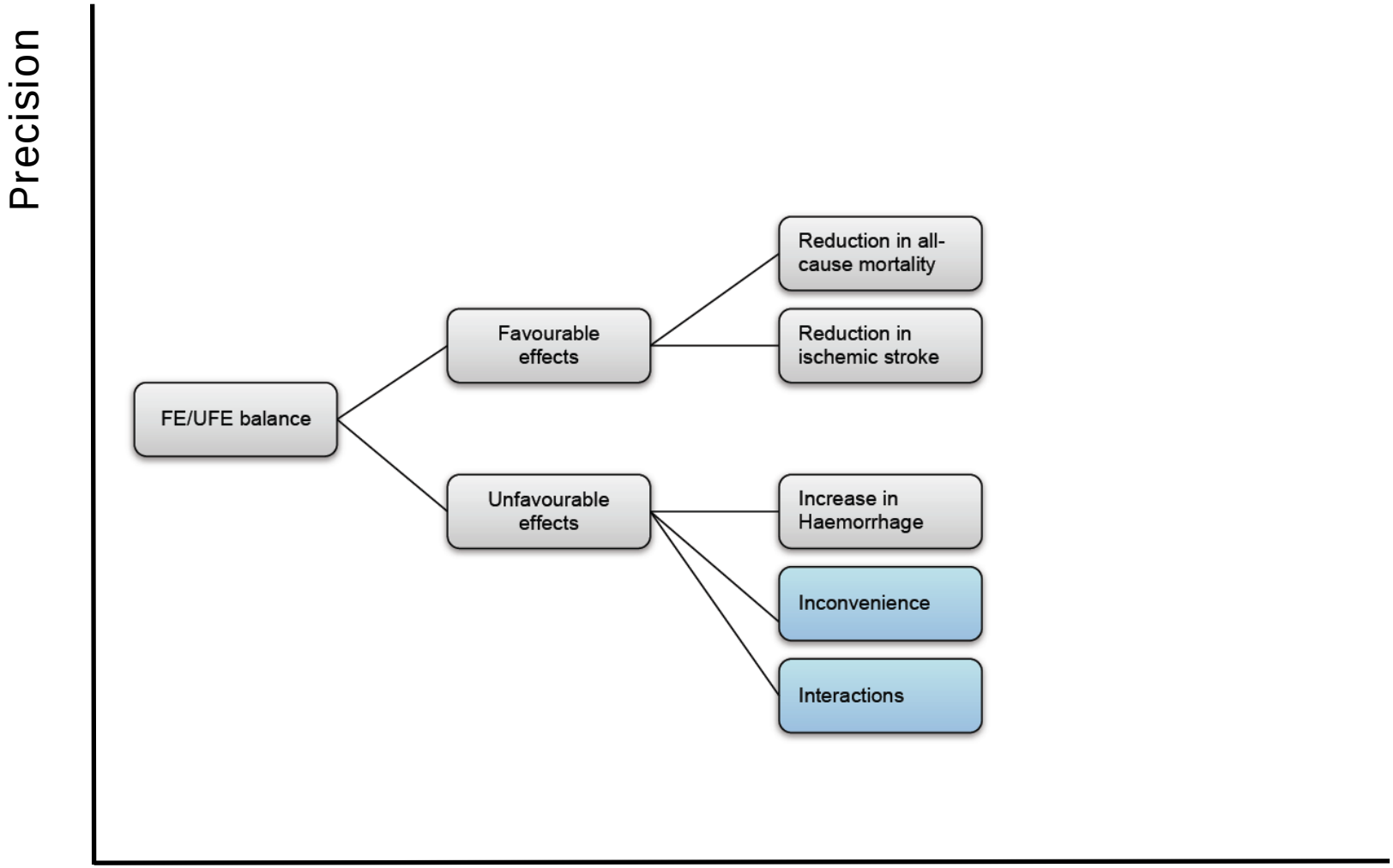
EMA benefit risk project

- Objectives
  - Improve consistency, transparency and communication of benefit-risk assessment
    - Implicit > Explicit
- Five Work Packages
  - Description of current practice
  - Applicability of current tools and methods
  - Field tests of tools and methods
  - Development of tools and methods for B/R
  - Pilot and training (ongoing)

EMAs PrOACT-URL Framework

- A generic framework to structure the decision problem
- Divide into 8 steps
- Emphasis on uncertainty via sensitivity analysis

Effort versus Precision Trade-off



Pignatti, CIRS Workshop 20-21 June 2013

Effort versus Precision Trade-off

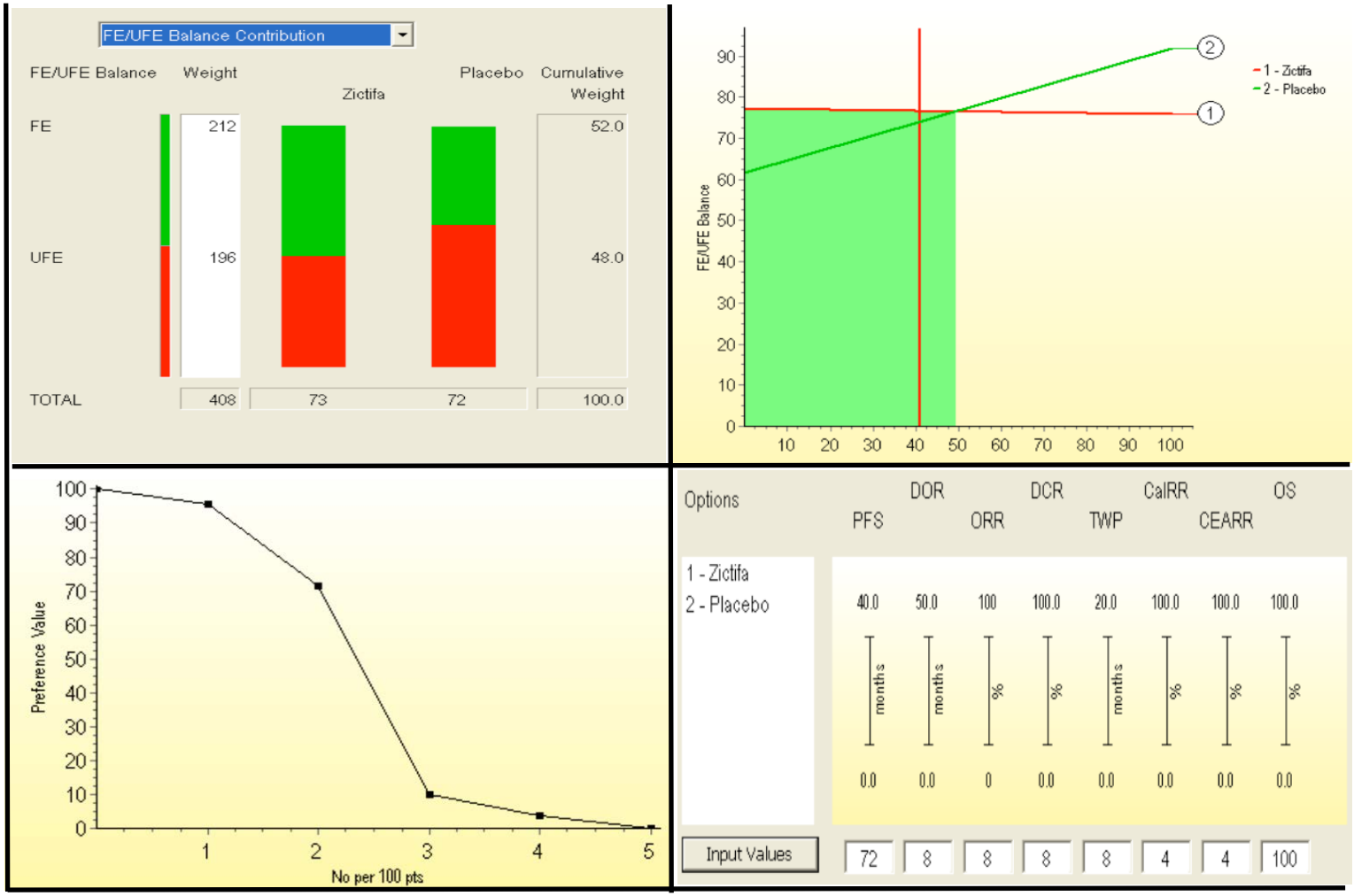
Precision

	Name	Description	Unit	Placebo	300 mg	Uncertainties	Reference in the text
Benefits	Progression-free survival Hazard Ratio	Date of randomization to the date of objective progression or death	unitless	1	0.46	Only a very low number of patients with definite RET negative status at baseline	Major Objection No. 1, Discussion on Clinical Efficacy (page 44)
	Progression-free survival (median)	Date of randomization to the date of objective progression or death (Weibull model)	months	19.3	30.5	From Weibull model – distributional assumptions probably do not hold	
	Objective Response (RECIST)	Proportion of complete or partial responders (at least a 30% decrease in the sum of the longest diameter from baseline)	%	13	45	Not a good surrogate. May provide some symptom relief (assumed)	
Risks	Diarrhoea CTC3 Grade 3-4	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; …	%	2.0	10.8	Duration of follow up in the pivotal study is quite short with regard to the need for long duration of treatment and therefore the risk of developing further major Cardiac SAEs including Torsades de pointe. Could the risk be underestimated? How well can oncologists monitor in clinical practice?	Major Objection No. 2, Discussion on Clinical Safety (page 65), Scientific Advisory Group answers to CHMP
	QTc related events CTC[3] Grade 3-4	QTc >0.50 second; life threatening signs or symptoms (e.g., arrhythmia, CHF, hypotension, shock syncope); Torsade de pointes	%	1.0	13.4		See RMP
	Infections CTC[3] Grade 3-4	IV antibiotic, antifungal, or antiviral intervention indicated; …; Life-threatening consequences (e.g., septic shock, hypotension, acidosis, necrosis)	%	36.4	49.8		Discussion on Clinical Safety (page 66)

Effort

Effort versus Precision Trade-off

Precision



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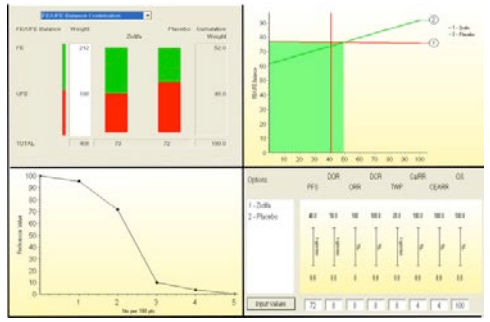
Pignatti, CIRS Workshop 20-21 June 2013

Effort versus Precision Trade-off

Precision



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	Objective Response (RECIST)	Proportion of complete or partial responders (at least a 30% decrease in the sum of the longest diameter from baseline)	%	13	43	Not a good surrogate. May provide some symptom relief (assumed)	
Risks	Diarrhoea CTCI Grade 3-4	Increase of ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; hospitalization; ...	%	2.0	10.8	Duration of follow up in the pivotal study is quite short with regard to the need for long duration of treatment and therefore the risk of developing further major Cardiac SAEs including Torsades de pointe. Could the risk be underestimated? How well can oncologists monitor in clinical practice?	Major Objection No. 2, Discussion on Clinical Safety (page 63), Scientific Advisory Group answers to CHMP See RMP
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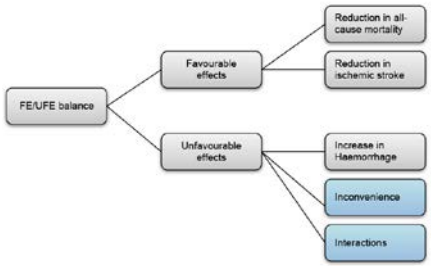


Effort

Pignatti, CIRS Workshop 20-21 June 2013

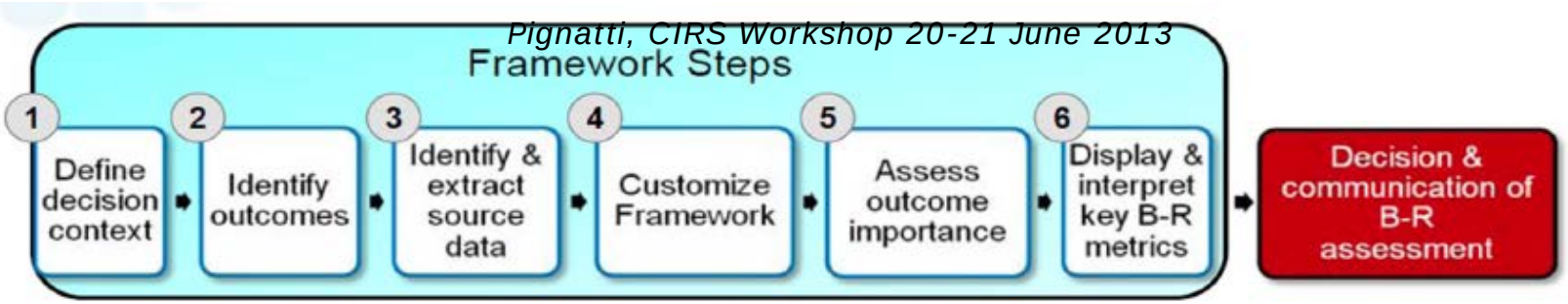
The BRAT Framework for B/R-Assessment

- Benefit Risk Action Team (BRAT) framework
- Developed by PhRMA (Pharmaceutical Research & Manufacturers of the US)
- Structured 6-step approach for defining the decision context and selecting, organizing, evaluating, and displaying relevant benefit-risk information

Coplan, Clin Pharmacol Ther 2010

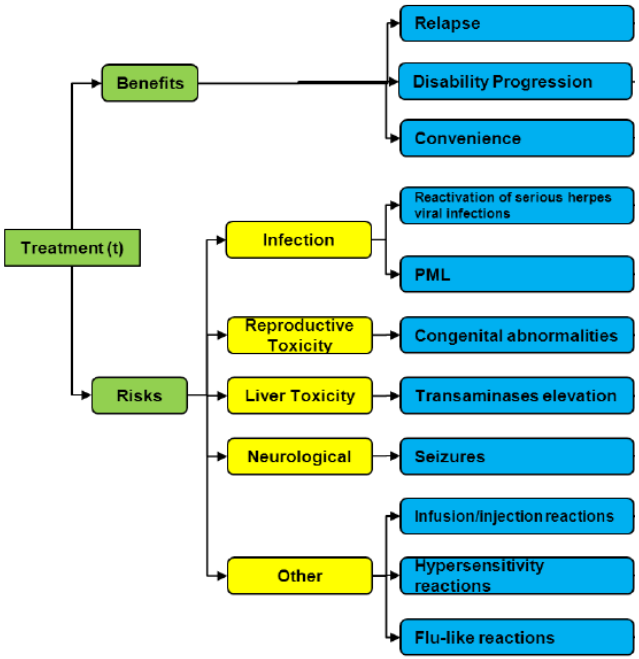
The BRAT Framework for B/R-Assessment

Pignatti, CIRS Workshop 20-21 June 2013



Coplan, Clin Pharmacol Ther 2010

BRAT / IMI PROTECT WP 5
Tysabri case study

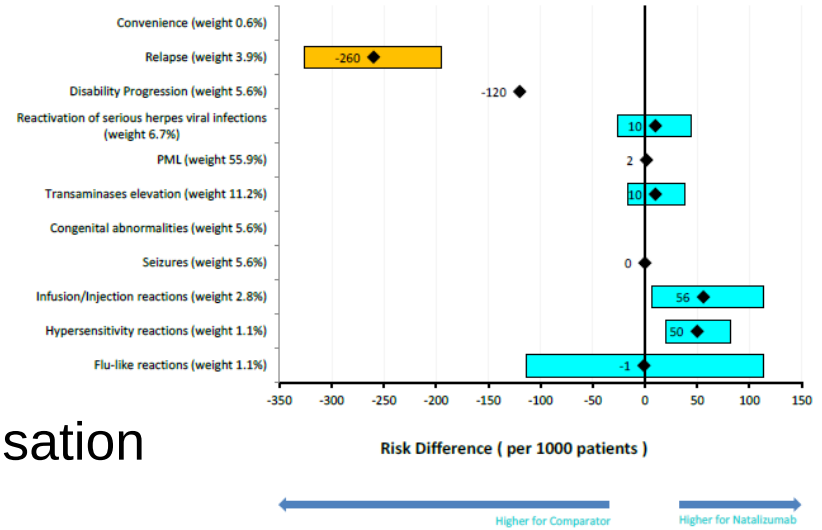


Value tree

	Outcome	Natalizumab Risk / 1000 pts	Comparator Risk / 1000 pts	Risk Difference (95% CI)/ 1000 pts
Benefits	Convenience (weight 0.6%)	-	-	(-, -)
Benefits	Relapse (weight 3.9%)	280	540	-260 (-326, -195)
Benefits	Disability Progression (weight 5.6%)	110	230	-120 (-, -)
Risks	Infection	Reactivation of serious herpes viral infections (weight 6.7%)	80	70	10 (-26, 45)
Risks	Infection	PML (weight 55.9%)	2	0	2 (-, -)
Risks	Liver Toxicity	Transaminases elevation (weight 11.2%)	50	40	10 (-16, 38)
Risks	Reproductive Toxicity	Congenital abnormalities (weight 5.6%)	-	-	(-, -)
Risks	Neurological Disorders	Seizures (weight 5.6%)	0	0	0 (-, -)
Risks	Other	Infusion/injection reactions (weight 2.8%)	236	180	56 (6, 114)
Risks	Other	Hypersensitivity reactions (weight 1.1%)	90	40	50 (20, 82)
Risks	Other	Flu-like reactions (weight 1.1%)	399	400	-1 (-114, 114)

Higher for Natalizumab
Higher for Comparator

Data Summary Table



Visualisation

Shahrul et al. Review of methodologies for benefit and risk assessment of medication, Protect website, April 2013 (Coplan, Clin Pharmacol Ther 2010)

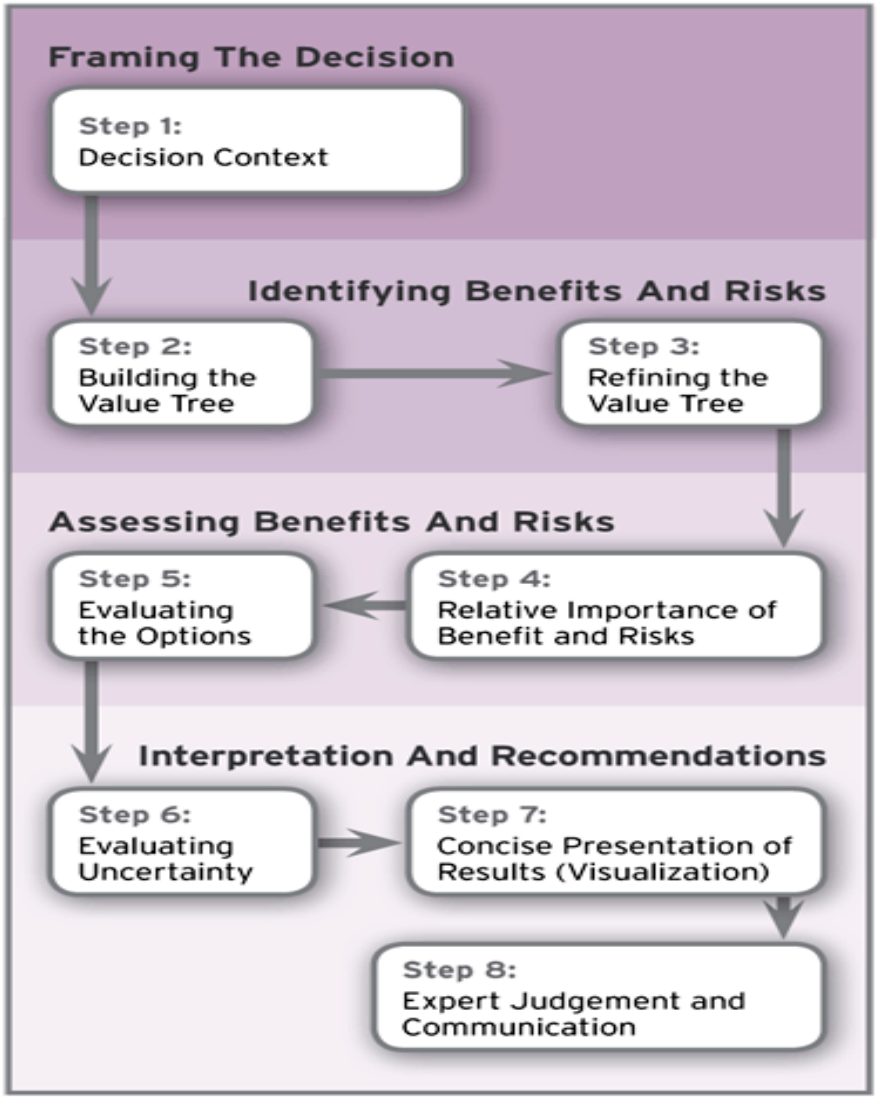
Centre for Innovation in Regulatory Science CIRS

- Mission: …advancing Regulatory and HTA policies and processes
- Workshops on BR since 2002
- CIRS Benefit-Risk Taskforce
- Key Regulatory authorities, HTAs, Patient Organisations, Industry

UMBRA 8-Step Benefit-Risk Framework

An international group of regulators and drug companies have agreed in principle to a framework that sets out eight steps for assessing a drug's benefits and risks and could set the stage for a global approach to evaluating drugs."

Pink Sheet, August 2012



Walker and McAuslane, EMA february 17th, 2014 London

The Consortium on Benefit-Risk Assessment (CASS/COBRA)

A consortium of CIRS, Swissmedic (Switzerland), TGA (Australia), HSA (Singapore) and Health Canada to pilot a standardised approach to benefit-risk assessment.

The Development of A Benefit Risk Assessment Template for COBRA

- Built on the BR guidance document of the EMA.
- A Qualitative or semi-quantitative approach to be used in line with Reviewer's current practice
- Assessed the feasibility in a retrospective study (2010)
- Carried out a validation of this approach in a retrospective pilot study where all four agencies assessed the same approved product (2011)
- Prospective Study (2012-2013)

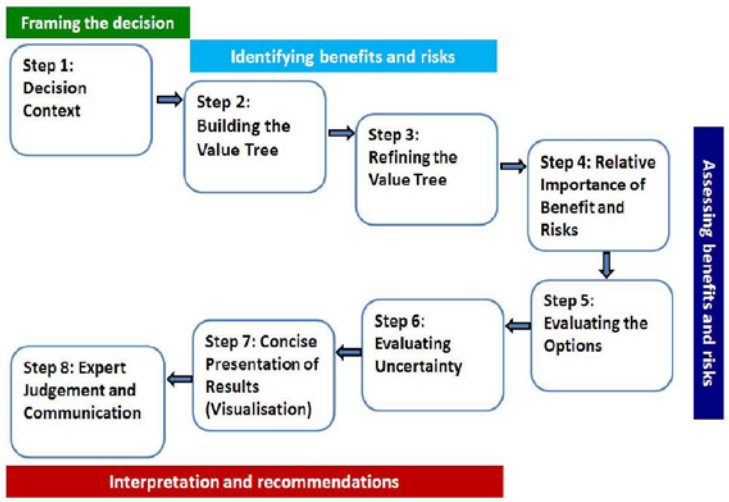
CIRS Centre for Innovation in Regulatory Science

Product Name:

Indication:

PROFORMA SECTION

The UMBRA Eight Step Benefit Risk Framework



The diagram shows the common elements of the UMBRA eight step Benefit Risk Framework that make up a systematic approach to benefit-risk assessment for medicines

At the CIRS annual workshop, 2012 (20-21 June) there was a consensus from those who are developing Benefit Risk methodologies for assessing medicines that there are four key stages namely;

- Framing the decision;
- Identifying the benefits and risks;
- Assessing the benefits and risks;
- and Interpretation and recommendation.

Underpinning these was an overarching eight step framework;

1. Discision context;
2. Building the Value Tree;
3. Value Tree refinement;
4. Assessing relative importance;
5. Evaluating options;
6. Evaluating uncertainty;
7. Concise presentation of results – visualisation;
8. Final recommendation.

All the methodologies currently being developed by regulators and companies have these steps whether explicitly or implicitly undertaken.

The UMBRA overarching framework provides the basis for a common agreement on the principles for benefit risk assessment of medicines.

Contents | Background | Overall Summaries | Identified B&R | B&R Study Info | Weights & Values | Conclusions | B&R Summary

CIRS Centre for Innovation in Regulatory Science

Product Name:

Indication:

Step 1

PROFORMA SECTION

SECTION 2. Background

The aim of this proforma is to provide the means whereby the key benefits and risks, together with the uncertainties (strengths of evidence and limitations of data) that drive the benefit-risk assessment can be documented systematically in the light of the available evidence and therapeutic indication in accordance with the CHMP Assessment Template. This section contains a mixture of factual key data and interpretation through value judgments.

2.1 Specify the claimed therapeutic indication *This prefills summary 1.2.1*

2.2 Treatment modalities evaluated in this submission *This prefills summary 1.2.2*

2.3 Other currently available treatment options NOT considered or evaluated

2.4 What are the known risks with compounds of the same therapeutic class?

2.5 Is this product for an unmet medical need? *This prefills summary 1.2.3* Please select

Reasons: Please provide justification for your decision on the product fulfilling or not fulfilling an unmet medical need.

2.6 Aims of treatment and expected effect size? i.e. define if there are established minimally significant

Walker and McAuslane, EMA feb. 17th, 2014 London

The SABRE Initiative

- The work by COBRA is now becoming the basis for other Agencies & Review divisions in the Emerging Markets to evaluate this methodology under different review models
- CIRS has established a consortium in South East Asia consisting of 7 agencies working in the region namely: China, Indonesia, Malaysia, Philippines, Singapore, South Korea & Taiwan

IMI PROTECT

- Objective: to strengthen the monitoring of benefit-risk of medicines in Europe by developing innovative methods
- Workpackages
  1. project management and organization
  2. Framework for epidemiological studies
  3. Methods for signal detection
  4. New tools for data-collections from consumers
  5. **Benefit Risk integration and representation**
  6. Validation studies involving an extended audience
  7. Training and communication

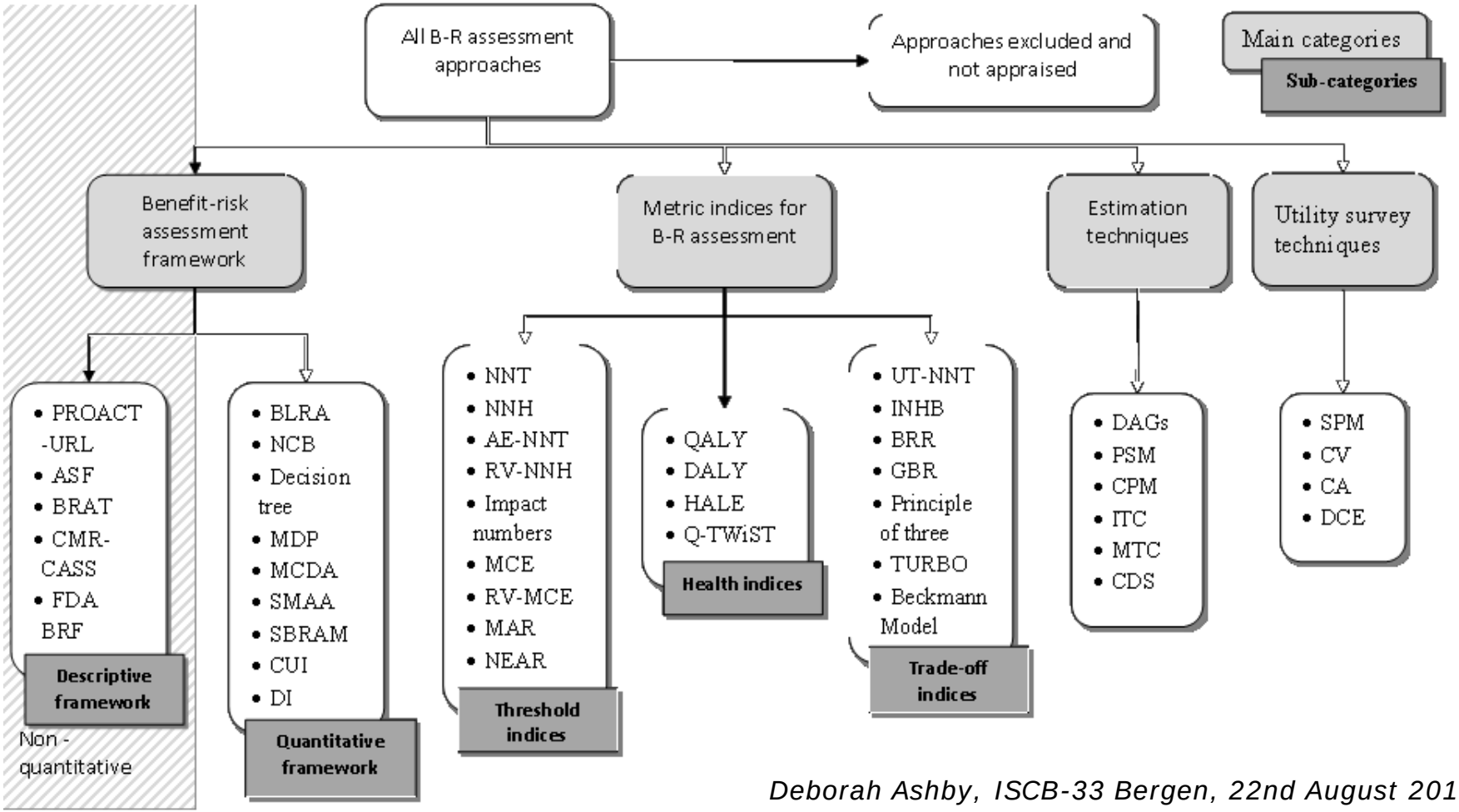
IMI: Innovative Medicines Initiative
PROTECT: Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium

IMO Protect WP5

- Challenges in medical decision-making
- Emerging methods in benefit-risk assessment
- Descriptive frameworks
  - Case study I: Applications of MCDA
  - Case study II: Applications of SMAA
- Patient involvement

IMI PROTECT

Assess and test methodologies for the BR assessment of medicines



Wave 1 Case studies: Applications

	Natalizumab	Rimonabant	Telithromycin	Efalizumab
PrOACT-URL	✓	✓	✓	✓
BRAT	✓	✓	✓	✓
MCDA	✓	✓	✓	✓
SMAA		✓	✓	
NNT & NNH	✓	✓		
Impact Number		✓		
QALY				
Q-TWiST				
INHB		✓		
BRR	✓	✓	✓	✓
PSM	✓	✓	✓	
MTC	✓			
DCE				
Other:	Decision conferencing	Direct utility elicitation	SBRAM, Swing-weighting	Decision conferencing

The Escher project

1. Regulatory environment (dialogue, alignment, rules of engagement)
2. Methods applied (trials, B/R, safety management, biomarkers)
3. Interactions with society (transparency, trust building, ethics)

Decision analysis, benefit-risk assessment and modeling (3.1, 3.2) *(www.drugis.org)*

Development | **Approval** | **P-approval**

Scientific advice, dialogue (1.1, 1.2)
Trial methods (2.1, 2.2)
Biomarkers (2.3, 2.4)

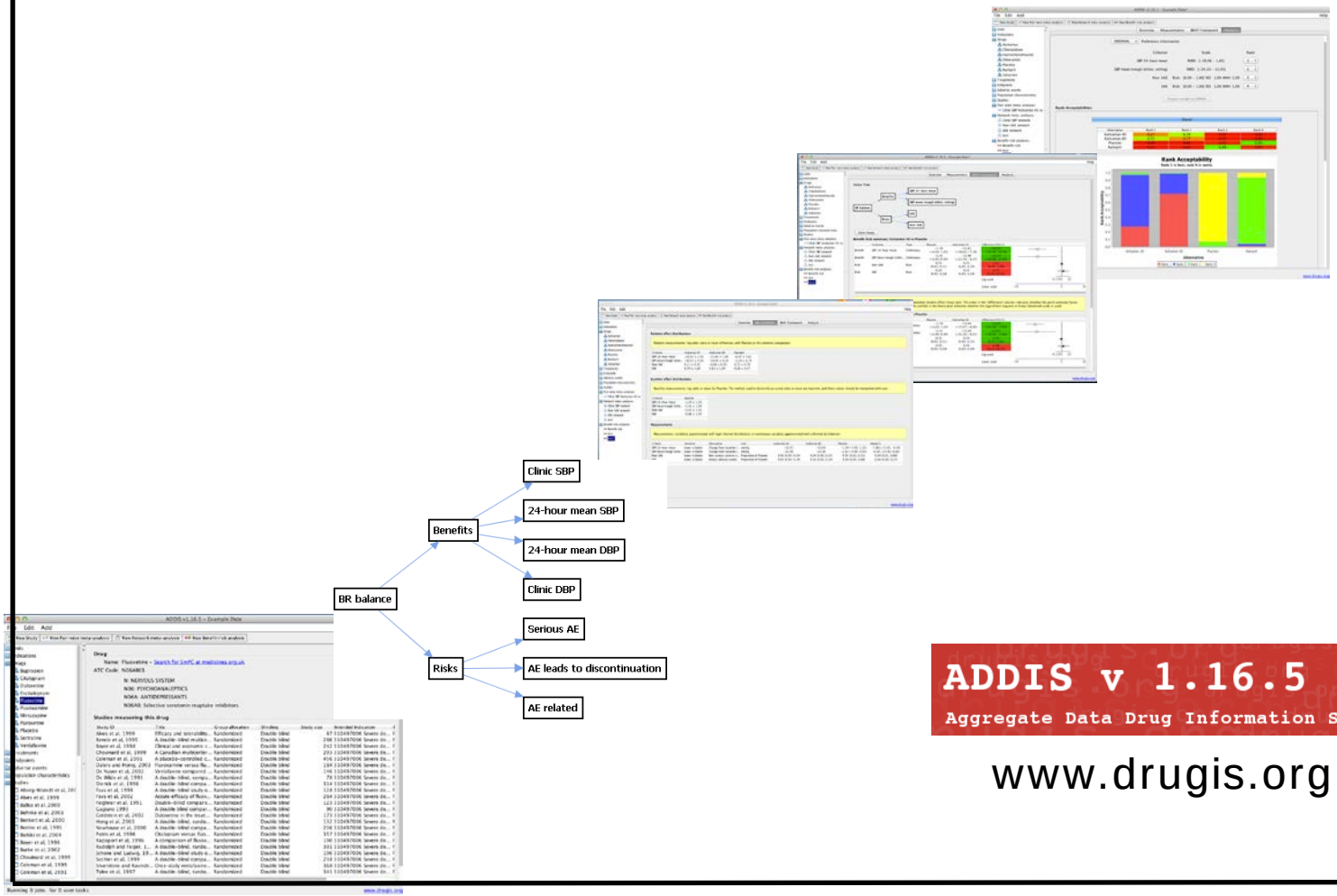
Safety management, PSURs (1.3, 2.5, 2.6, 2.7)
HTA, access and reimbursement (1.4, 1.5)
Ethics of late phase studies (2.8)

Time

Continued development throughout the product life-cycle (1.6)

Effort versus Precision Trade-off

Precision

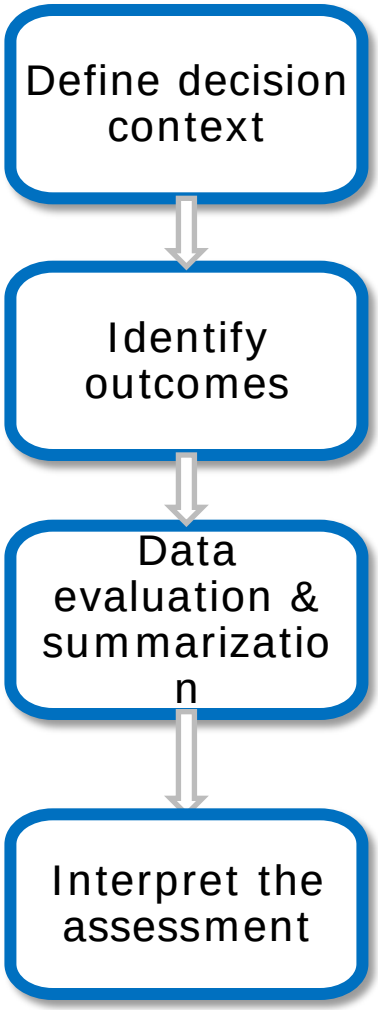


ADDIS v 1.16.5
Aggregate Data Drug Information System

www.drugis.org

Effort

Commonalities Across Frameworks



Decision context

- Recognition that benefit–risk assessments are dependent on:
  - Indication and severity of the condition
  - Unmet medical need
  - Population(s) being treated
  - Other available treatments
  - Perspective (e.g. , regulator, sponsor, patient, clinician)

Decision profile

- Defining benefit and risk criteria, noting the measures for the criteria and rigorous documentation of the rationale for inclusion or exclusion in the assessment

Assessing outcome importance

Evaluating, summarizing, and communicating data relevant to the decision

- Effects tables
- Key Benefit-Risk Summary Table

Track uncertainties

Communicate the rationale underpinning the assessment and the subsequent decision

Noel B (Eli Lilly): BIO June 2012 Boston

Walker and McAuslane, EMA feb. 17th, 2014 London

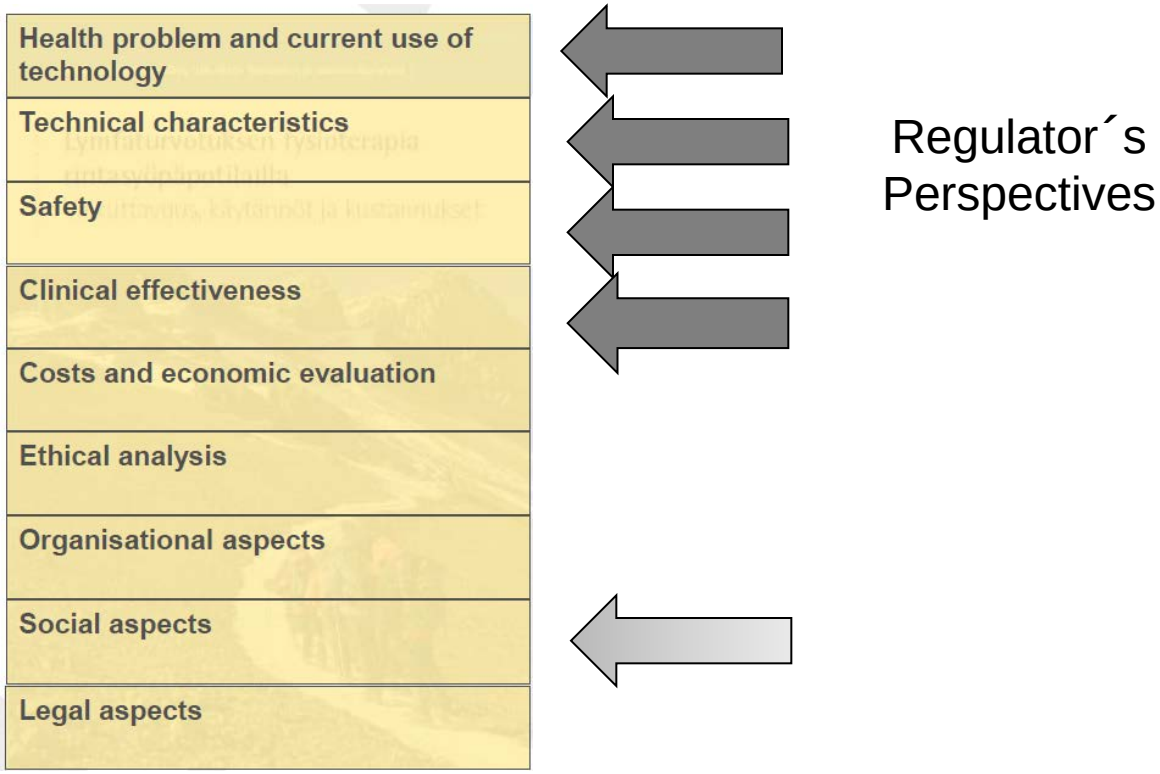
Mapping different frameworks to the UMBRA

	Framing the Decision	Identifying Benefits and Risk		Assessing Benefits and Risks		Interpretation and Outcome		
Frame-work	Step 1: Decision Context	Step 2: Building the Value Tree	Step 3: Refining the Value Tree	Step 4: Assessing Relative Importance	Step 5: Evaluating the Options	Step 6: Evaluating Uncertainty	Step 7: Concise presentation of Results (Visualisation)	Step 8: Final Recommendation
FDA	Analysis of conditions Unmet medical need	Clinical Benefits & Risks	Evidence and uncertainties				Words: Telling the Story	Conclusions and Rationale Risk Management Plans
EMA	Nature & Framing of the Problem	Objectives; Favourable & Unfavourable Effects		Options to be evaluated & the Consequences	Trade offs Benefit/ Risk Balance	Evaluating Uncertainty	Effects Table Risk tolerance	Consistency of Decisions (Linked Decisions)
BRAT	Define Decision Context	Identify Outcomes:Build Value Tree	Customise framework : Refine Value Tree	Assess relative importance of different outcomes: Weighting or Ranking Other Stakeholders		Evaluating Uncertainty ?	Display & Interpret Key BR metrics Validate Results	Decision & communication of BR Assessment
CIRS	Decision Context	Building the Value Tree All Benefits All Risks	Rationale for Benefits & Risks in overall BR assessment	Weighting of Benefits & Risks	Valuing or Scoring of Options		Visualisation	Expert Judgement & Risk Management

Walker and McAuslane, EMA feb. 17th, 2014 London

EUnetHTA´s HTA Core Model

- Domains of HTA



In conclusion

- Areas where convergence and harmonization is needed
  - BR assessment structure and process
  - Transparent and agreed favourable and unfavourable domains of benefits and risks
  - Standard data exchange models that will streamline the transfer of data between different stakeholders (eCTD)
  - Precompetitive data exchange
  - Communication of uncertainties

Adapted from Can the benefit-risk landscape converge? Isabelle Stöckert

Thank you very much for your attention !