Assessing Benefit-Risk discussion

EFSPI Statistical Leaders Meeting

June 20th 2012

Presenter: Ian Hirsch

Facilitator: Sara Hughes

Assessing Benefit-Risk

- Update on the Benefit Risk SIG
- Benefit-Risk drivers and initiatives
- Overview of Benefit-Risk and personal perspective of key issues
- So what now? Potential strategic direction
- Wrap up

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Assessing Benefit-Risk

Benefit-Risk Special Interest Group

Formed as many statisticians are “catching up” with Benefit-Risk

Current membership

- Ian Hirsch (AstraZeneca-chair of SIG)
- Susan Shepherd (Amgen)
- Martin Gebel (Bayer)
- Rebecca Sudlow and George Quartey (Roche and George link to epidemiology/safety SIG)
- Guenter Heimann and Ekkehard Glimm (Novartis)
- Maylis Coste and Veronique Robert (IRIServier)
- Carl-Fredrik Burman (AstraZeneca and member until EFSPI R-B one day meeting)
- Dan Evans (Pfizer)
- Yunxia Lu (Karolinska Institutet)
- Alan Phillips (Icon)
- Alberto Garcia-Hernandez (Astellas)
- link to BRAT initiative tbc

Assessing Benefit-Risk

Benefit-Risk Special Interest Group

The main aims of the Benefit-Risk Special Interest Group are split into 5 key areas

1. To understand how best to apply Benefit-Risk Methodologies across the Pharmaceutical Industry including processes for implementation, issues that arise and recommendations

2. To share examples of how Benefit-Risk has been used within pharmaceutical companies, any best practices arising from them and how they can best be used from an industry perspective across all phases of development and post licensing. Examples include portfolio decision making and key regulatory documents such as Development/Periodic Safety Update Reports

3. To discuss and make recommendations on key methodological issues for example utility functions and weighting approaches

4. To share external information including new developments around Benefit-Risk including those in the literature and outputs from Benefit-Risk initiatives and to produce guidance on how best they can be used within the EFSPI arena

5. *Outputs from the first 4 areas will then be used to inform, educate and pass on learning for those within EFSPI and its affiliations of what information is available, proposed best practices, implementation guidelines/processes together with information on different methodologies via various forums such as an EFSPI Benefit-Risk website/WIKI and supporting specific Benefit-Risk meetings.*

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Benefit-Risk Special Interest Group

It is expected that different ways of communicating outputs from the SIG will be used including:

- Meetings/training courses via EFSPI affiliates
- Best practice documents
- An EFSPI Benefit-Risk website/wiki
- Articles/publications
- Expert forums
- Others?

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Benefit-Risk Special Interest Group

Current status of SIG:

- Kicked off this year

- Had 2 meetings
  - Finalised Charter
  - Brainstorm of ideas/topics
    - Literature/publications summary
    - Review of barriers to implementing B-R methodology
    - Collate EFSPI comments for EMA report
    - Review of the tools that are available to carry out Benefit Risk assessments
    - Share case studies
    - Combining types of trial data
    - Summary of Initiatives

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Periodic Safety Update Reports

Section 2

Periodic safety update reports

Article 107b

1. Marketing authorisation holders shall submit to the Agency periodic safety update reports containing:

(a) summaries of data relevant to the benefits and risks of the medicinal product, including results of all studies with a consideration of their potential impact on the marketing authorisation;

(b) a scientific evaluation of the risk-benefit balance of the medicinal product;

(c) all data relating to the volume of sales of the medicinal product and any data in possession of the marketing authorisation holder relating to the volume of prescriptions, including an estimate of the population exposed to the medicinal product.

Directive 2010/84/EU, Article 107b

"Integrated benefit/risk analysis for approved indications"

Assessing Benefit-Risk
External initiatives

- ISPOR (http://www.ispor.org/workpaper/risk_benefit_management_guo.pdf)

  …*to identify and describe published quantitative RBA methods for pharmaceuticals.*

- EMA
  (http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000314.jsp&mid=WC0b01ac0580223ed6&jsenabled=true)

  …*to identify decision-making models that can be used in the Agency's work, to make the assessment of the benefits and risks of medicines more consistent, more transparent and easier to audit.*

- IMI Protect WP5 (http://www.imi-protect.eu/wp5.html)

  …*to develop methods for use in benefit-risk assessment, including both the underpinning modelling and the presentation of the results, with a particular emphasis on graphical methods. The various options will be compared and tested out on a range of case-studies with patients, healthcare providers, pharma industry and regulators.*

- BRAT PhrMA -> CIRS (http://cirsci.org/benefit-risk)

  …improving benefit-risk assessments during the drug development and regulatory approval process and increasing the transparency, predictability and consistency with which benefit-risk assessments are conducted. …to further the technical development of the work pioneered by the PhRMA Benefit-Risk Action Team (BRAT) and to broaden input from the scientific community into the evolution of this methodology.

- TI Pharma/ADDIS (Netherlands)

  …aim of ADDIS is to provide quantitative meta-analytic data on outcomes in terms of safety and efficacy, within and across pharmaceutical classes and to provide decision support based on quantitative benefit-risk assessment

- CASS Initiative (Canada, Australia, Switzerland, Singapore)

  …*to determine the feasibility and the practical application of a systematic and standardized approach to BR assessment*

Benefit-risk methodology

The European Medicines Agency's opinions are based on **balancing** the desired effects or '**benefits**' of a medicine against its undesired effects or '**risks**'. The Agency can recommend the authorisation of a medicine whose benefits are judged to be greater than its risks. In contrast, a medicine whose risks outweigh its benefits cannot be recommended for marketing.

Weighing up the benefits and risks of a medicine is a complex process, since it involves the evaluation of a large amount of data. In addition, there is always some uncertainty around the actual benefits and risks of a medicine, because they can only be determined by looking at the information that is available at a given point in time.

The benefit-risk methodology project

The Agency strives towards making its opinions on the balance of benefits and risks as **consistent and transparent** as possible. To date, however, there is no standard methodology that is used to aid regulatory decisions on the benefits and risks of medicines.

To help address this problem, the Agency began a three-year project on benefit-risk methodology in early 2009. The project aims to identify **decision-making models** that can be used in the Agency's work, to make the assessment of the benefits and risks of medicines more consistent, more transparent and easier to audit.

The project began on the recommendation of a working group of the Committee for Medicinal Products for Human Use (CHMP) on benefit-risk assessment methods, which met between 2006 and 2008. The working group's conclusions were published in a reflection paper in March 2008.

Work package	Status
1. Describing the benefit-risk assessment models already being used in the European Union's regulatory network	Completed March 2010
2. Assessing the suitability of the current tools and processes used in benefit-risk assessments	Completed August 2010
3. Field-testing the most appropriate models in five European medicine regulatory agencies	Completed June 2011
4. Refining the most suitable models for use in medicines regulation to create a new benefit-risk tool	Completed February 2012
5. Training European assessors to use the final tool	Started March 2012

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- What do we mean by Benefit-Risk models?
  - Frameworks
  - Quantitative models

Example of a B-R Framework-BRAT

Clinical Pharmacology & Therapeutics (2011) **89** 2, 312–315. doi:10.1038/clpt.2010.291

Development of a Framework for Enhancing the Transparency, Reproducibility and Communication of the Benefit–Risk Balance of Medicines

P M Coplan[1,2], R A Noel[3], B S Levitan[4], J Ferguson[5] and F Mussen[6]

The current process of benefit–risk assessment of medicines relies primarily on intuitive expert judgment. Frameworks are needed for transparent, rational and defensible decision making that benefits patients, drug developers, and decision makers. The Benefit Risk Action Team framework is a set of processes and tools for selecting, organizing, summarizing, and interpreting data that is relevant to decisions based on benefit–risk assessments. It provides a standardized yet flexible platform for incorporating study outcomes and preference weights as well as for communicating the rationales for decisions.

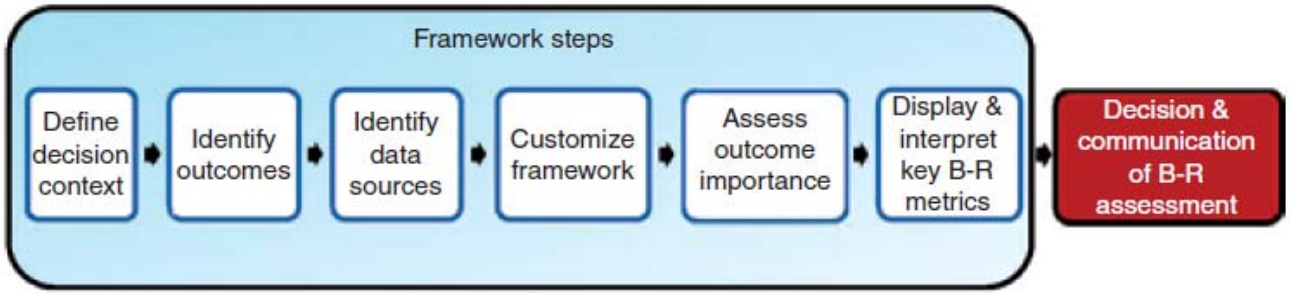

Figure 1 Steps in using the Benefit Risk Action Team (BRAT) benefit–risk assessment framework.

Example of a B-R Framework -BRAT

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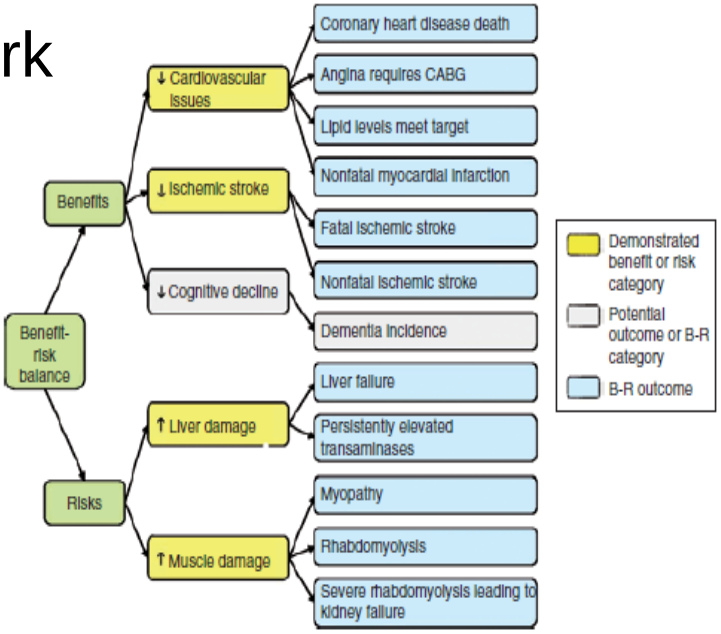


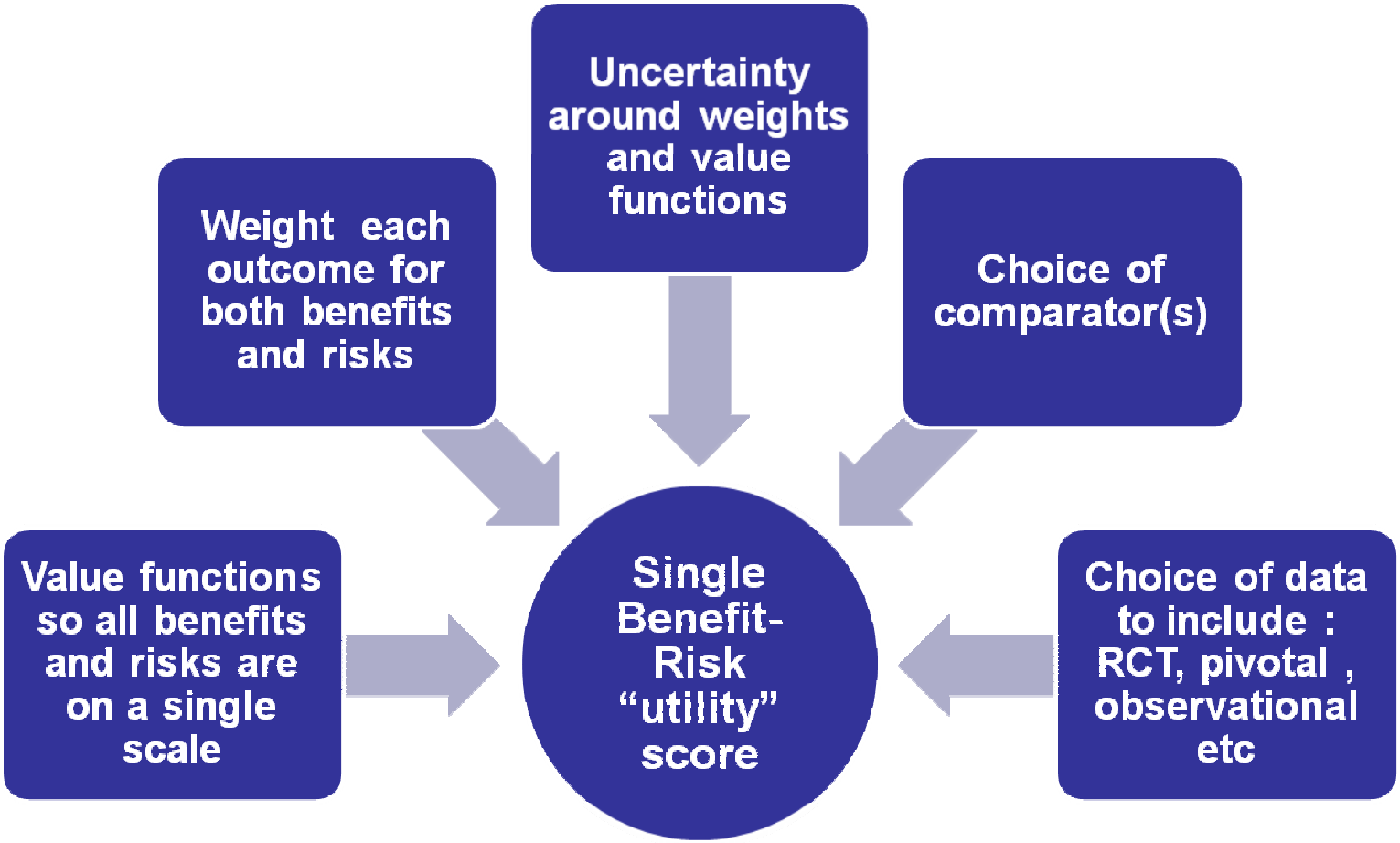
Figure 2 Example of a value tree: prioritization of benefit and risk outcomes for inclusion in a comparative benefit–risk assessment of two statins for the prevention of cardiovascular disease (regulator's perspective). CABG, coronary artery bypass graft.

		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 −50 0 50

Figure 3 Example of Key Benefit–Risk Summary table. CABG, coronary artery bypass graft.

Creating a single B-R utility score…a "quantitative" model



A good overview of MCDA in: *Mussen F, Salek S, Walker S. Benefit-Risk Appraisal of Medicines. John Wiley & Sons, Ltd.; 2009.*

An example of MCDA / quantitative approach

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 August 2011
EMA/718294/2011
Human Medicines Development and Evaluation

Benefit-risk methodology project

Work package 3 report: Field tests

Revised version of the adopted report with any confidential information removed

Table 3: The Effects Table for Drug X.

	Name	Description	Fixed Lower†	Fixed Upper†	Units	Placebo	Drug X 200 mg+MTX	Drug X 400mg+MTX
Favourable Effects	ACR 20	Proportion of patients achieving ACR* 20 at week 24	0	100	%	11.7	58.2	59.6
	ACR 50	Proportion of patients achieving ACR* 50 at week 24	0	100	%	5.8	34.8	36.6
	ACR 70	Proportion of patients achieving ACR* 70 at week 24	0	100	%	2.4	18.8	16.1
	mTSS	Mean amount of progression of joint damage in hands and feet at week 52**	0	10	Change Score±SD	2.8±7.8	0.4±5.7	0.0±4.8
Unfavourable Effects	Infections	Proportion of patients experiencing infections & infestations	70	80	No. per 100 pt-yrs	72.13	79.88	76.62
	SAEs	Proportion of patients experiencing musculoskeletal & connective tissue disorders	25	60	No. per 100 pt-yrs	57.05	28.39	25.88
	Deaths	Proportion of patient deaths	0	3	%	0.15	0.42	0.97
	Tuberculosis	Number of patients contracting tuberculosis	0	30	Number	0	5	28
	Malignancies	Proportion of patients developing at least one malignancy	0	2	%	0.9	1.9	1.4

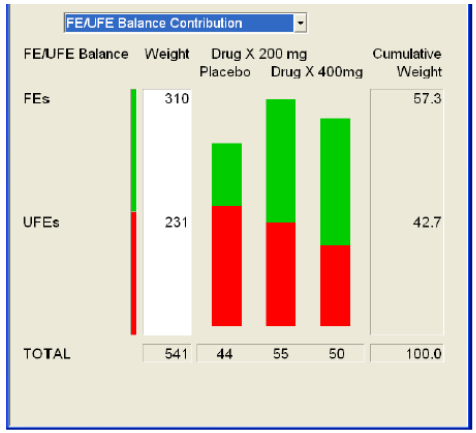


Figure 3: Added-value bar graphs for the favourable and unfavourable effects of Drug X 200mg+MTX, Drug X 400mg + MTX, and for the placebo. Longer green bars indicate more benefit, longer red bars indicate more safety.

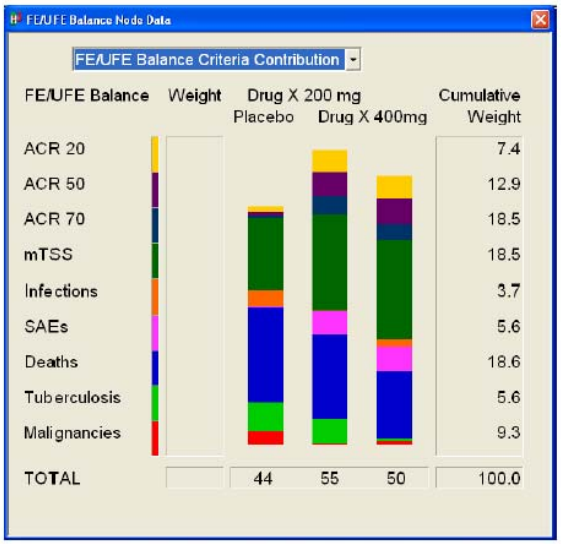


Figure 4: Added-value bar graphs for all effects of Drug X 200mg+MTX, Drug X 400mg + MTX, and for the placebo.

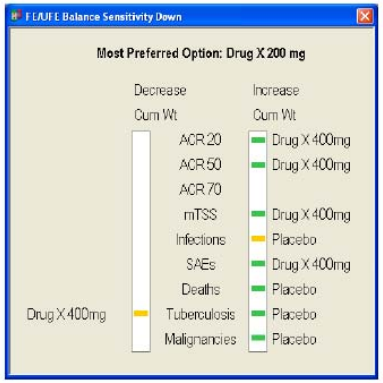


Figure 8: Sensitivity analyses on the cumulative weights separately for each of the effects for Drug X. The coloured bars indicate by how much the cumulative weight must change for a different option to become most preferred: green—more than 15 points, yellow—between 5 and 15 points, red—less than 5 points. With no red bars, and only two yellow ones, substantial changes in weights would be required to change the overall most preferred option from the 200mg dose.

Creating a single utility score…a “quantitative model

Key questions

- *Should we put a single number on a subjective assessment?*

- How do we weight each outcome? How is that related to each measure?

- How do we put each outcome onto the same scale i.e. transform to 0-100 scale
    - Linear/non-linear

- How do we assess uncertainty especially given we now have subjective weighting?

- How do we choose most appropriate data?

Assessing Benefit-Risk

Personal thoughts…

– Special interest group has a few people heavily involved and others who dial in to find out more about the topic. This is indicative of:
  - A few companies are carrying out pilots with and without statistical input (at varying levels)
  - Benefit-Risk is currently a cross functional topic statisticians want/need to be involved in
  - A thirst for information on the topic

– The statistical element is relatively straightforward however putting a number on a subjective opinion is seen by many as controversial:
  - Frameworks or quantitative Benefit-Risk assessments should be seen as a tool to help make better decisions for those having to make a Benefit-Risk judgement
    – Perspectives of regulators, industry decision makers, patients, physicians perspectives differ so one size will not fit all
    – *Just having the right people in the room to discuss within a "framework" with simple visualisation can help us answer the right questions and concentrate on the real issues*

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Today…so what now?

- **Any questions clarifications on the presentation?**
- **Discussion**

Assessing Benefit-Risk

Today…so what now?

Questions for discussion

- What have been your experiences relating to the challenges of implementation of formal B-R assessments within your companies?
- What is the best strategic ways forward for B-R for EFSPI and affiliates
  - Do we use dedicated resources or is this carried out within peoples “day jobs”?
  - How should we use the SIG for education/producing training materials or to carry out research into methodologies etc?
- What level of support is there within the statistics functions within your companies to carry out work for the B-R SIG/EFSPI?
  - Without this is will be difficult to put together guidelines and materials
- What do you need within your companies to support B-R capability build?
  - Meetings/training courses, best practice documents, EFSPI Benefit-Risk website/wiki, Articles/publications, outputs from expert forums
  - Valuable input to take forward to develop targeted material and implementation guidelines to support statisticians increase their capability in the Benefit-Risk area.