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Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

PROTECT RESOURCES FOR FURTHER LEARNING

IMI-PROTECT Symposium

Benefit-Risk Integration and Representation Workshop

18th February 2015

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Disclaimer

"The processes described and conclusions drawn from the work presented herein relate solely to the testing of methodologies and representations for the evaluation of benefit and risk of medicines.

This report neither replaces nor is intended to replace or comment on any regulatory decisions made by national regulatory agencies, nor the European Medicines Agency."

PROTECT is receiving funding from the European Community's Seventh Framework Programme (F7/2007-2013) for the Innovative Medicine Initiative (www.imi.europa.eu)

Dissemination of results/recommendations arising from PROTECT*

- Publications & Presentations
- PROTECT Web Portal
- The ENCePP network
- Training Programmes (WP7)
- The EMEA Scientific Committees, Working Parties and regulatory activities
- Other possible means

http://protectbenefitrisk.eu/

* PROTECT Full Project Proposal / IMI Call #6 (20th January 2009)

Web design

- Responsive Web Design: “Reponses or addictiveness Quickly and Positively” to the users. It responds to users environment based on screen-size, platform and orientation.

- Offers : Smooth Navigation , Easy reading, Reduces scrolling and zooming, social media integration and excellent user experience – across a good vary of devices (from smartphones to desktops).

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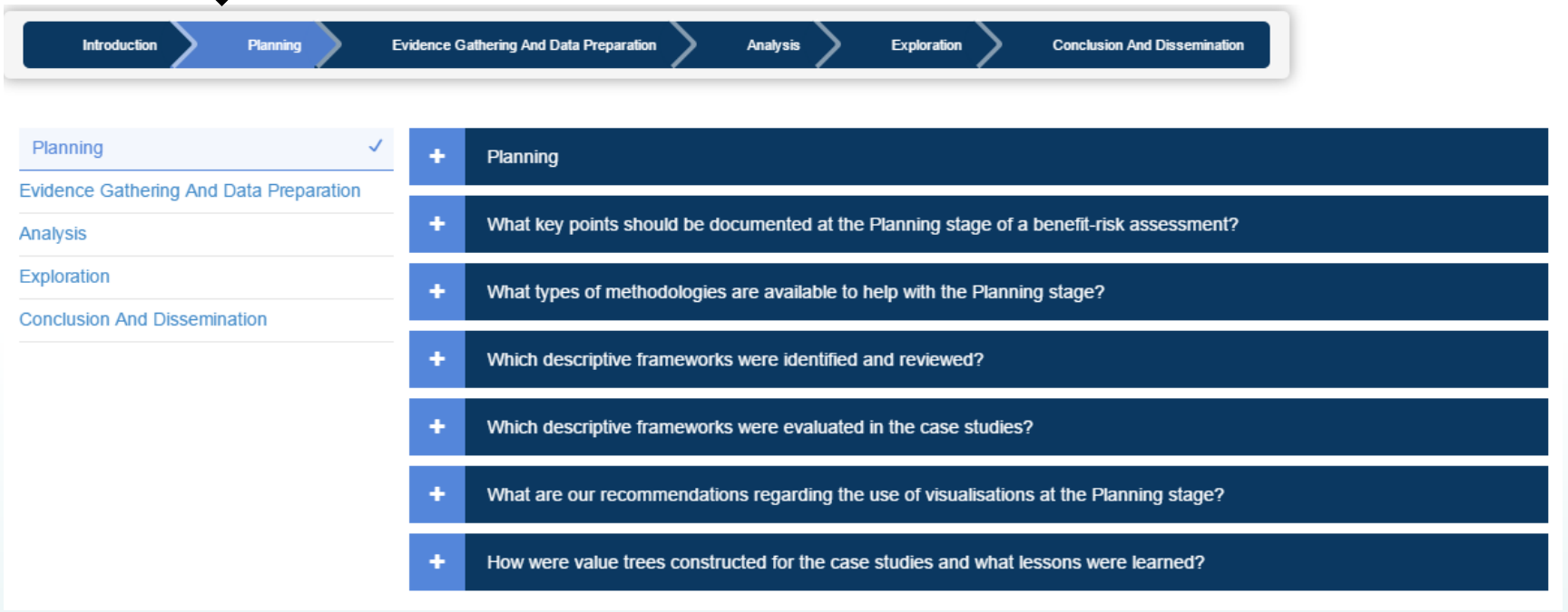

- Recommendations tab is organised into five broad stages common to all benefit-risk assessments
- Interactive version of final recommendations report (Hughes et al, Nov 2013)

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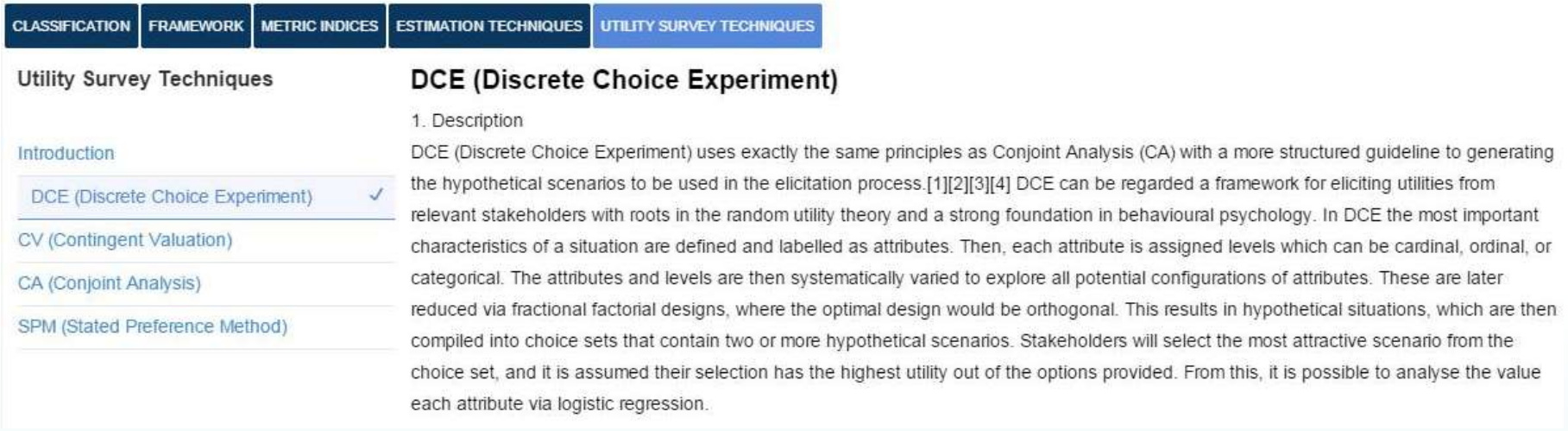
CLASSIFICATION | FRAMEWORK | METRIC INDICES | ESTIMATION TECHNIQUES | UTILITY SURVEY TECHNIQUES

Framework		Metric Indices			Estimation Techniques	Utility Survey Techniques
Descriptive	Quantitative	Threshold	Health	Trade-Off		
PrOACT-URL	MCDA	NNT	QALY	INHB	PSM	DCE
BRAT	SMAA	NNH	Q-TWiST	BRR	ITC	CV
ASF	Decision Tree	Impact Numbers	HALE	UT-NNT	MTC	CA
CMR-CASS	MDP	AE-NNT	DALY	GBR	CPM	SPM
COBRA	BLRA	RV-NNH		Principle Of threes	DAGS	
FDA BRF	NCB	MCE		TURBO	CDS	
SABRE	SBRAM	RV-MCE		BECKMAN		
UMBRA	CUI	MAR				
	DI	NEAR				

- Classification of methodologies used in benefit-risk assessment



- Taken together, they would be a sufficiently powerful toolbox for most benefit-risk assessments
- Interactive version of systematic review of methodologies (Mt-Isa et al, 2014)

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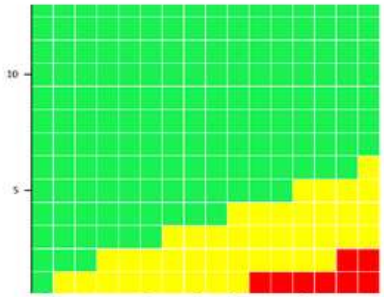
INTERACTIVE GRAPHICS | LINE GRAPHICS | PICTOGRAM | PIE CHARTS | RISK LADDERS AND RISK SCALE | SCATTER PLOT | TABLES | TREE DIAGRAM | STATISTICAL MAPS

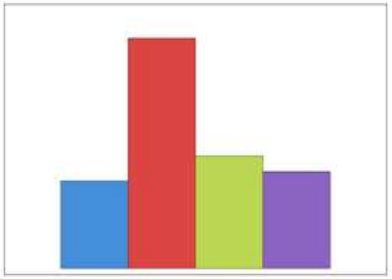
Introduction

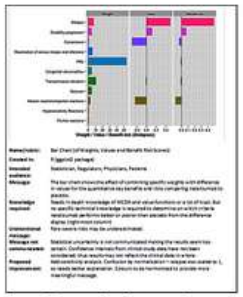
There are many ways in which benefits and risks are presented and communicated. There is an absence of a consensus on which visual representations are most suitable to display benefit-risk profiles.

The visual representation of benefits and risks review has been conducted in two stages. The first stage provided a level of evaluation as to the suitability of visuals presented in the application of benefit-risk approaches in PROTECT methodology review. However, external circumstances such as the intended audience, complexity of the benefit-risk problem, time in drug lifecycle, and other factors that are not related to the benefit-risk methodology may influence the type of visual representation to use. The second stage therefore explored and identified suitable visuals to communicate benefits and risks to different stakeholders in different situations. This included the use of visualisations in dynamic and interactive settings.



Area graph and volume chart


Bar chart/graph


Baseball cards

- Appraisal of visual representations used in benefit-risk assessment

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- Introduction
- Flow chart of systematic review literature screening
- Flow chart to illustrate BR score
- Simple descriptive table
- BRAT master data summary table
- BRAT key benefit-risk summary table ✓
- Value function for continuous variable
- Value function for categorical variable
- Line graph of two-way sensitivity analysis
- BRAT value tree

Section 6 BRAT key benefit-risk summary table

Natalizumab versus Placebo (Comparator) at time of CHMP re-evaluation

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

Higher for Natalizumab
Higher for Comparator

- Seventeen recommendations for the application of visuals at key stages proposed
- Interactive version of visual review (Mt-Isa et al, Part 1 & Part 2; 2013)

- Each case study applied several methodologies and visual representations
- Interactive summary of Case Study Reports:
  - Efalizumab (Micaleff et al Wave 1 & Suppl 1; Phillips et al Suppl 2; 2013)
  - Natalizumab (Nixon et al Wave 1 and Wave 2, 2013)
  - Rimonabant (Juhaeri et al Wave 1; Mt-Isa et al Suppl 1; Juhaeri et al Wave 2, 2011/2012)
  - Rosiglitazone (Philips et al Wave 2, 2013)
  - Telithromycin (Quartey et al Wave 1, 2012)
  - Warfarin (Hallgreen et al, Wave 2, 2013)

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Patient And Public Involvement

- What is Patient and Public Involvement?
- What is the Patient and Public Involvement project? ✓
- What is benefit-risk assessment
- How benefit-risk assessment is done: our experiences
- How we found out what is important to patients: an example
- How can we display benefits and risks?
- A case study of visual preferences in obese adults

What is the Patient and Public Involvement project?

The Patient and Public Involvement project was a working group in PROTECT Benefit-Risk. We were created following a strong interest in patient and public involvement (PPI) from the PROTECT Benefit-Risk case study task forces. Our aim was to develop a toolbox for those who wish to involve patients and the public in medical benefit-risk decision making. Our technical report can be found on the IMI PROTECT website (http://www.imi-protect.eu/benefitsRep.shtml).

Our research focussed on three areas of involving patients and the public: (a) testing formal methods which can be used to value the benefits and risks of medicines, (b) testing out different visual images to see if they are understandable, trustworthy, and useful , and (c) understanding how to communicate the process and results of benefit-risk assessment.

We developed this section of the website to provide information to patients and the public and professionals who are interested and would like to learn more about the benefit-risk assessment of medicines. We would like to thank the following organisations for reviewing the content on this section of the PROTECT benefit-risk website: organisations name should be added here.

- A guide for patients and interested members of the public who are new to the benefit-risk assessment of medicines or would like to know more
  - Example case-study on "visual communication of the benefits and risks of weight loss interventions"

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About Us

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT), a collaboration amongst private and public sector partners, is a project set up under the Innovative Medicines initiative (IMI). Its goal is to strengthen the monitoring of the benefit-risk balance of medicines in Europe. This website is developed as part of the PROTECT Benefit-Risk Group who has advanced the understanding of both the integration, communication and visual representations of benefit and risk assessment methodologies.

PROTECT Benefit-Risk aims to provide practical recommendations for benefit-risk decision processes and supporting tools to various stakeholders, particularly the regulators.

We advocate for increased transparency and robust decision making by making explicit and effectively communicating the methodologies, assumptions, and outcomes utilised in the assessment of benefit-risk balance in medicine. Our experience makes what we believe is a unique contribution that complements and builds on the efforts of other benefit-risk assessment initiatives.

Our Team

LINKS AND GLOSSARY

REPORTS AND DATABASES

PUBLICATIONS

PRESENTATIONS

GLOSSARY AND REFERENCES

Glossary

Term	Description
Approach	The system of methods and principles used in a particular discipline
Aseptic meningitis	A syndrome characterized by headache, neck stiffness, low grade fever, and CSF lymphocytic pleiocytosis in the absence of an acute bacterial pathogen. Viral meningitis is the most frequent cause although mycoplasma, and rickettsia infections; diagnostic or therapeutic procedures; neoplastic procedures; septic perimeningeal foci; and other conditions may result in this syndrome. (From Adams et al., Principles of Neurology, 6th ed, p745)
Aspect ratio	The ratio of the lengths of the two axes on a graph; a square graph has an aspect ratio of 1
Benefit	The positive results of a given treatment for an individual or a population (i.e., efficacy, convenience, or even quality of life)
Benefit-risk assessment	An evaluation of medical product either quantitatively or qualitatively taking both benefits and risks of the product into account
Benefit-risk model	A formal way to analyse benefit and risk consequences and their balances from a set of actions and to aid making choices amongst actions when risk aversion and preferences are specified
Bias	The systematic tendency of any factors associated with the design, conduct, analysis, and evaluation of the results of a benefit-risk assessment to make the estimate of a treatment effect deviate from its true value

- Links to all published reports from IMI PROTECT Benefit Risk.
- Complete Glossary, Abbreviations and References also provided.

Questions …

An online space has been created so that findings and recommendations can be explored interactively and will continue once PROTECT closes following this symposium.

Thank you from the IMI PROTECT Benefit-Risk Team (http://protectbenefitrisk.eu/)

ACKNOWLEDGEMENT

Support

- The research leading to these results was conducted as part of the PROTECT consortium (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium, www.imi-protect.eu) which is a public-private partnership coordinated by the European Medicines Agency.

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