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Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

Visualizing Benefit-Risk for Drug Regulations

Basel PhUSE SDE
3rd July 2014
Basel, CH

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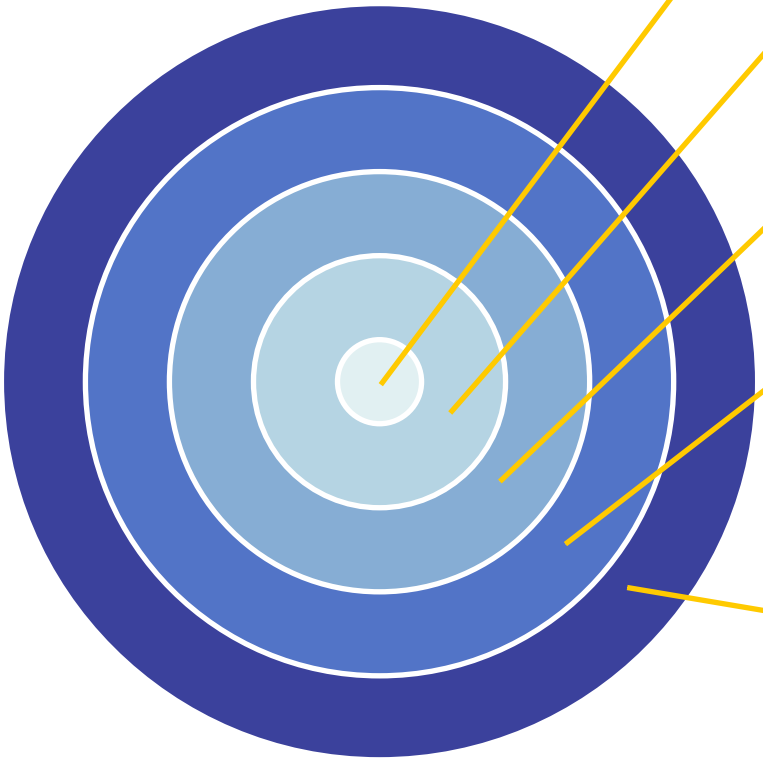
London

Decision makers – who are they?



Patients

- Make decisions for themselves

Healthcare providers

- Make decisions based on prescribing lists

Health technology assessors

- Makes decisions on cost-effectiveness

Regulators

- Makes decisions on quality, safety, efficacy and benefit-risk balance to individuals and public health

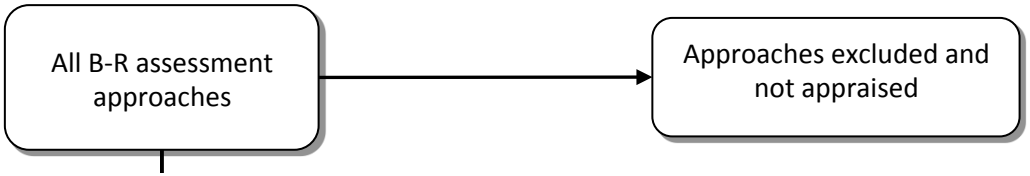
Pharmaceutical companies

- Makes decisions on what to develop for which licenses to apply

The licensing challenge

- The task of regulators (e.g. EMA, FDA) is to make a good and defensible decisions on which medicines should receive a license for which indications, based on the available evidence of risks and benefits
- It is increasingly important to be able to justify and explain these decisions to patients and other stakeholders.
- Can more formal approaches of decision-making, and especially more modern methods of graphical display help regulators do these better?

Methodologies available



Mt-Isa *et al*. Balancing benefit and risk of medicines: a systematic review and classification of available methodologies. Pharmacoepidemiology and Drug Safety 2014. DOI: 10.1002/pds.3636.

Disclaimers

"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."

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Natalizumab case study

It is an interesting case study because: It is an effective treatment for a serious disease, with a rare but very serious side effect. License suspended in the US but then reintroduced due partly to patient pressure.

Drug of interest	Natalizumab
Indication	Relapsing remitting multiple sclerosis
Severe side effect	Progressive Multifocal Leukoencephalopathy (PML)
Regulatory history	2004 Approved in the US 2005 License suspended in the US 2006 Re-introduced because of patient demand in the US and approved in the EU 2009 CHMP reassessed the PML risk and continued approval

Recommendation Roadmap

Planning

- critical issues
- think & discuss purpose and context
- documentation
- foundations for future analyses and updates

Evidence gathering and data preparation

- relevant evidence
- data collection
- data aggregation
- missing/incomplete data

Analysis

- Evaluate data
- Quantify benefits and risks
- Weigh or integrate

Exploration

- robustness
- sensitivity
- assumptions and uncertainties
- other consequences
- impact or added value to the RMPs

Conclusion and dissemination

- communicate results/consensus
- any influence on future actions
- transparent audit trail
- ensures "big picture" is not lost

Recommendation Roadmap

Planning

Evidence gathering and data preparation

Analysis

Exploration

Conclusion and dissemination

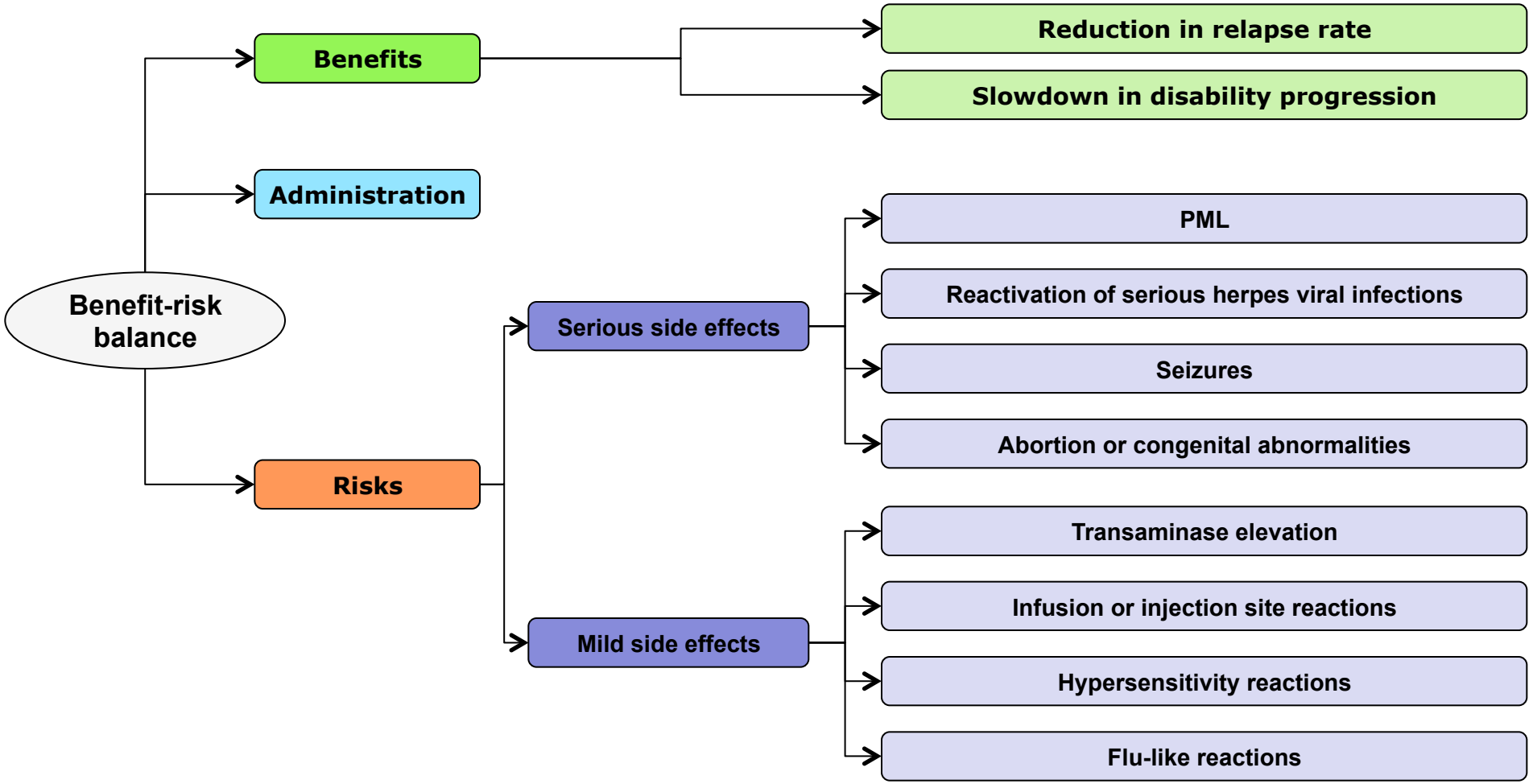
Planning Toolbox

- Useful methodologies include:
  - non-quantitative / descriptive frameworks to organize data e.g. PrOACT-URL and BRAT frameworks
- Preferred visualisation techniques include:
  - tree diagrams and structured tables providing useful means of visualisation

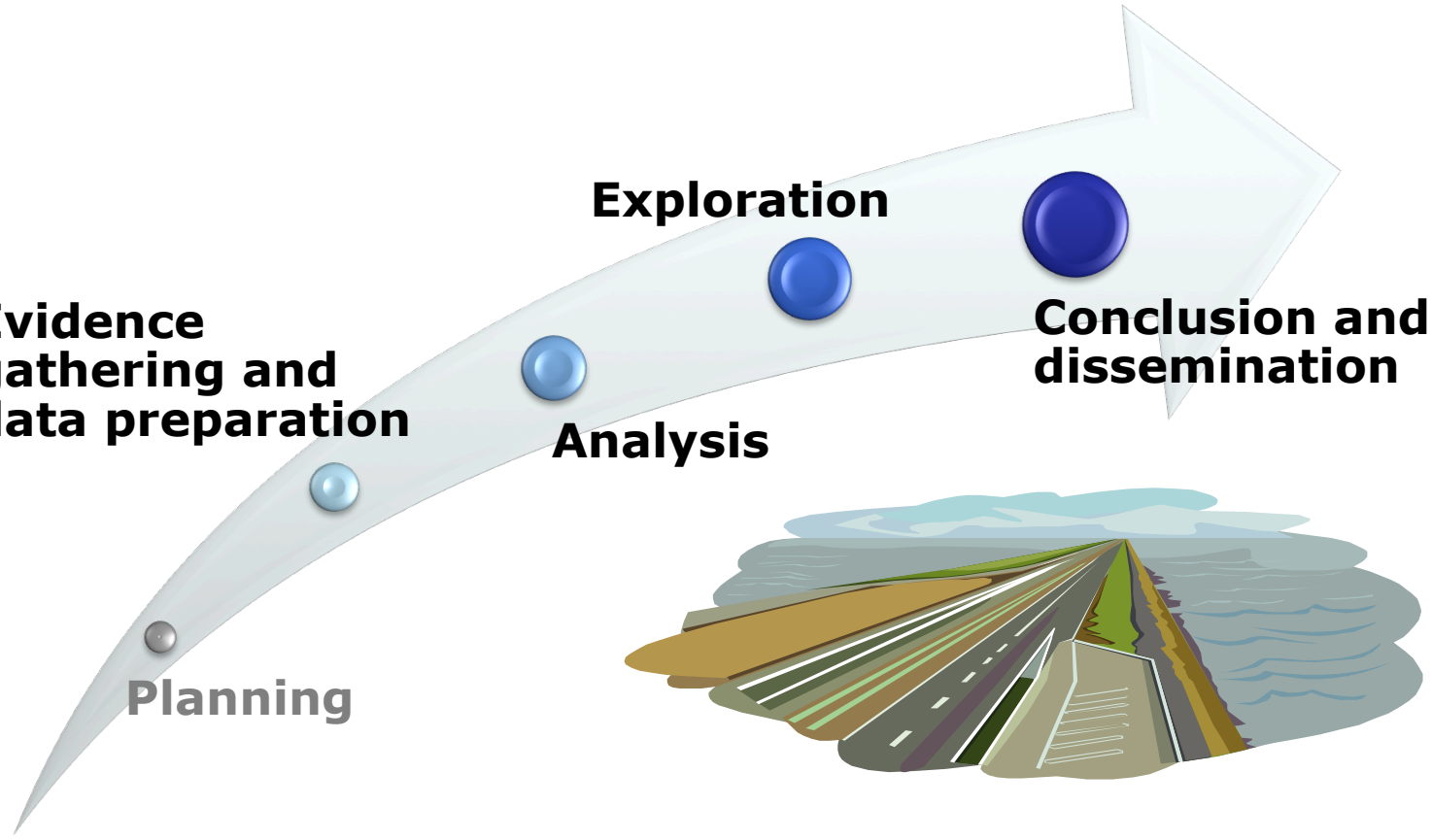
Planning the Natalizumab case study

PrOACT-URL	BRAT	Specifications
Problem	Define decision context	What is the benefit-risk balance of natalizumab following the occurrence of PML cases?
Objective	Identify benefit and risk outcomes	Benefits: Reduction in relapse rate, slowdown in disability progression. Risks: PML, reactivation of serious herpes viral infections, seizures, abortion or congenital abnormalities, transaminases elevation, infusion or injection site reactions, hypersensitivity reactions, flu-like reactions
Alternative	Define the decision context	Interferon beta-1a, glatiramer acetate, placebo. Which option to choose?
Consequence	Extract source data	*Build a data source data table (BRAT) or an effects table (PrOACT-URL)*
	Customise framework	*If required, repeat step 2 following in regards to available data*
Trade-off	Assess outcome importance	*Dealt with in stages 3 (Analysis) and 4 (Exploration)*
Uncertainty	Display & interpret key BR metrics	
Risk tolerance		
Linked decisions		

Value tree: Natalizumab case study



Recommendation Roadmap



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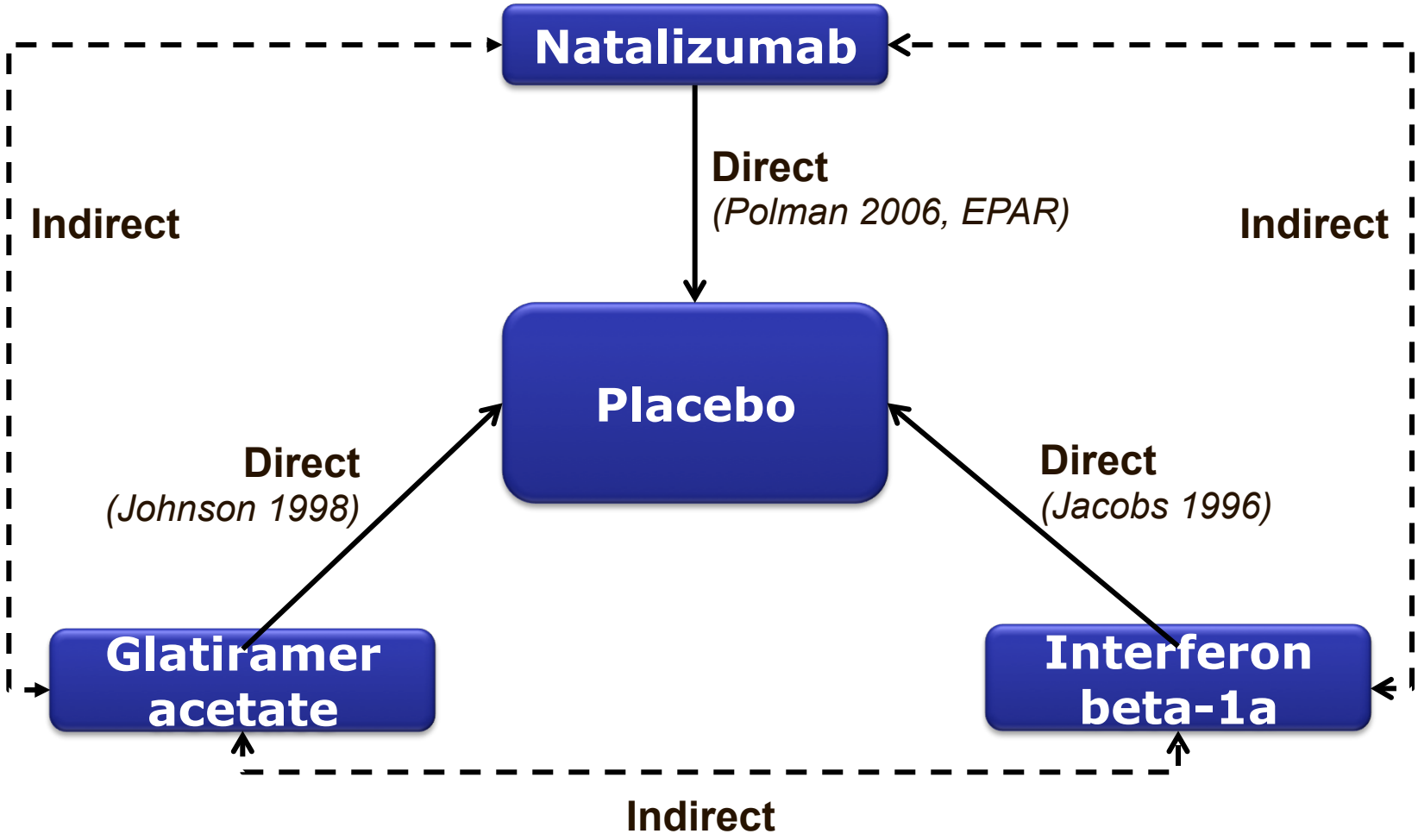
Evidence Gathering and Data Preparation Toolbox

- Useful methodologies include:
  - Indirect/Mixed Treatment Comparison (ITC/MTC)
  - Probabilistic Simulation Method (PSM)
- Preferred visualisation techniques include:
  - visualisation techniques such as structured and colour-coded tables, and network graphs to enhance the communication of data.

An example of MTC network in the natalizumab case study



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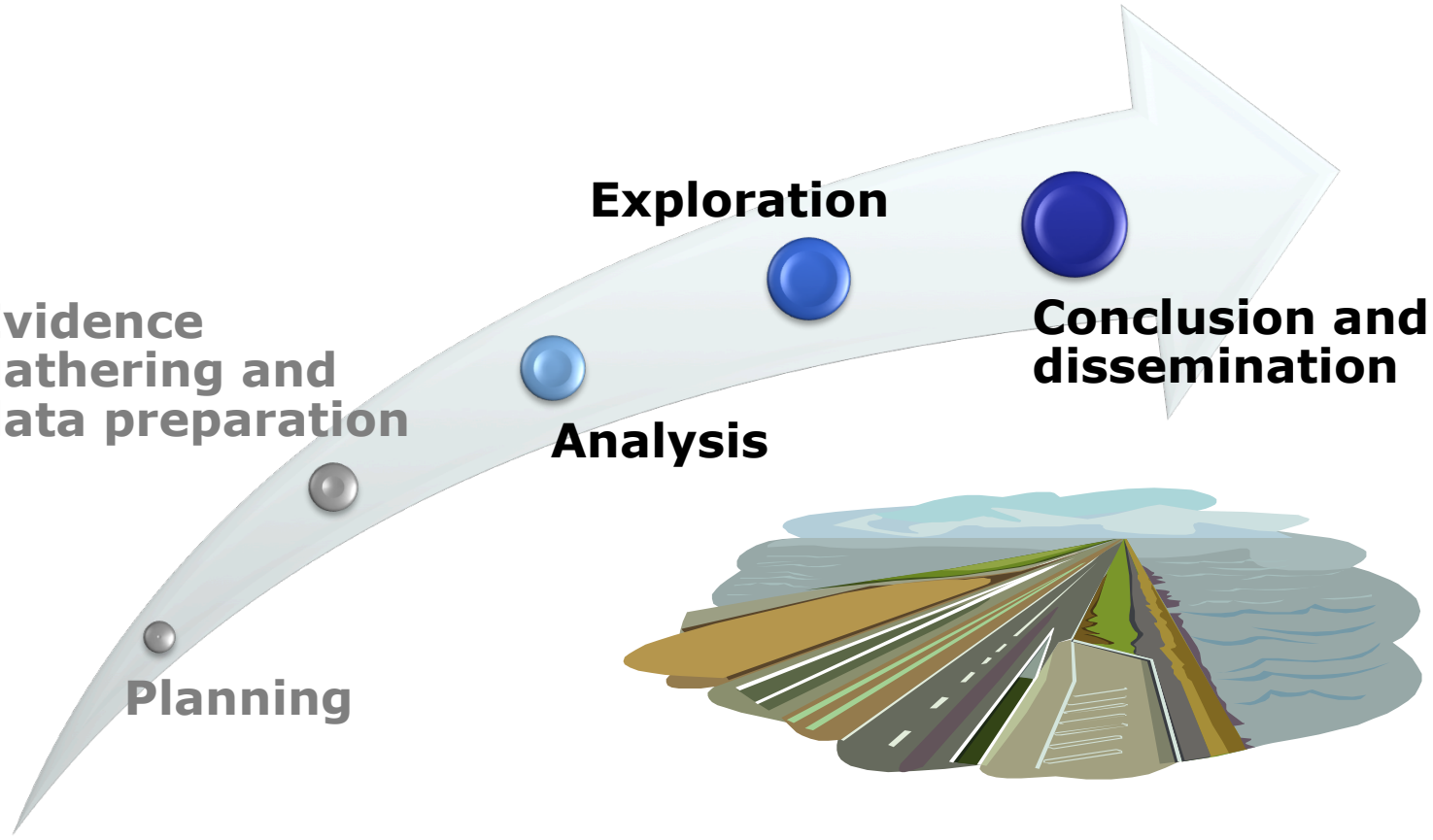
An example of colour-coded tables of data summary

		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	450	-170	(-, -)
		Disability Progression (weight 5.6%)	110	140	-30	(-, -)
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	11	-11	(-23, 0)
	Other	Infusion/Injection reactions (weight 2.8%)	236	312	-76	(-, -)
		Hypersensitivity reactions (weight 1.1%)	90	40	50	(20, 82)
		Flu-like reactions (weight 1.1%)	399	608	-209	(-320, -98)

Higher for Drug A

Higher for Comparator

Recommendation Roadmap



Analysis toolbox - methodologies

- Useful methodologies include
  - metric indices which provide numerical representations of benefits and risks e.g. Number Needed to Treat / Number Needed to Harm (NNT/NNH), Impact numbers
  - quantitative frameworks which model benefit-risk trade-off and balance benefits and risks e.g. Multi-Criteria Decision Analysis (MCDA), Stochastic Multi-criteria Acceptability Analysis (SMAA)
  - utility survey techniques which elicit stakeholders' preference information e.g. Discrete Choice Experiment (DCE)

Analysis toolbox – visualisations

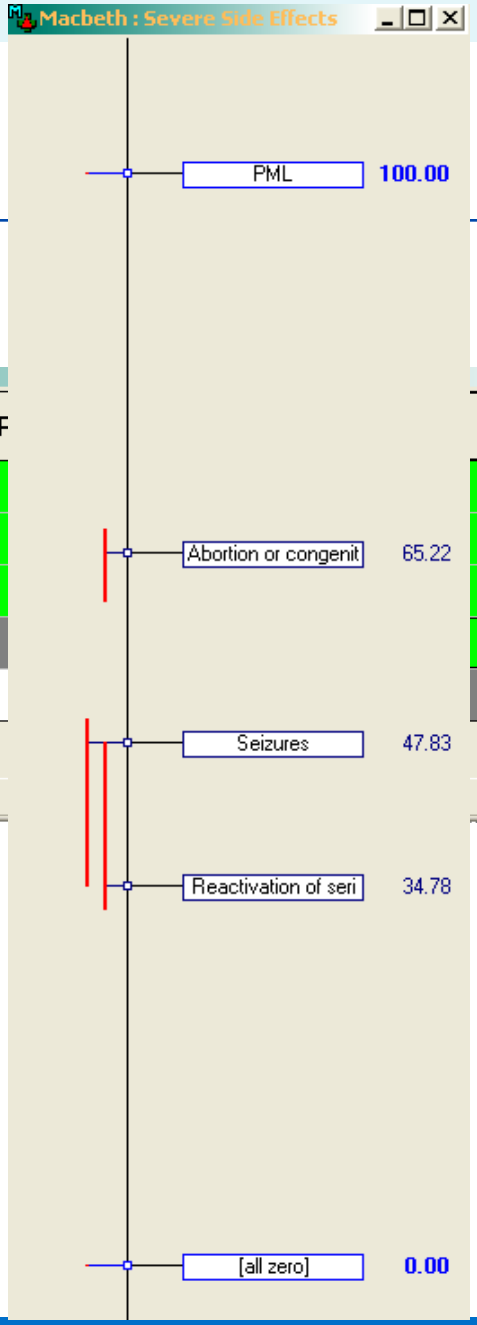
- Preferred visualisation techniques include:
  - visualisation techniques specific for eliciting value preferences e.g. tree diagram, method-specific visualisations such as MACBETH grid, Analytic Hierarchy Process (AHP) table, swing-weighting 'thermometer' scale, drop-down list
  - visualisations for presenting analysis results e.g. tables, forest/interval plots for descriptive analyses; 'Difference display' (MCDA) and stacked or grouped bar charts for quantitative analyses

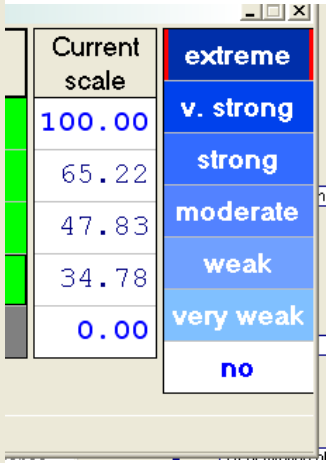
MACBETH grid and scale

Macbeth : Severe Side Effects

	PML	Abortion or congenit	Seizures	P
PML	no	extreme	extreme	
Abortion or congenit		no	strong	
Seizures			no	
Reactivation of seri				
[all zero]				

Consistent judgements

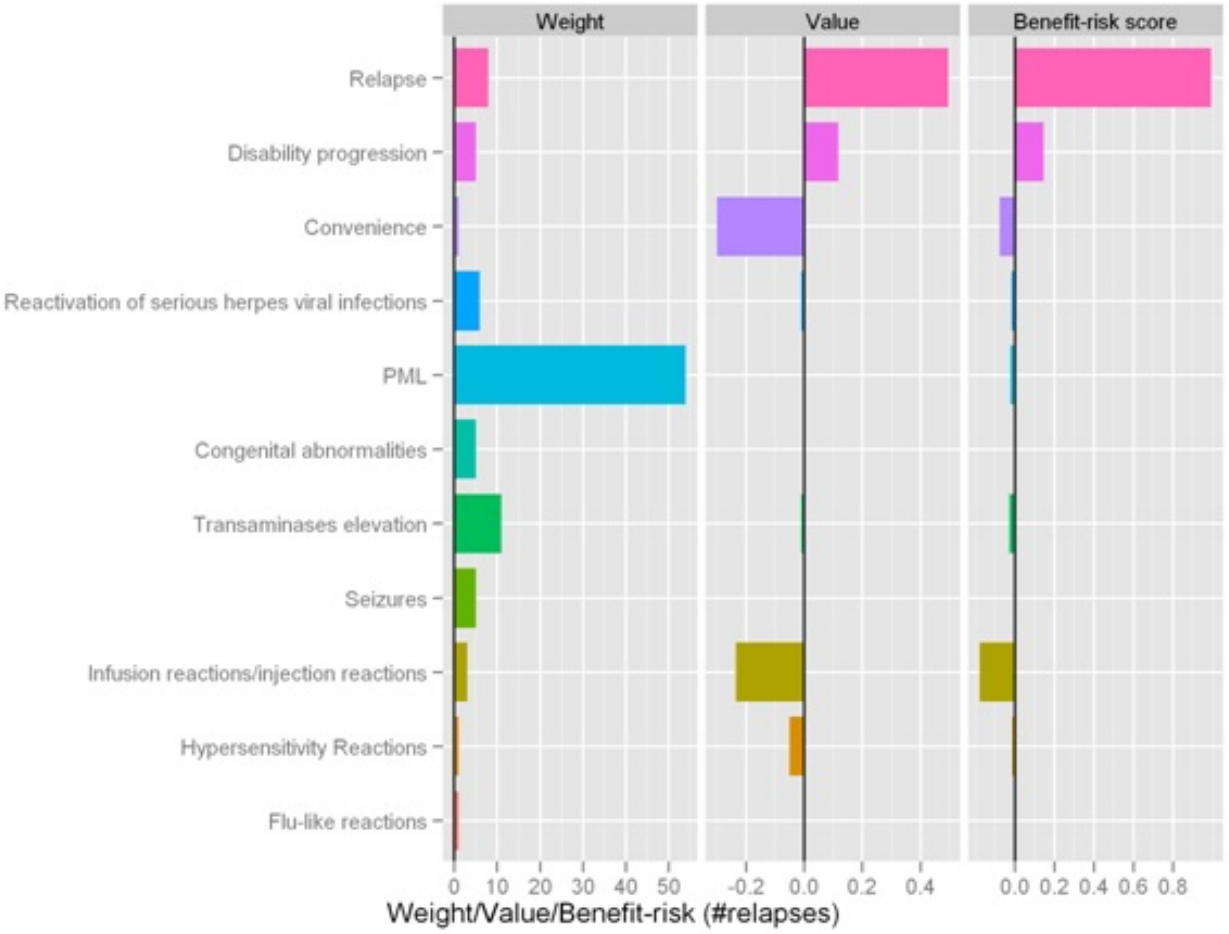




Fine tuning…

Natalizumab: MCDA weighted utilities analysis

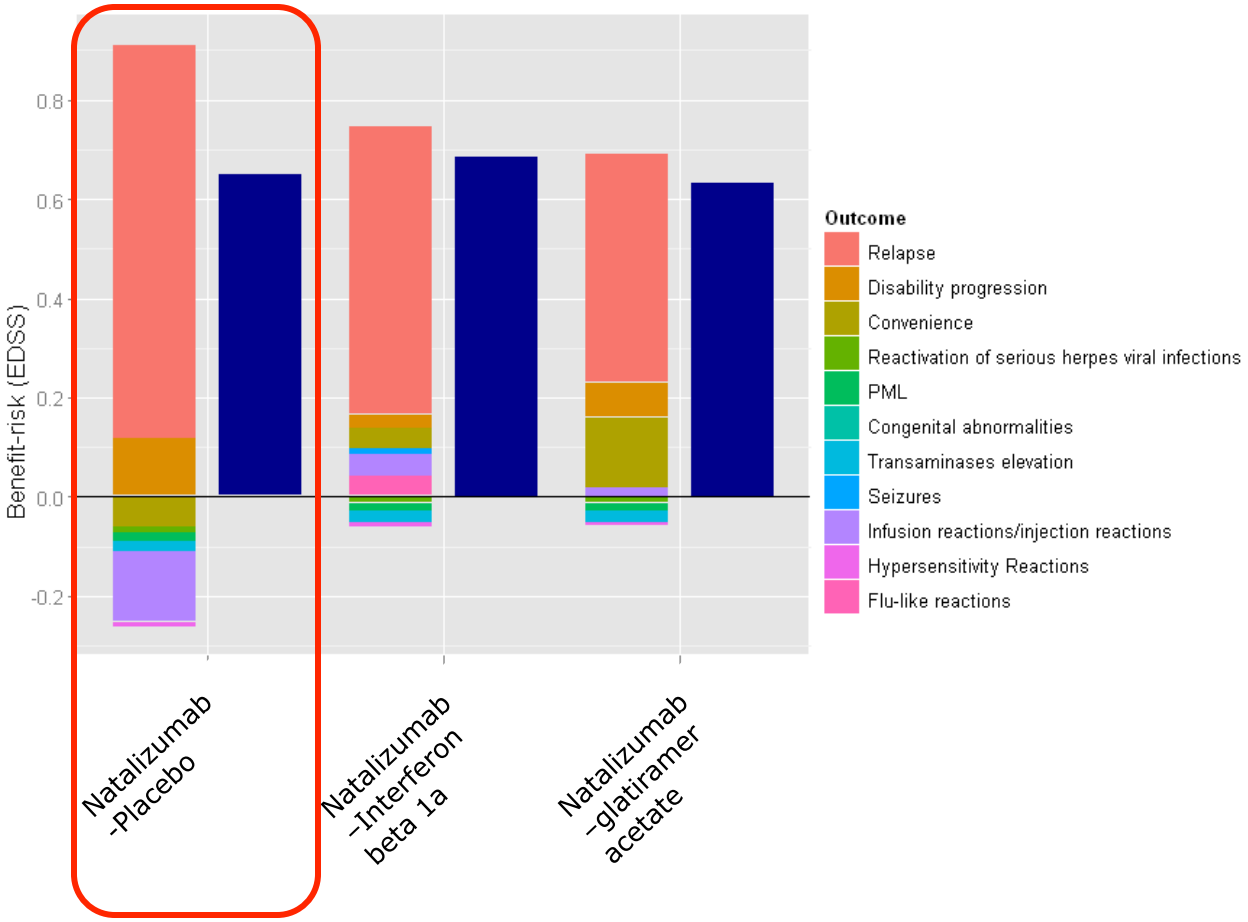
Contribution of each outcome for Natalizumab vs. placebo



- The Benefit-risk is the product of the weight and the value.
- Most of the Benefit-risk contribution is coming from prevention of relapses.
- Infusion site reactions are the worst risk

Natalizumab: Criteria contribution

Stacked bar chart for natalizumab vs. all the other treatments.



- Same information shown as a stacked bar chart.
- Positive incremental benefit-risk components above the x-axis and negative ones below.
- Total benefit-risk shown as the dark blue bar.

Natalizumab: Criteria contribution

Waterfall plot for Natalizumab vs. placebo

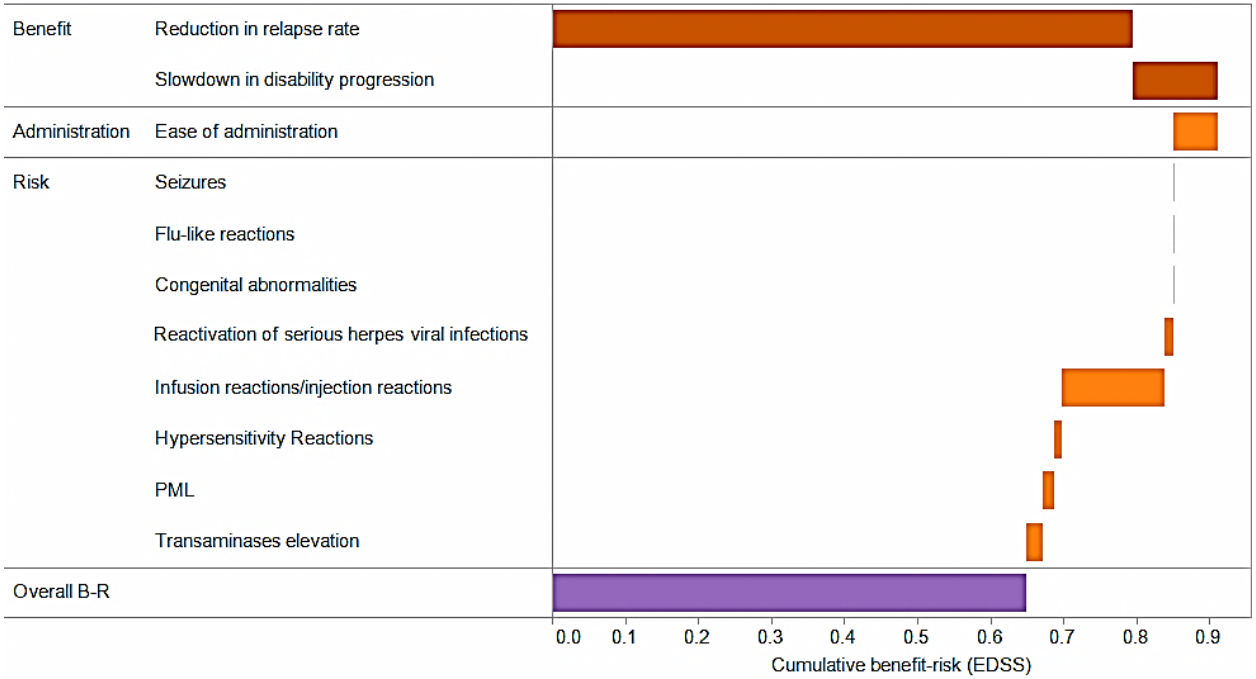
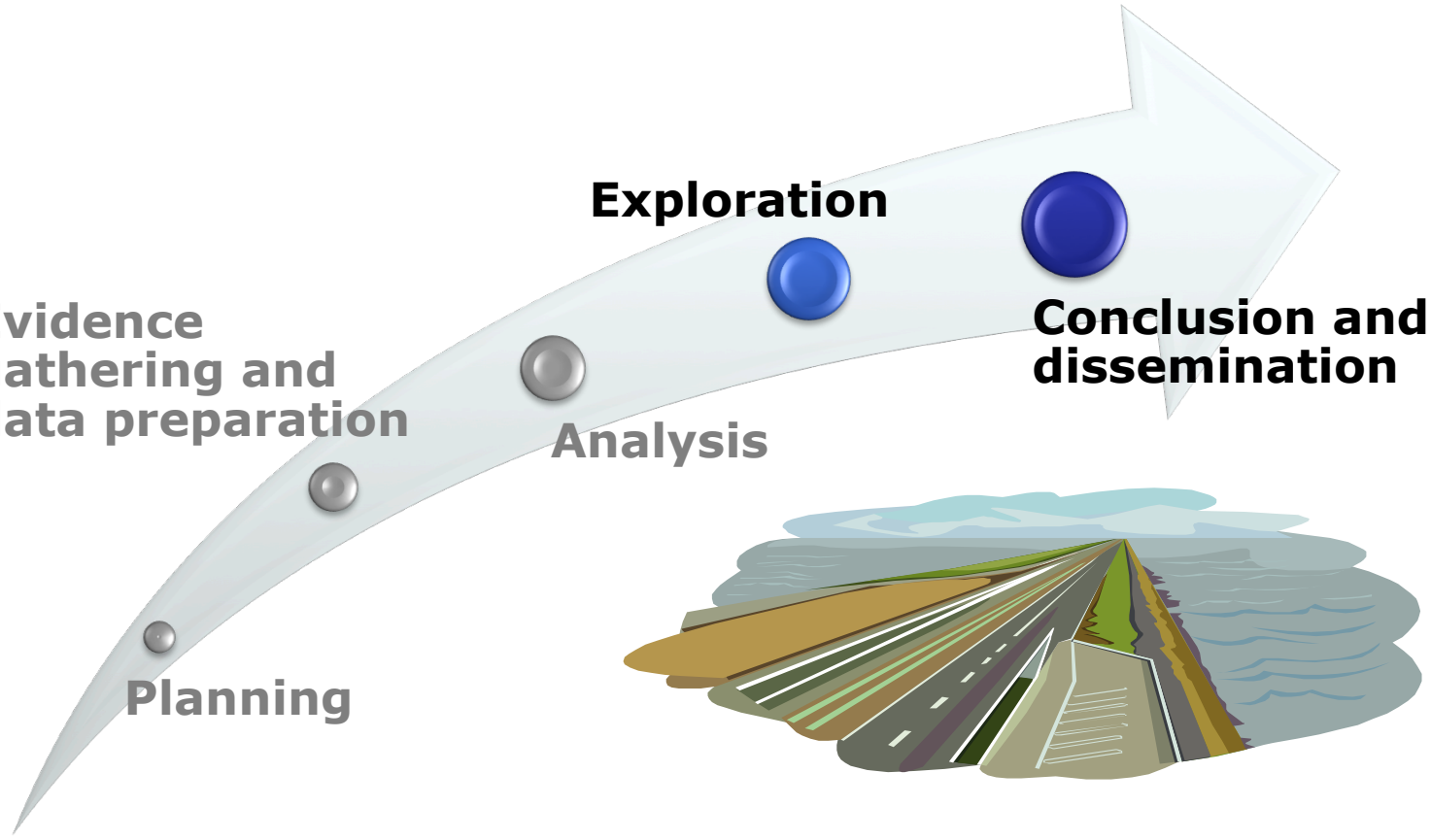


tableau SOFTWARE

http://public.tableausoftware.com/views/T_Waterfall/WaterfallRisk

- a horizontal bar chart, except that end of the previous bar determines the start of the next bar
- End of the last bar gives the overall benefit-risk.
- Brown= positive BR; Orange = negative BR; Purple = overall

Recommendation Roadmap

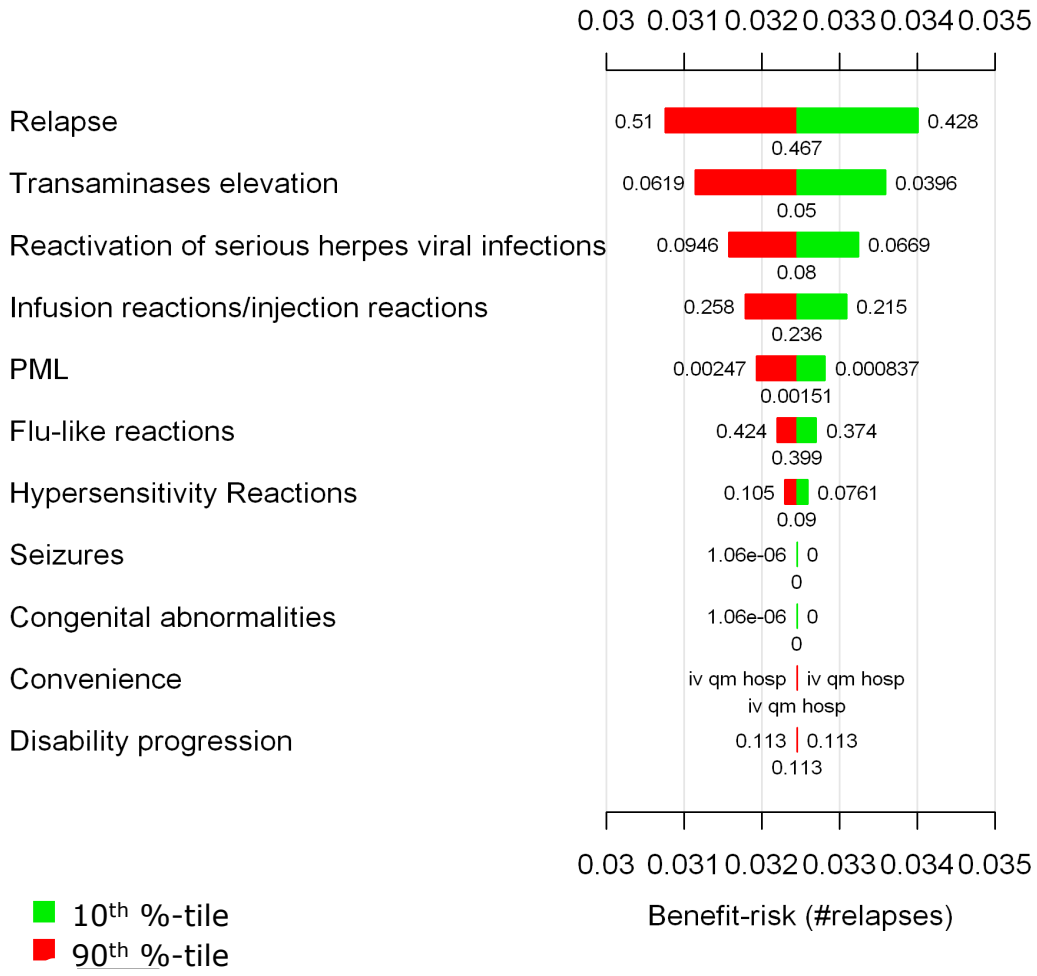


Exploration toolbox

- Useful methodologies include:
  - ITC/MTC, PSM, SMAA
  - Utility survey techniques e.g. DCE, AHP, Swing-weighting, MACBETH
- Preferred visualisation techniques include:
  - the box, distribution, scatter, and forest/interval plots; tornado diagram; and techniques that are interactive with the user.

Natalizumab: Uncertainty

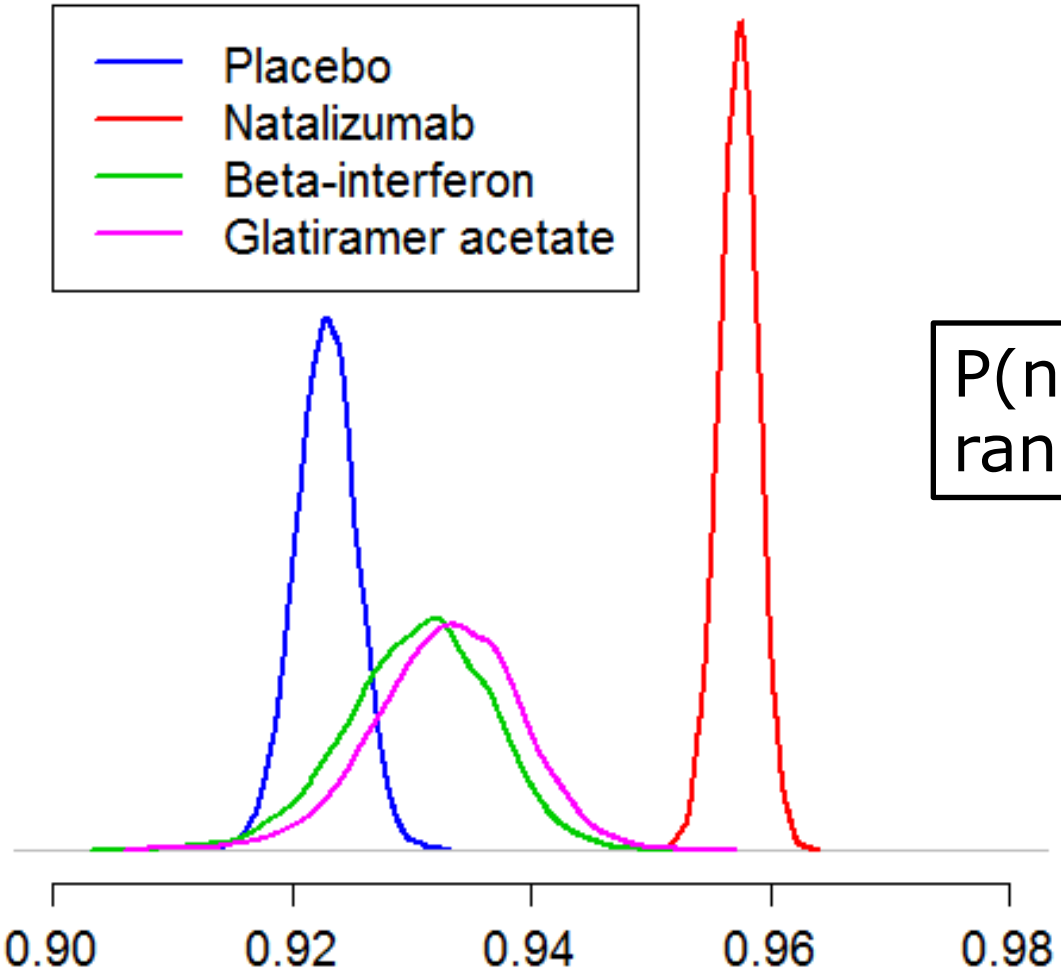
Tornado plot for Natalizumab vs. placebo



- Clinical parameters uncertain
- So benefit-risk balance is uncertain
- Perform sensitivity analysis

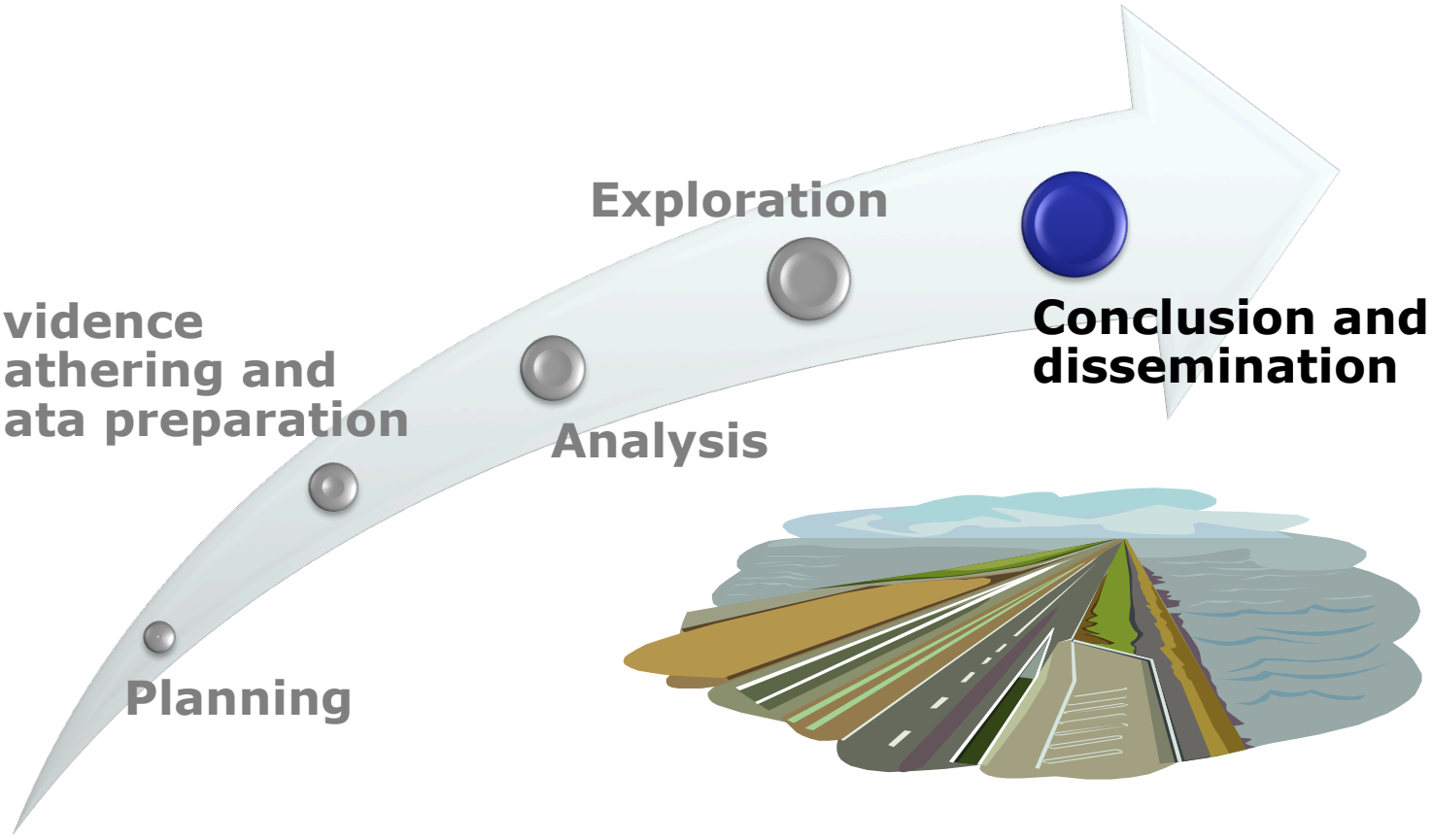
Natalizumab: Bayesian sensitivity analysis

Distribution of overall benefit-risk score



P(natalizumab ranked 1st) = 1

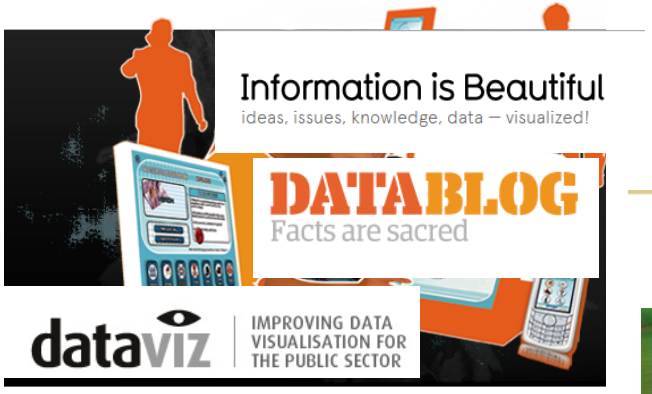
Recommendation Roadmap

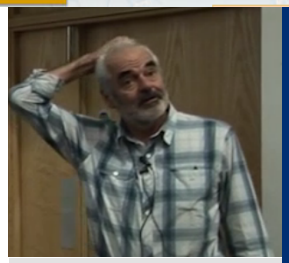


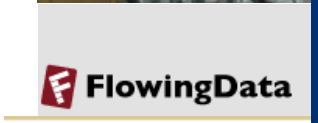
Stage 5: Conclusion and dissemination

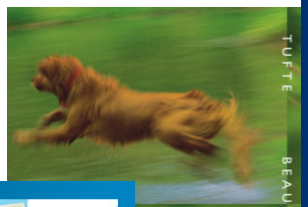
- The point at which a conclusion is reached
- The results and consensus from the BR assessment are communicated to a wider audience
- Explicitly states findings and conclusions that could influence future actions
- Emphasises a transparent audit trail of the whole assessment process i.e. brings everything together and sets the course of action
- Ensures the "big picture" overview is not lost

Other data visualisation initiatives









https://www.ctspedia.org

http://www.thedrugsbox.co.uk

http://www.cirsci.org

http://www.gapminder.org

http://understandinguncertainty.org

http://www.improving-visualisation.org

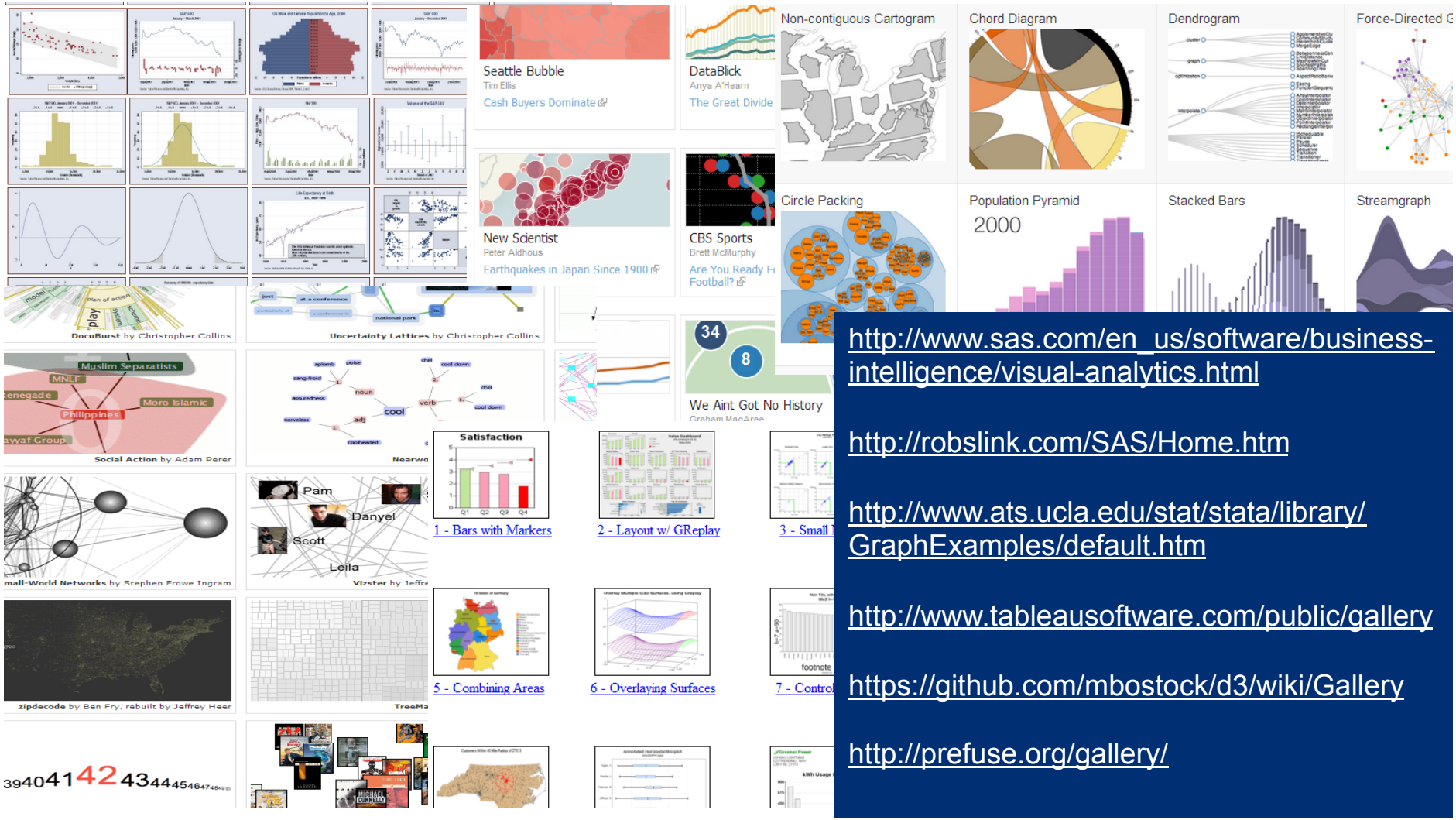
http://www.informationisbeautiful.net

http://flowingdata.com

http://www.perceptualedge.com

http://www.guardian.co.uk/news/datablog

Fishing for ideas



http://www.sas.com/en_us/software/business-intelligence/visual-analytics.html

http://robslink.com/SAS/Home.htm

http://www.ats.ucla.edu/stat/stata/library/GraphExamples/default.htm

http://www.tableausoftware.com/public/gallery

https://github.com/mbostock/d3/wiki/Gallery

http://prefuse.org/gallery/

Remarks

- Formally structured benefit-risk assessment can aid with transparency and communication of benefits and risks
- These methodologies do not make decisions themselves. They support decision-making and are not intended to replace medical expertise.
- Stakeholders such as patients and public involvement may add value and would lead to more clinically relevant decisions.

Benefits and risks of quantitative B-R modelling and visual representation

Benefits

- Puts benefits and risks on same page
- Gives a framework to include patients' views
- Transparency facilitates discussion
- Visual representations assist cognition & influence perception
- It's fun!

Risks

- Trade-off between being too simplistic or just incomprehensible
- Can be seen as a 'black box'
- Pharma want to know what regulators want
- Visual representations influence perception

RESOURCES

Acknowledgements

- 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.
- The PROTECT project has received support from the Innovative Medicine Initiative Joint Undertaking (www.imi.europa.eu) under Grant Agreement n° 115004, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.

IMI- PROTECT Work Package 5
Benefit-risk integration and representation

Objectives:

- To assess and test methodologies for the benefit-risk assessment of medicines
- To develop tools for the visualisation of benefits and risks of medicinal products

➔ Individual and population-based decision making

➔ Perspectives of patients, healthcare prescribers, regulatory agencies and drug manufacturers

➔ From post-approval through lifecycle of products

Work Package 5 of PROTECT (membership)

Public	Private
Imperial College (co-leader)	Merck KGaA (co-leader)
EMA	AMGEN
DHMA	AstraZeneca
MHRA	Bayer
Mario Negri Institute	GSK
GPRD	Lilly
La-SER	Novartis
IAPO	Novo Nordisk
	Pfizer
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	Sanofi-Aventis
	Takeda

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Results

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- Collaborations
- Training Opportunities
- Pregnancy Study
- Adverse Drug Reactions Database NEW
- Drug Consumption Databases in Europe NEW

Key achievements of PROTECT

Framework for pharmacoepidemiology studies
- Presentations (24)
- Publications (5)
- Reports and Databases (1)

Methods for Signal Detection
- Presentations (14)
- Publications (4)
- Reports and Databases (1)

New Methods for data collection from consumers
- Presentations (3)
- Publications
- Reports and Databases

Benefit- Risk integration and representation
- Presentations (14)
- Publications
- Reports and Databases (14)

Replication studies
- Presentations (1)
- Publications
- Reports and Databases

Training and Communication
- Presentations
- Publications
- Reports and Databases (1)

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REVIEW

Balancing benefit and risk of medicines: a systematic review and classification of available methodologies†

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http://onlinelibrary.wiley.com/doi/10.1002/pds.3636/pdf

ABSTRACT

Background The need for formal and structured approaches for benefit–risk assessment of medicines is increasing, as is the complexity of the scientific questions addressed before making decisions on the benefit–risk balance of medicines. We systematically collected, appraised and classified available benefit–risk methodologies to facilitate and inform their future use.

Methods A systematic review of publications identified benefit–risk assessment methodologies. Methodologies were appraised on their fundamental principles, features, graphical representations, assessability and accessibility. We created a taxonomy of methodologies to facilitate understanding and choice.

Results We identified 49 methodologies, critically appraised and classified them into four categories: frameworks, metrics, estimation techniques and utility survey techniques. Eight frameworks describe qualitative steps in benefit–risk assessment and eight quantify benefit–risk balance. Nine metric indices include threshold indices to measure either benefit or risk; health indices measure quality-of-life over time; and trade-off indices integrate benefits and risks. Six estimation techniques support benefit–risk modelling and evidence synthesis. Four utility survey techniques elicit robust value preferences from relevant stakeholders to the benefit–risk decisions.

Conclusions Methodologies to help benefit–risk assessments of medicines are diverse and each is associated with different limitations and strengths. There is not a 'one-size-fits-all' method, and a combination of methods may be needed for each benefit–risk assessment. The taxonomy introduced herein may guide choice of adequate methodologies. Finally, we recommend 13 of 49 methodologies for further appraisal for use in the real-life benefit–risk assessment of medicines.

KEY WORDS—review; benefit–risk; decision-making; medicines; quantitative; qualitative; framework; pharmacoepidemiology

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References

- Principles:

  - Cleveland WS, Mcgill R. Graphical Perception - Theory, Experimentation, and Application to the Development of Graphical Methods. Journal of the American Statistical Association 1984;79(387): 531-54.
  - Cleveland WS, McGill R. Graphical perception and graphical methods for analyzing scientific data. Science 1985 Aug;229(4716):828-33.
  - Carswell CM. Choosing specifiers: An evaluation of the basic tasks model of graphical perception. Human Factors 1992;34(5):535-54.
  - Lipkus IM, Hollands JG. The visual communication of risk. Journal of the National Cancer Institute Monographs 1999;25:149-63.
  - Tufte ER. The Visual Display of Quantitative Information. 2 ed. Cheshire, CT: Graphics Press; 2001.
  - Wickens CD, Lee J, Liu YD, Gordon-Becker S. An introduction to human factors engineering. 2 ed. Upper Saddle River, NJ: Pearson Prentice-Hall; 2004.
  - Kosslyn SM. Graph design for the eye and mind. Oxford University Press; 2006.

References

- Visual design guides:
  - Tufte ER. Visual explanations: images and quantities, evidence and narrative. Graphics Press; 1998.
  - Few S. Information Dashboard Design: The Effective Visual Communication of Data. O'Reilly Media, Incorporated; 2006.
  - Few S. Now You See It: Simple Visualization Techniques for Quantitative Analysis. Analytics Press; 2009.
  - Juice Analytics. A Guide to Creating Dashboards People Love to Use. White paper. http://www.juiceanalytics.com/.
  - Tableau Software Inc. Tableau Visual Guidebook. http://mkt.tableausoftware.com/files/VisualGuidebookTabRead.pdf
- Colour choices:
  - The Color Brewer website (http://colorbrewer2.org)
  - J*FLY website (http://jfly.iam.u-tokyo.ac.jp/color)

References

- Reviews:
  - Ancker JS, Senathirajah Y, Kukafka R, Starren JB. Design features of graphs in health risk communication: a systematic review. J Am Med Inform Assoc 2006;13(6):608-18.
  - Mt-Isa S. et al. Review of visualisation methods for the representation of benefit-risk assessment of medication: Stage 1 of 2. In the IMI-PROTECT Benefit-Risk Assessment and Representation series. http://www.imi-protect.eu/documents/ShahruletalReviewofvisualisationmethodsfortherepresentationofBRassessmentofmedicationStage1F.pdf. London: IMI-PROTECT; 2013 (15/02/2013). Report No.: 2:i. Accessed on 10/06/2013.
  - Mt-Isa S. et al. Review of visualisation methods for the representation of benefit-risk assessment of medication: Stage 2 of 2. In the IMI-PROTECT Benefit-Risk Assessment and Representation series. http://www.imi-protect.eu/documents/ShahruletalReviewofvisualisationmethodsfortherepresentationofBRassessmentofmedicationStage2A.pdf. London: IMI-PROTECT; 2013 (15/02/2013). Report No.: 2:ii. Accessed on 10/06/2013.