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Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

Why and how do we do benefit-risk assessment in drug regulation: lessons from IMI-PROTECT

EFSPI/PSI European Statistical Meeting – Structured Benefit-Risk Assessment
17th September 2013
London

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Evidence Based Medicine

"EBM is the conscientious explicit, and judicious use of current best evidence in making decisions about the care of individual patients" taking into account "individual patients predicaments, rights and preferences using best evidence from clinically relevant research."

Sackett et al, 1996

The IMI-PROTECT

- PROTECT[1] (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium)

- "Improving and strengthening the monitoring of the benefit/risk of medicines marketed in the EU" including graphical representation of risk-benefit led by EMA with 31 public and private partners, 2009-2014 (www.imi-protect.eu)

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

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

Objectives:

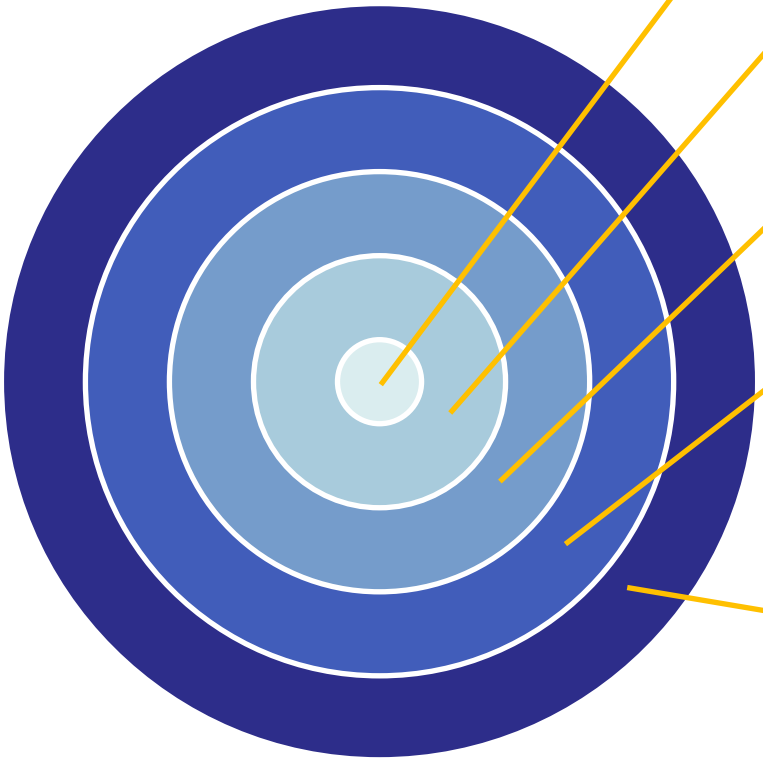
- To assess and test methodologies for the benefit-risk assessment of medicines
- To develop tools for the visualisation of benefits and risks of medicinal products

➔ Individual and population-based decision making

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

➔ From post-approval through lifecycle of products

Decision makers – who are they?



Patients

- Make decisions for themselves

Healthcare providers

- Make decisions based on prescribing lists

NICE

- Makes decisions on cost-effectiveness

EMA/MHRA etc.

- 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

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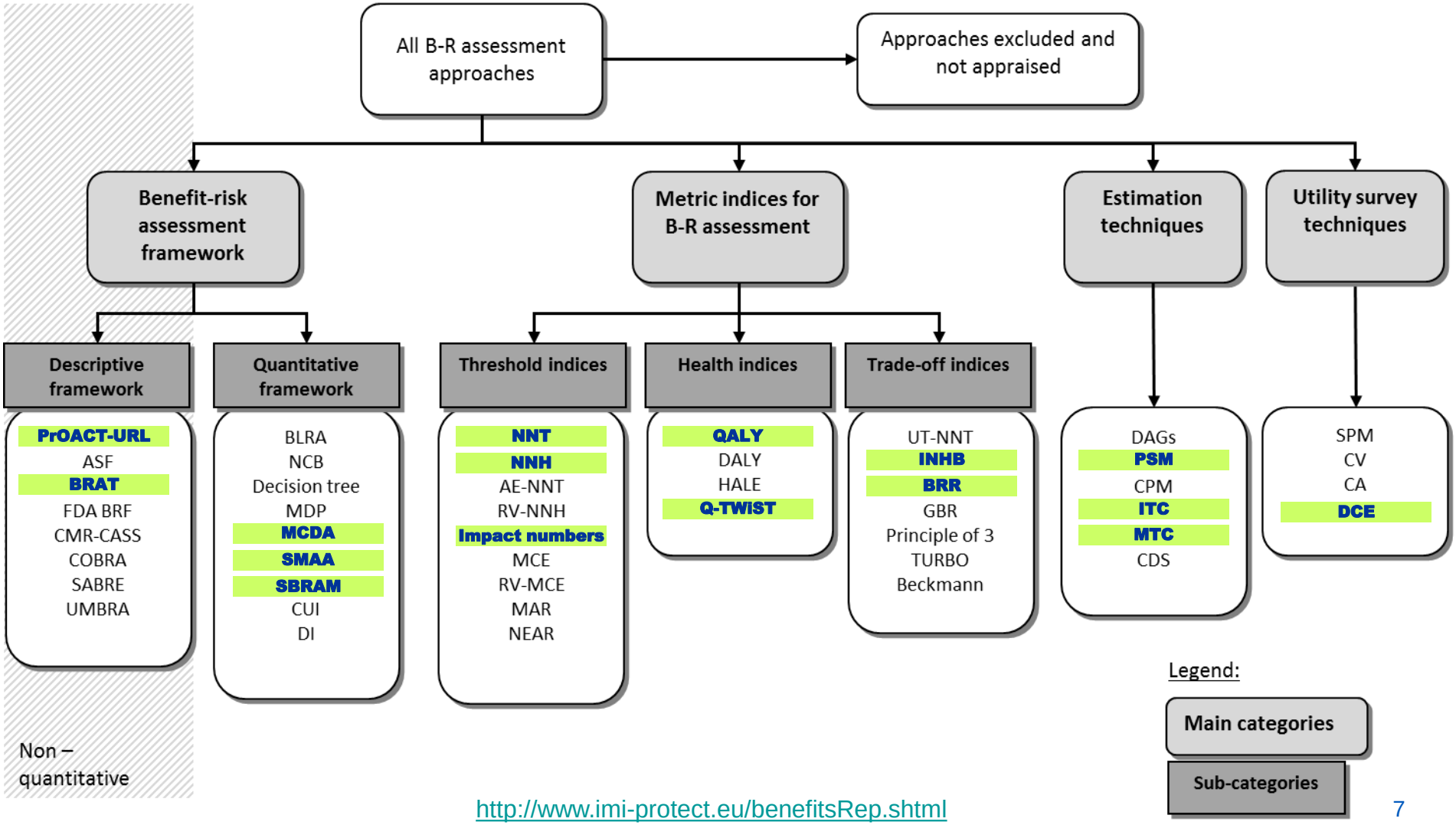
Challenges in medical decision-making

- Should we formalise decision-making at all?
- Which quantitative approach(es) to use?
- Whose value preferences take priority – regulators, pharma, physicians or patients?
- How do we find these preferences – simple elicitation, decision conferencing, discrete choice experiments….?
- Do we need stakeholders' preference a priori, or should we provide tools to allow individual decision-makers to explore their own preferences and the consequent decisions?
- How do we communicate benefits and risks?

Methodologies available (and tested)



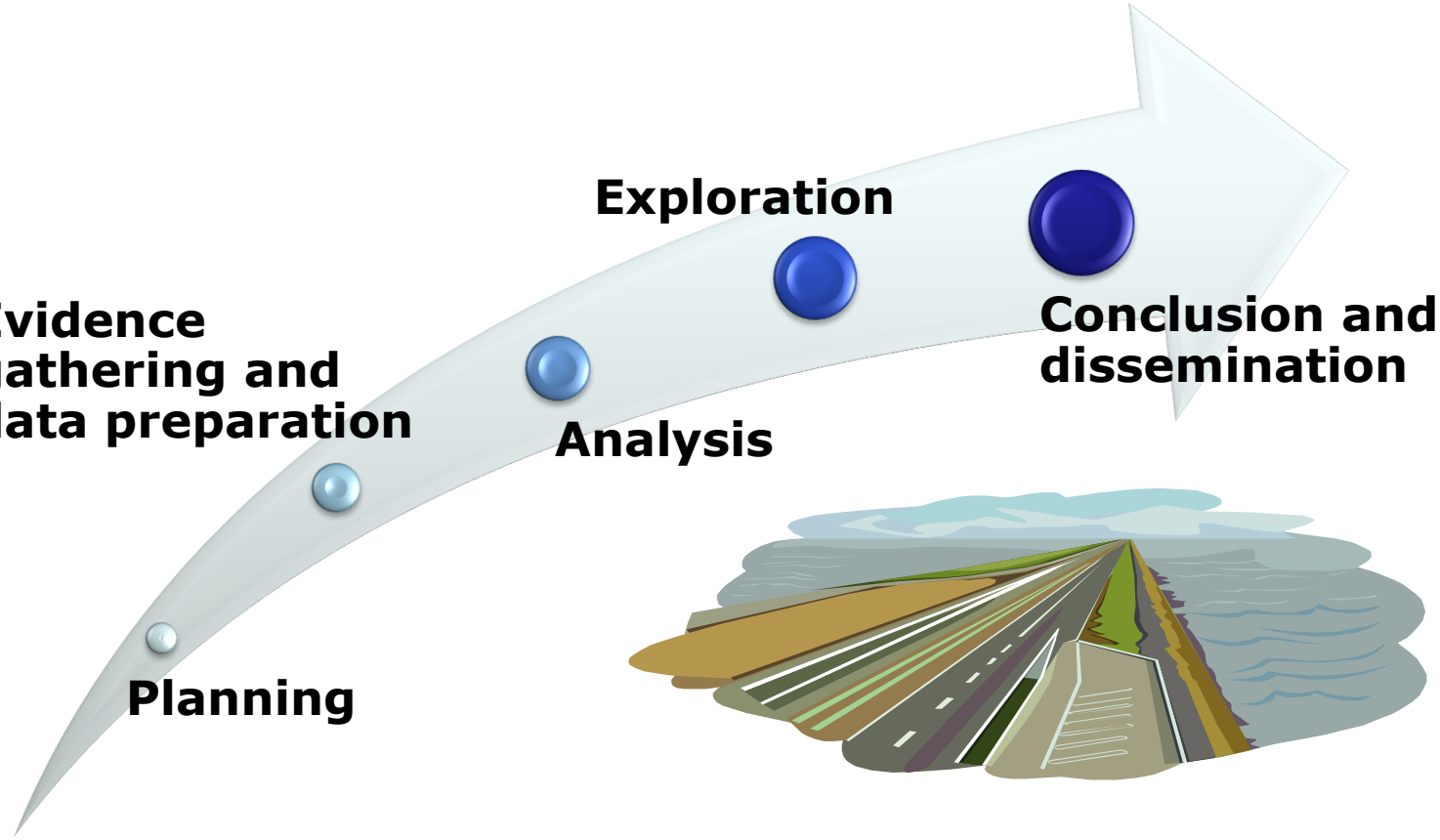
http://www.imi-protect.eu/benefitsRep.shtml

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."

Recommendation Roadmap



Stage 1: Planning

- encourages stakeholders to focus on critical issues related to BR assessment
- encourages sufficient thinking and thorough discussions between stakeholders to clearly define the purpose and context of the BR assessment
- ensures clear detailed summary documentation of discussions and results
- allows future analyses and updates to utilise the same foundations

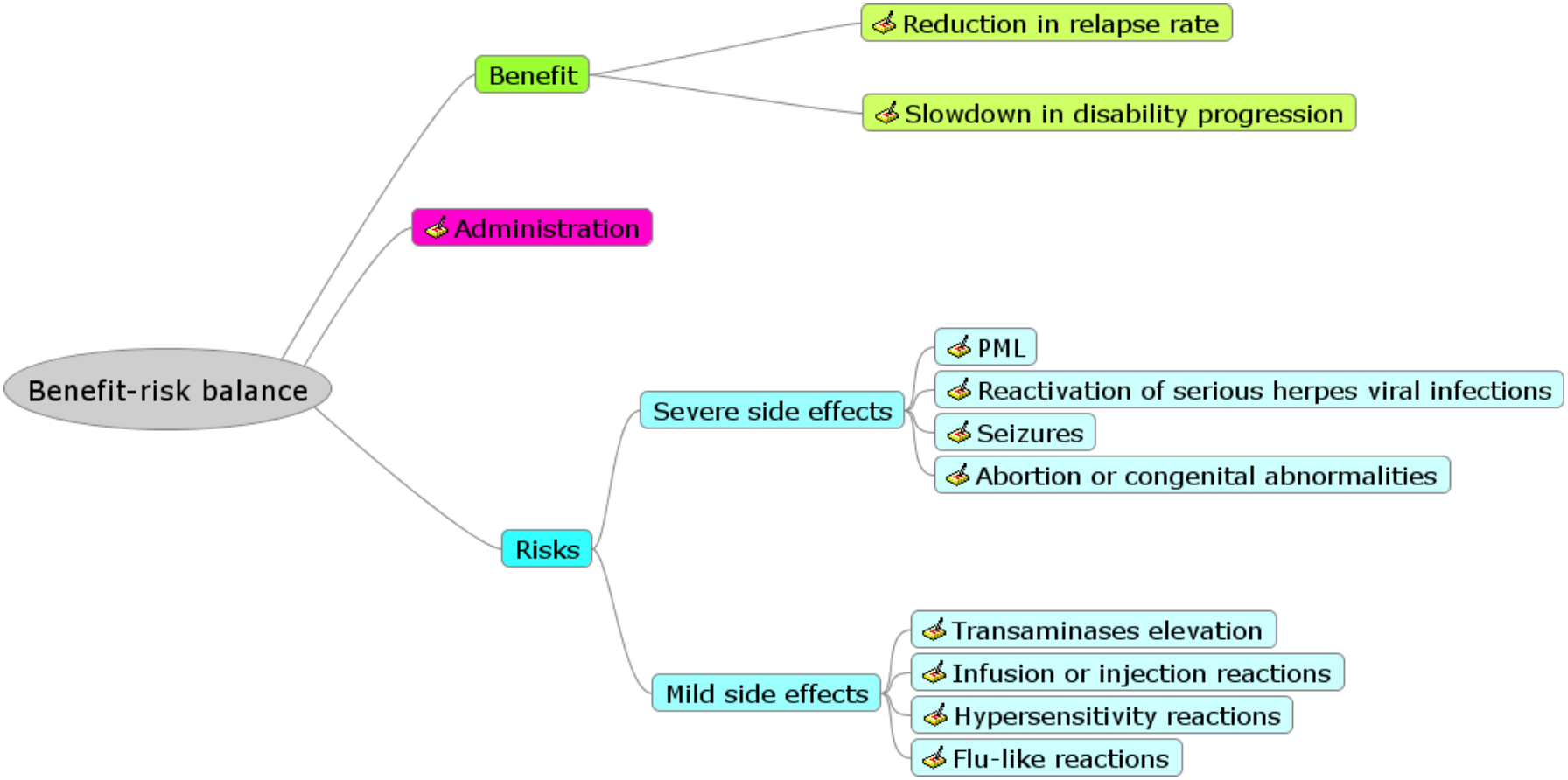
Planning Toolbox

PrOACT-URL	BRAT
Problem	Define decision context
Objective	Identify benefit and risk outcomes
Alternative	Define the decision context
Consequence	Extract source data
	Customise framework
Trade-off	Assess outcome importance
Uncertainty	Display & interpret key BR metrics
Risk tolerance	
Linked decisions	

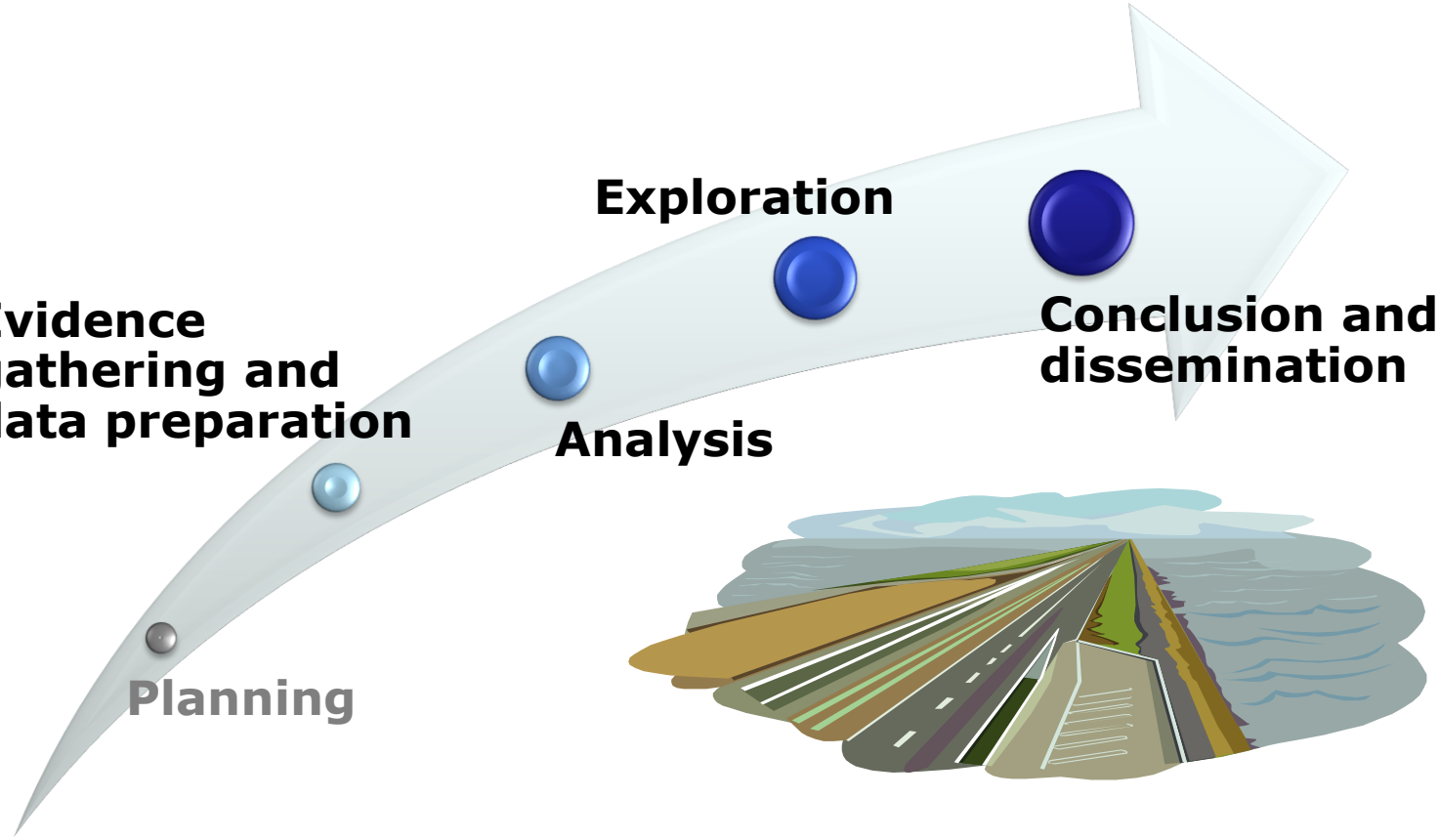
Useful methodologies include:

- non-quantitative / descriptive frameworks to organize data
- tree diagrams and structured tables providing useful means of visualisation

An example of (value) tree diagram from natalizumab case study



Recommendation Roadmap



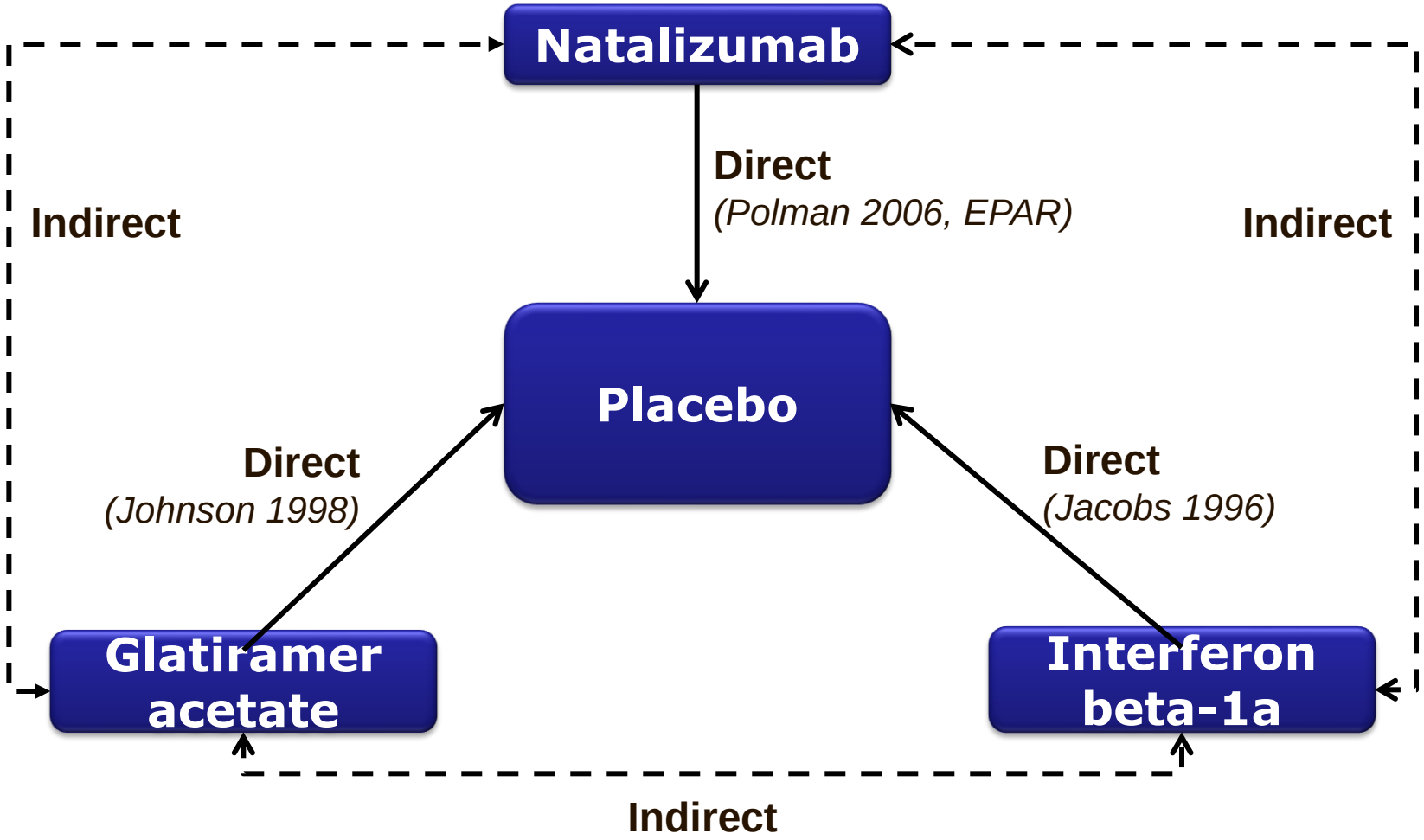
Stage 2: Evidence gathering and data preparation

- Identifies and extracts evidence relevant to the BR assessment in relation to the set criteria
- Determines what data to be collected from anticipated type of BR analysis
- Aggregating multiple sources of evidence, may require the use of estimation techniques
- Encourages systematic handling of missing data
- Requires engagement of clinical, statistical, epidemiological and database expertise

Evidence Gathering and Data Preparation Toolbox

- Useful methodologies include:
  - Indirect/Mixed Treatment Comparison (ITC/MTC)
  - Probabilistic Simulation Method (PSM)
  - 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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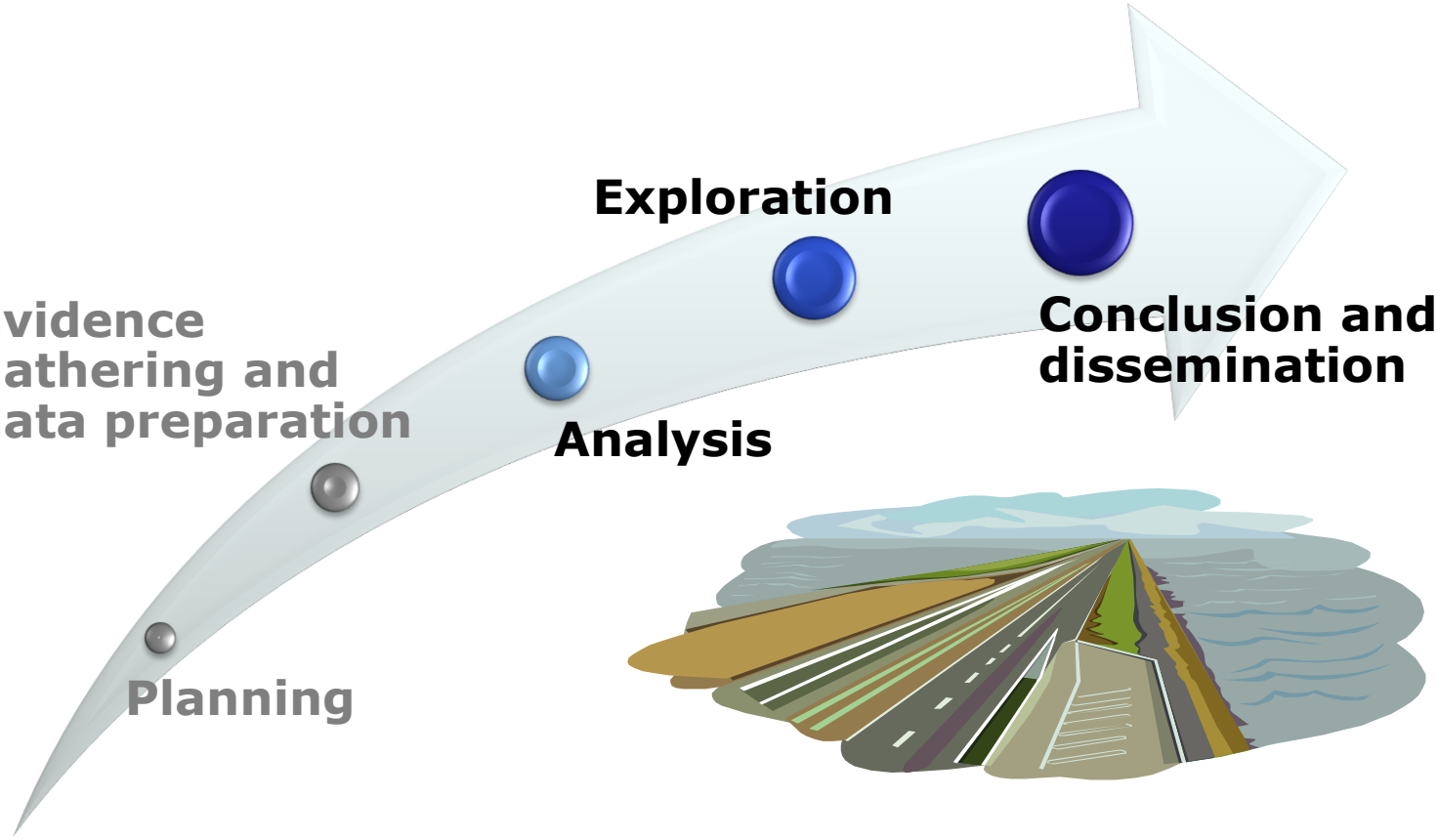
An example of colour-coded tables of data summary

		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



Stage 3: Analysis

- Evaluates data collected at previous stage in a BR assessment
- Quantifies the magnitudes of benefits and risks
- Weighs or integrates quantitative measures of the BR balance depending on the type of analysis

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

- Visualisations recommended for the analysis stage 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

Examples on analysis

Natalizumab and telithromycin presentations later

Recommendation Roadmap

Planning

Evidence gathering and data preparation

Analysis

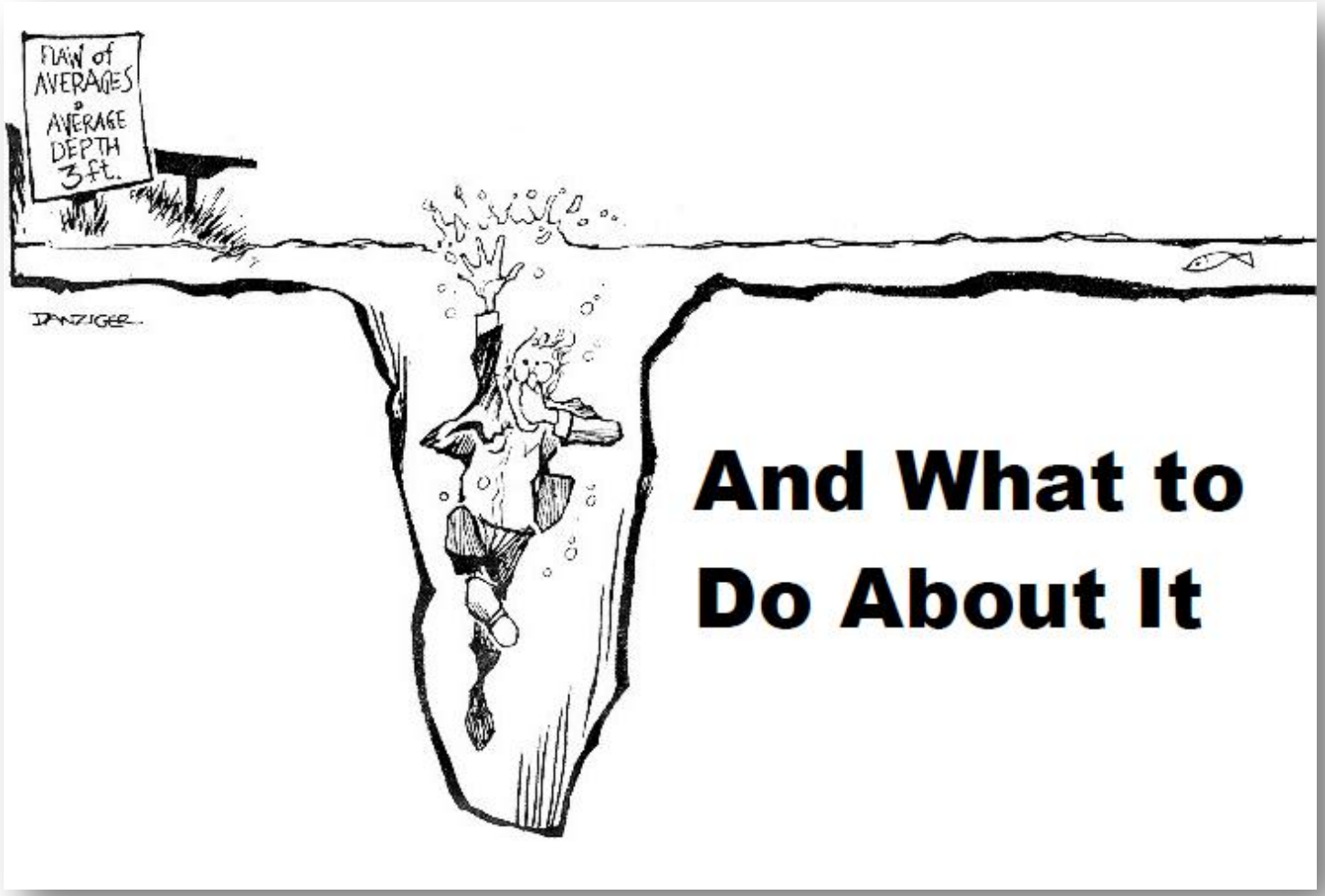
Exploration

Conclusion and dissemination

Stage 4: Exploration

- Assesses the robustness and sensitivity of the main results to various assumptions and sources of uncertainties
- Assesses further consequences of a decision
- Considers any impact or added value to the RMPs
- Requires both statistical and clinical input

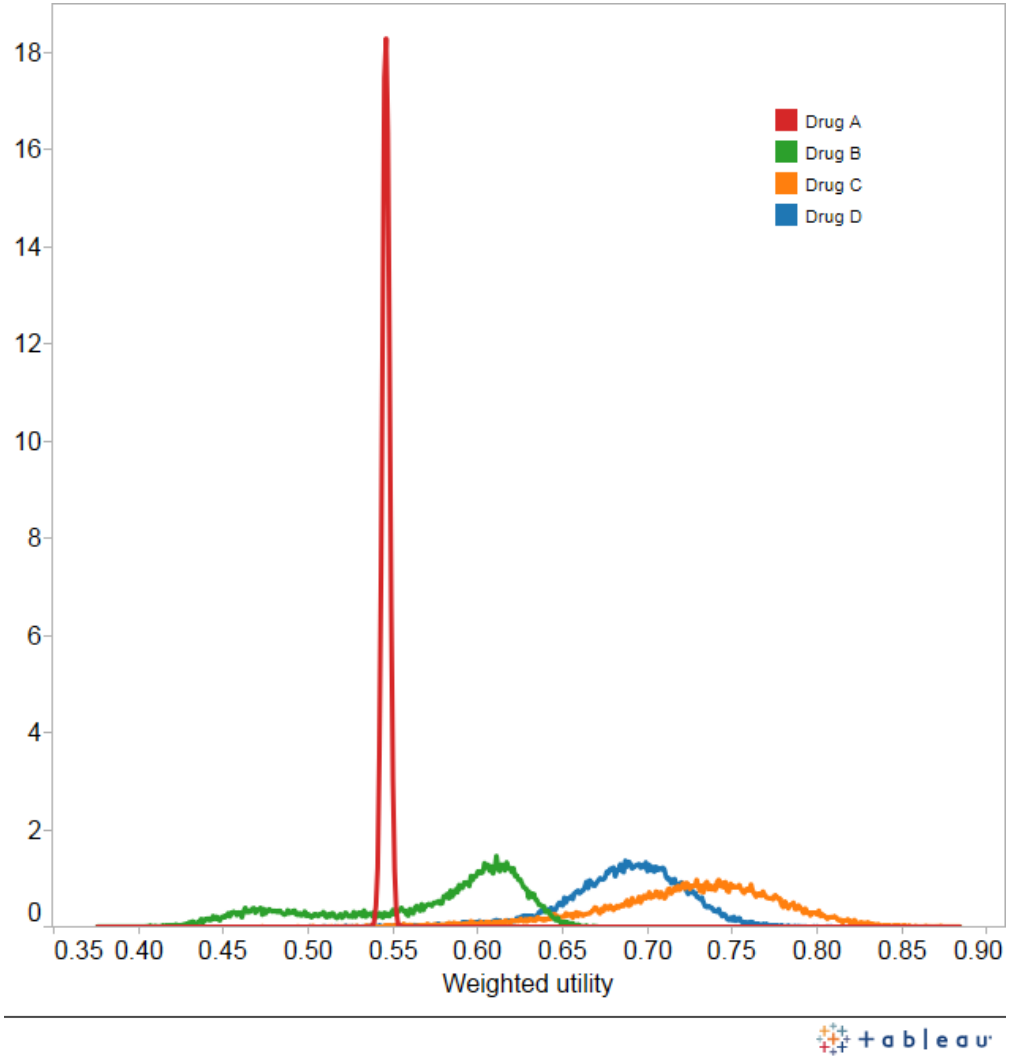
The flaw of averages



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.

An example of (interactive) distribution plot on uncertainty in the rimonabant case study

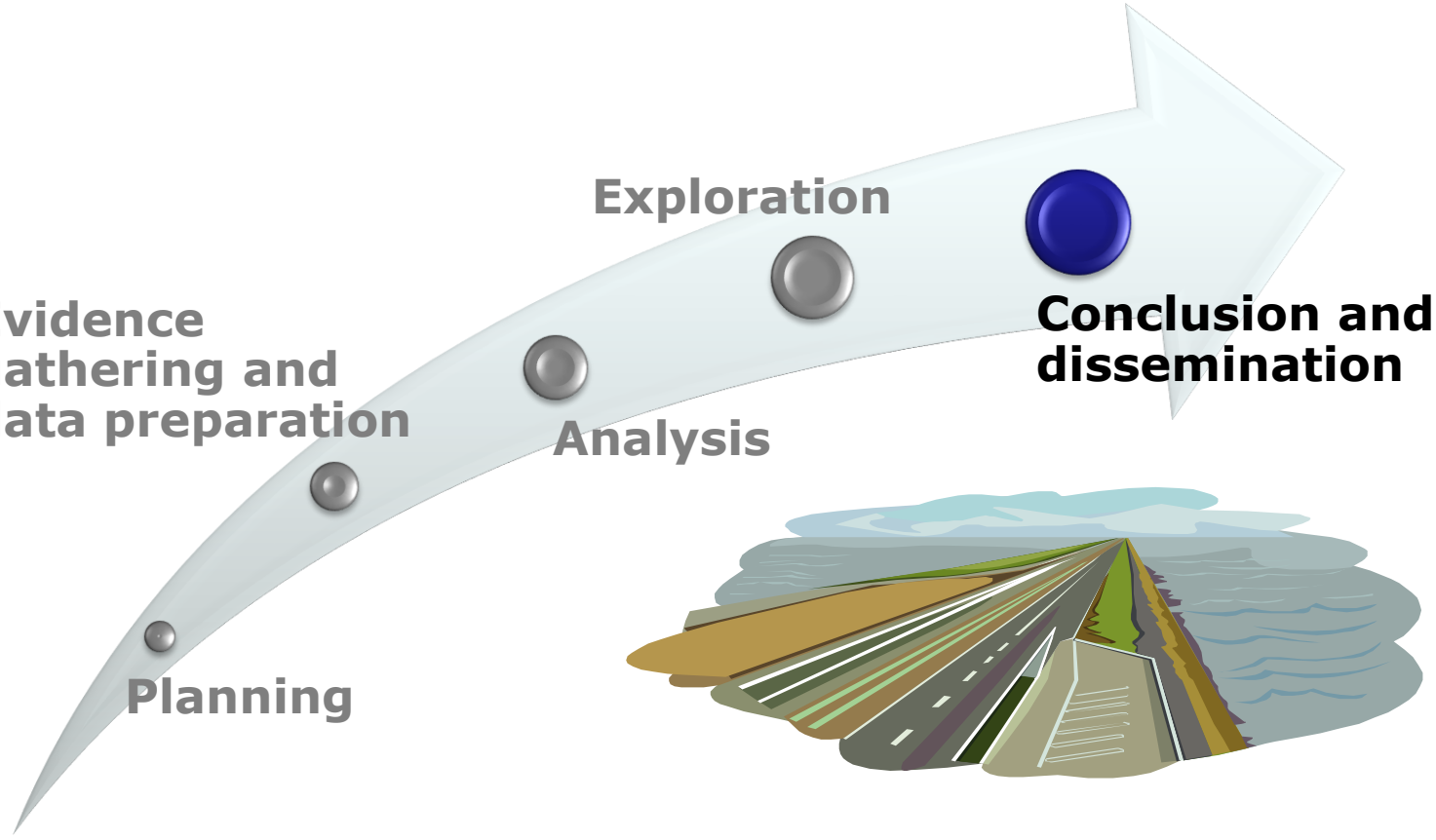


- Drugs
  - A = Placebo
  - B = Orlistat
  - C = Sibutramine
  - D = Rimonabant

- Online interactive version allowing own weights is available

http://public.tableausoftware.com/views/Finalwave2dashboard-fullrangeweight_0/Dashboarddifference?:embed=y&:display_count=no

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

Summary

- Choice of approach should match the complexity of the problem.
- In most simple problems, simple descriptive framework is likely to be sufficient.
- For more complex problems, a framework supplemented by quantitative models can facilitate consideration of trade-offs amongst the benefits and risks, address uncertainty, and potentially lead to a more comprehensive overall assessment.
- To understand the perspective of a particular stakeholder, elicitation of preference values for weighing benefits and risks may be required.

Final remarks

- Benefit-risk assessment methodologies support decision-making and are not intended to replace medical expertise.
- It is not a linear or sequential but an iterative process.
- Stakeholders such as patients and public involvement may add value and would lead to more clinically relevant decisions.

Acknowledgements

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