An industry case study: Using impactful presentations to support structured Benefit-Risk assessments in practice

EFSPI-PSI One Day Meeting

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Chair EFSPI/PSI Benefit-Risk Special Interest Group

With thanks to Rick Hermann (AZ)

Content

- Experiences within AstraZeneca
- How we carry out a structured Benefit-Risk assessment in practice

The BRAT framework is a set of principles, guidelines and tools to guide decision-makers in selecting, organizing, summarizing and weighing the clinical importance of data using sound clinical judgment. The framework is NOT a mathematical model. Results of the framework exercise inform but alone do not constitute the overall or final assessment by AstraZeneca of the benefit-risk profile of any drug compound. Benefit Risk Assessments must be undertaken as consistent with the Clinical Standard Operating Procedure on Conduct and Documentation of Benefit-Risk Assessments. The inclusion of information relating to an event , effect , risk or potential risk within the framework should not be taken to imply that causal association with the use of the drug has been established.

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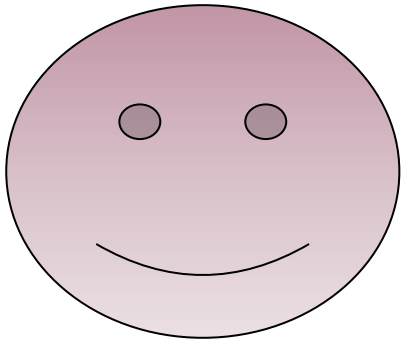
A Benefit-Risk Assessment

"The Benefit Risk is positive"



For each B-R effect/outcome are they:

- *Real*
- *Different*
- *Prevalent in the population*
- *Manageable*
- *Impactful to the "stakeholder"*

Integrate all the information "UTILITY" of each Benefit and Risk

Risks

Benefits

Data from new trial

Data from previous trial (s)

External information e.g. about comparators

The BRAT Framework

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.

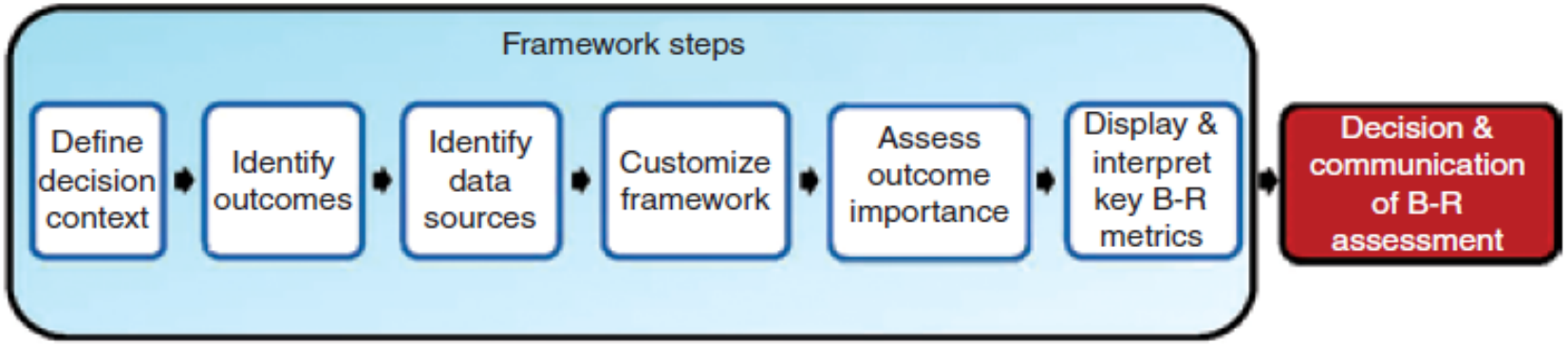


Figure 1 Steps in using the Benefit Risk Action Team (BRAT) benefit–risk assessment framework.

Expectations

TIMING

- A formal Benefit-Risk assessment based on the BRAT framework is required at the end of phase IIb and phase III

- Projects in earlier development are encouraged to use an abbreviated BRAT Framework

- All require a Benefit-Risk Statement based on the assessment

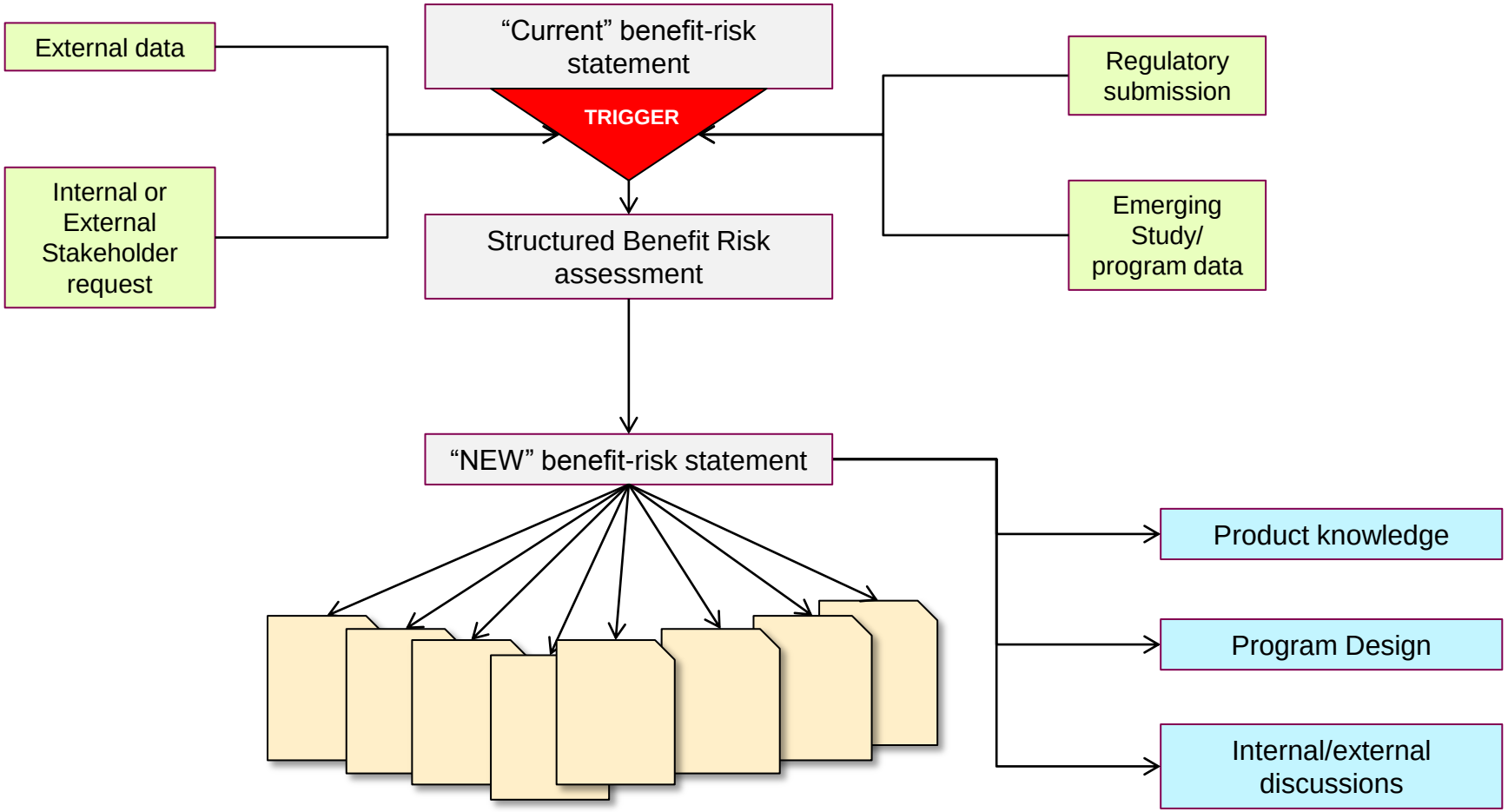
USES

- The BR Statement represents the definitive company position on the Benefit-Risk profile for a given compound.

- The BR informs future designs and a clear, data driven assessment regarding the benefits and risks of the product

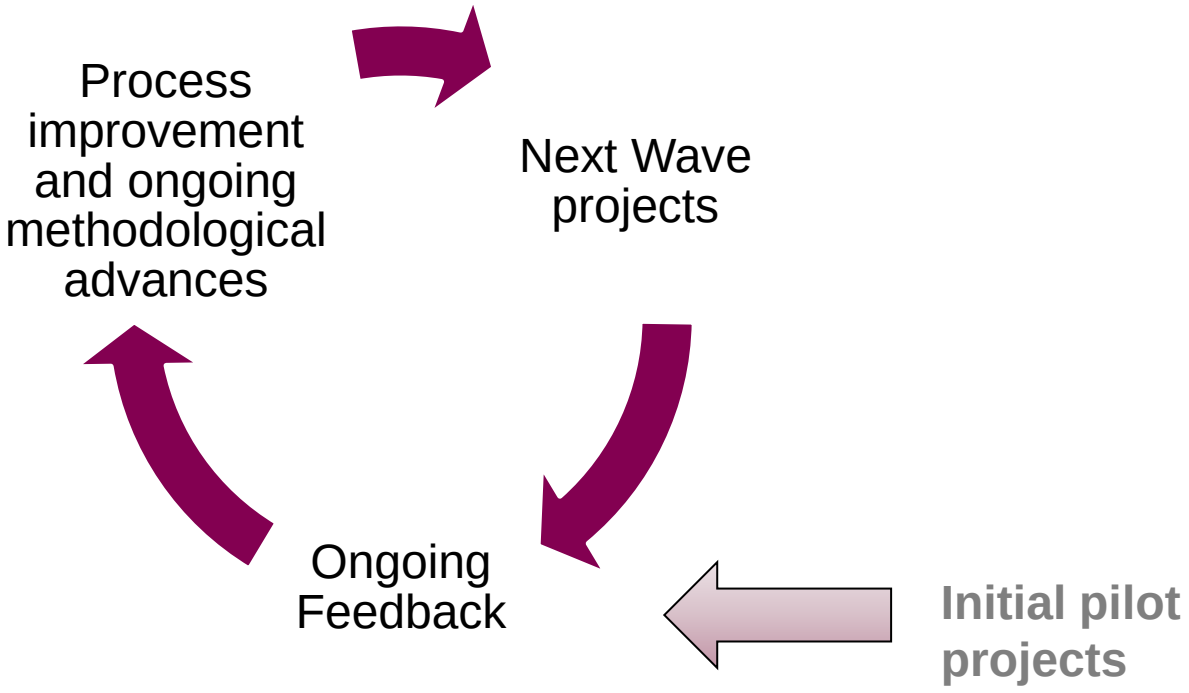
- Supports both internal and external discussions

Triggers and outputs for the formal Benefit-Risk assessment



Current status

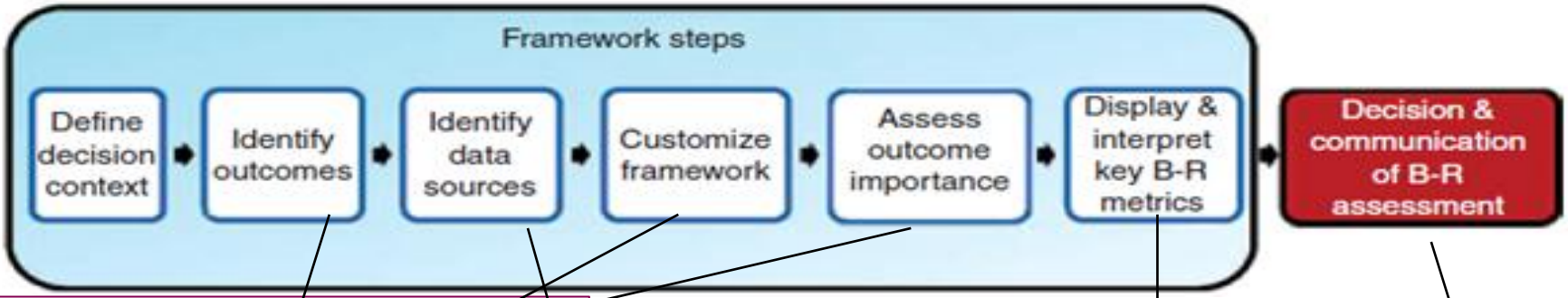
~30 projects in 2013 with P2b and P3 readouts needed to use BRAT



Current status

- Support given from an internal Core Team
- Template for key BR outputs and for BR Statement
- Workgroup to put together PtC for key methodological issues based on feedback
- External collaboration
  - Fast evolving
  - Many initiatives EFSPI, QSPI, IMI, COMET, FDA, EMA, ISPOR, UMBRA/CIRS…

Methodology workgroup



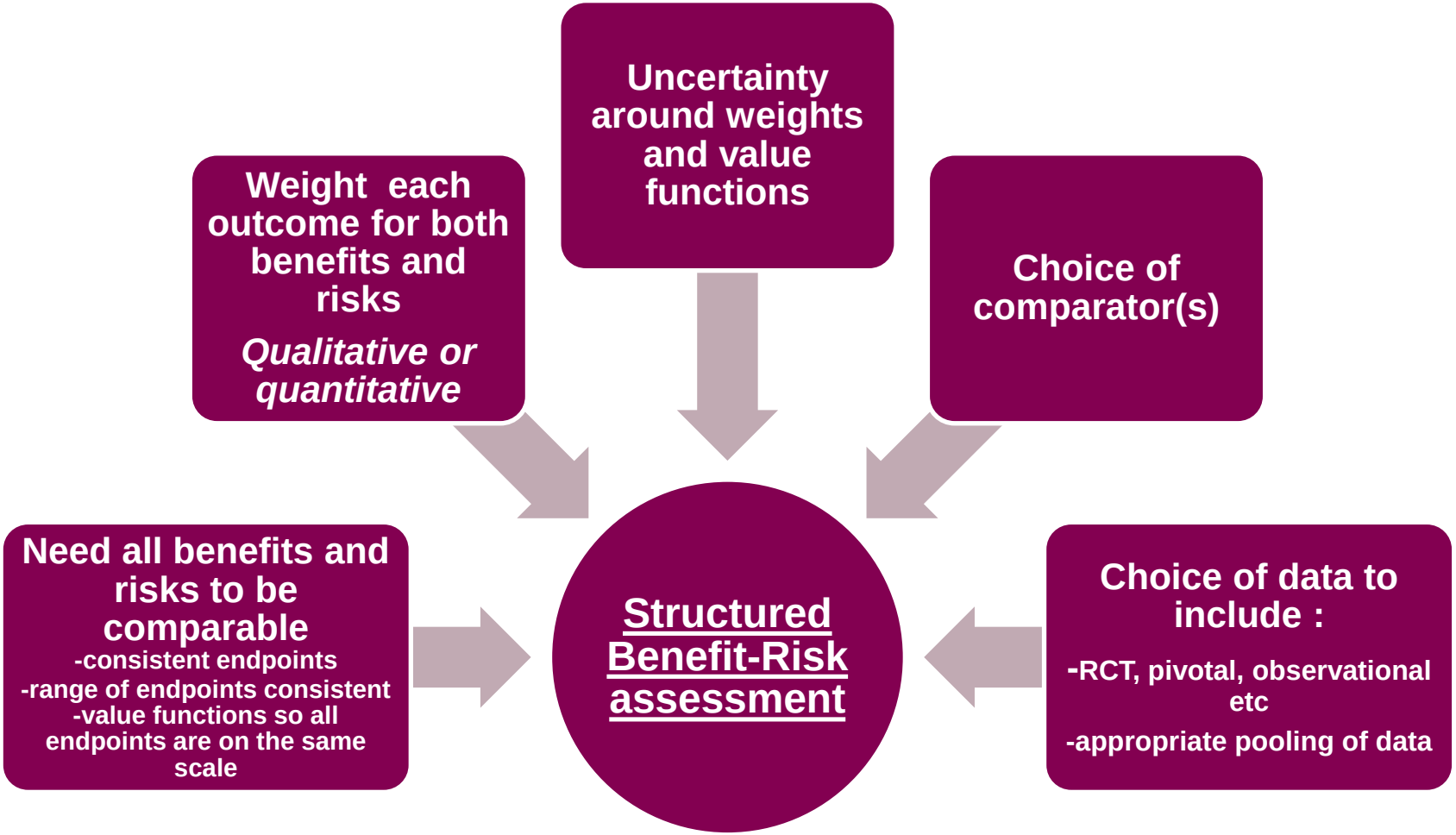
1) WEIGHTING
-Assess different methods (pro's / con's / simplicity / reproducibility)?
-Do any make quantitative or qualitative weighing more robust?
-Come up with recommendation for using qualitative vs quantitative – look at pros and cons
-Recommend which way AZ should go quantitative or qualitative or combination

3) PRESENTATION OF DATA
-Adding in "level of evidence"
-Automating forest plots
-Other visual presentations
-Presentations to include in BR assessments and statement

2) DATA SOURCES/STATS METHODS
-Automated process for inputting data/outcomes
-Summarising analyses methods via effects tables
-Adding in limitations of data/endpoints/trials/pooling
-How to link to pooling strategies
-Presenting low prevalence events
-Subjective ranges of data

4) QUANTITATIVE METHODOLOGY
-Assess methods and presentations
-Incorporating uncertainty
-Look at software to facilitate
-Link to Probability of Success

A Structured Benefit-Risk Assessment
Key Statistical Input/Issues



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Structured B-R Output Template

BRAT Framework for XXX in XXX

This document is a template to enable teams see the types of outputs used to complete a BRAT Framework for their structured benefit-risk assessment.

DRAFT AND CONFIDENTIAL-

The AZ benefit Risk Assessment Tool (BRAT) framework is a set of principles, guidelines and tools to guide decision-makers in selecting, organizing, summarizing and weighing the clinical importance of data using sound clinical judgment. The framework is NOT a mathematical model. Results of the framework exercise inform but alone do not constitute the overall or final assessment by AstraZeneca of the benefit-risk profile of any drug compound. Benefit Risk Assessments must be undertaken as consistent with the Clinical Standard Operating Procedure on Conduct and Documentation of Benefit-Risk Assessments. The inclusion of information relating to an event , effect , risk or potential risk within the framework should not be taken to imply that causal association with the use of the drug has been established.

Decision Context

Objective:

Indication:

Formulation and Dose:

Comparator:

Population:

Contraindications:

Perspective:

Timepoint for primary assessment:

Pooling strategy

State how data was pooled for effects tables and forest plots. Justification for the different populations are needed and this should align with other key analyses for example with a pooling analysis plan for a regulatory submission.

Value Tree

The final value tree is given below. This should be based on an assessment of the key benefits and important identified and potential risks as applicable. Risks may include both identified and potential risks which are considered either serious and/or frequent and/or that may be of potential public health consequence.

The justification and considerations for choice of each benefit and risk may be included here or in subsequent sections of this document, including any potential limitations.

Structured B-R Output template Sections

1. Decision context
2. Value tree with justification
3. Data and pooling strategy with justification
4. Effects table - Endpoints and caveats to interpretation
5. Effects table - Summary of analyses used to present data
6. Justification of outcome ranges used in presentations
7. Weighting/Ranking discussion
8. Structured Benefit-Risk Forest Plot
9. Summary

APPENDIX for source tables or links to source tables

1. Decision Context

Objective: Submit NDA for approval of AZD

Indication: Generic Indication

Formulation and Dose: Dose XX

Comparator: e.g. Placebo

Population:

Contraindications:

Perspective: Industry presenting to Regulators

2. Identify outcomes

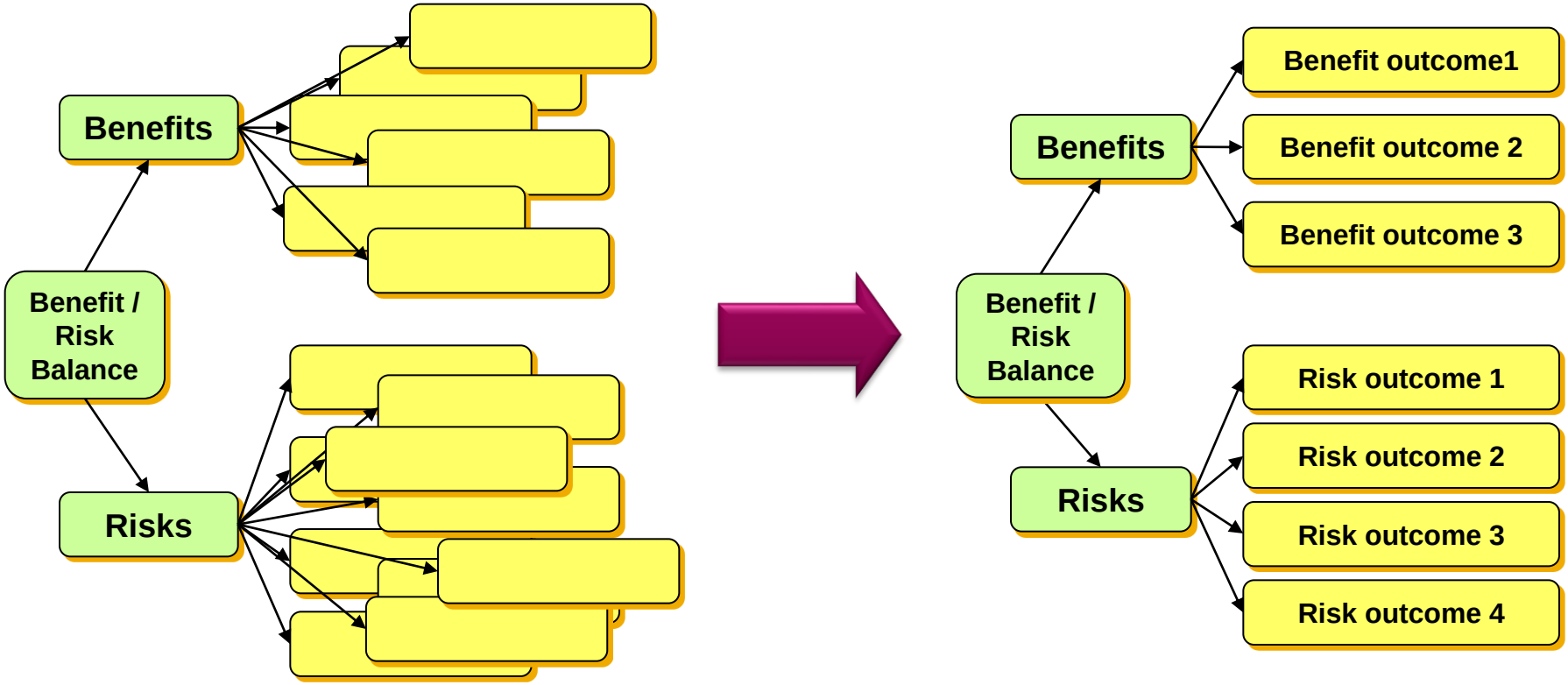
Value tree

- *Present value tree. This is based on an assessment of the key benefits and risks. Risks may include both identified and potential risks which are considered either serious and/or frequent and/or that may be of potential public health consequence.*

- *The justification and considerations for inclusion of each benefit and risk should be included here including any potential limitations.*

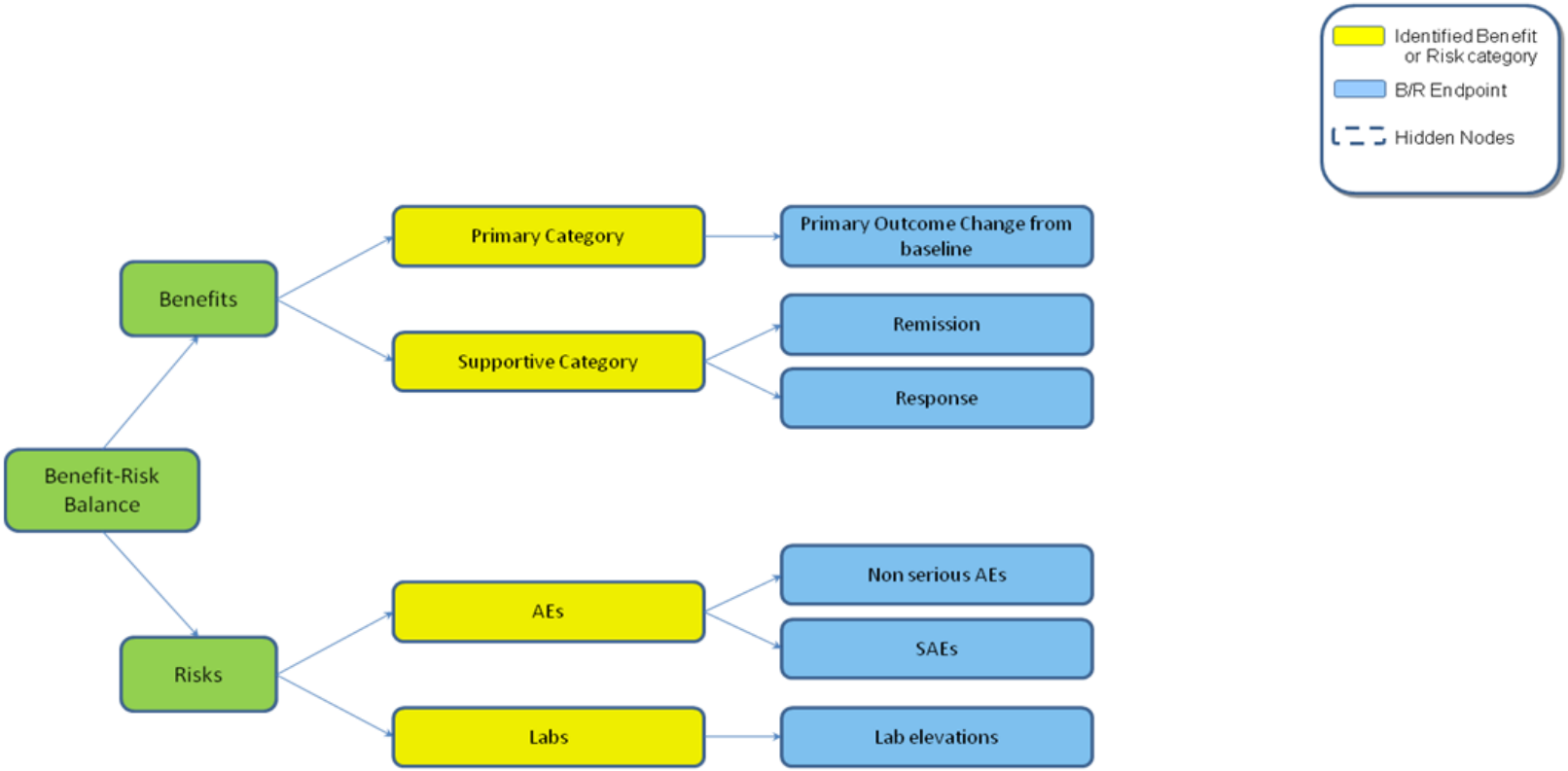
2. Identify outcomes

Establish a preliminary scope for the benefit-risk assessment by identifying and paring down potential benefit/risk outcomes



2. Identify outcomes

Value tree



3. Data and pooling strategy with justification

- *State how data was chosen for inclusion*
- *State how data was pooled for summarisation*
- *Justification for the populations used*
  - *Should align with other key analyses for example with a pooling analysis plan for a regulatory submission.*

4. Effects table –Endpoints and caveats to interpretation

- *Presentation (and justification) of ranges for each endpoint*
- *The outcome/endpoints should be as for the value tree.*
- *Summaries for each treatment should be given here*
  - *These should be sourced from formal study or regulatory submission tables which should be included in the footnote as source tables.*

Effects Table (based on EMA pilot on Caprelsa)

Source: Regulatory Rapporteur – Vol 9, No 6, June 2012

		Effect	Description	Best	Worst	Units	Study used	Placebo (95% CI)	Active (95% CI)	Comments/ Limitations	Qualitative ranking
BENFITS/FAVOURABLE EFFECTS	Primary endpoint	Primary Outcome Change from baseline	Outcome change from baseline score at week X	-60	60	Unit less	Study 2A	-10 (-10.5, -9.5)	-15 (-15.5, -14.5)	Regulatory endpoint is at week Y	
	Key secondary	Supportive endpoint- Remissions	Outcome<= YY at week X	100	0	%	Study 2A	10 (2,20)	20 (10,30)	Regulatory endpoint is at week Y and double counting with primary outcome using this endpoint	
	Key secondary	Supportive endpoint - Responders	Outcome change from baseline <=YY % at week X	100	0	%	Study 2A	15 (5,25)	40 (25,55)	Regulatory endpoint is at week Y and double counting with primary outcome using this endpoint	
RISKS/UNFAVOURABLE		AEs	Non-serious	0	100	%	Study 2A	50 (25,65)	60 (45,75)	Only X weeks of exposure- Correlation of AEs not accounted for	
			Serious	0	100	%	Study 2A	0	0	Only X weeks of exposure Correlation of AEs not accounted for	
		Labs	Labs Elevation	0	100	%	Study 2A	4 (-2,9)	12 (3,20)	Only X weeks of exposure	
		*adjusted for XXX, ** unadjusted									

5. Effects table: Summary of analyses and results table

	Effect	Description	Best	Worst	Units	Analyses methods used and limitations	Active vs Placebo (95% CI)
BENFITS/FAVOURABLE EFFECTS	Primary Outcome Change from baseline	Outcome change from baseline score at week X	-120	120	Unit less	Includes any pooling strategy and analyses methods for active vs placebo estimates	
	Supportive endpoint-Remissions	Outcome<=YY at week X	100	-100	%		
	Supportive endpoint - Responders	Outcome change from baseline <=YY % at week X	100	-100	%		
RISKS/UNFAVOURABLE EFFECTS	AEs	Non-serious	-100	100	%		
		SAEs	-100	100	%		
	Labs	Labs Elevation	-100	100	%		

6. Justification of ranges used to present outcomes

- *The endpoints used for each outcome can have different ranges.*
- *In order to ensure the endpoints are presented in the most comparable way a proportion of the full range of the endpoint should be used for each presentation*
- *Some endpoints do not have an explicit range so an assessment of possible ranges should be made*
  - *Not simple in practice will discuss later*
- *Details of any transformation of variables being used should also be given*
  - *This has been seen as a potential approach which is being worked through given ranges can be arbitrary*
- *Example text*
  "The summary for benefits and risks in each forest plot are presented on ZZ% of the full range to ensure comparability i.e XXX to YYY for endpoint 1, XXX to YYY for endpoint 2 and XXX to YYY for the risk differences."

7. Weighting/Ranking discussion

- *To include the high level discussion on how ranking/weighting of all Benefits and Risks was carried out*
- *Simple table….difficult discussion*

Risk/Benefit	Ranking of importance in benefit risk assessment	Justification for inclusion of risk/benefit and ranking

7. Weighting/Ranking discussion

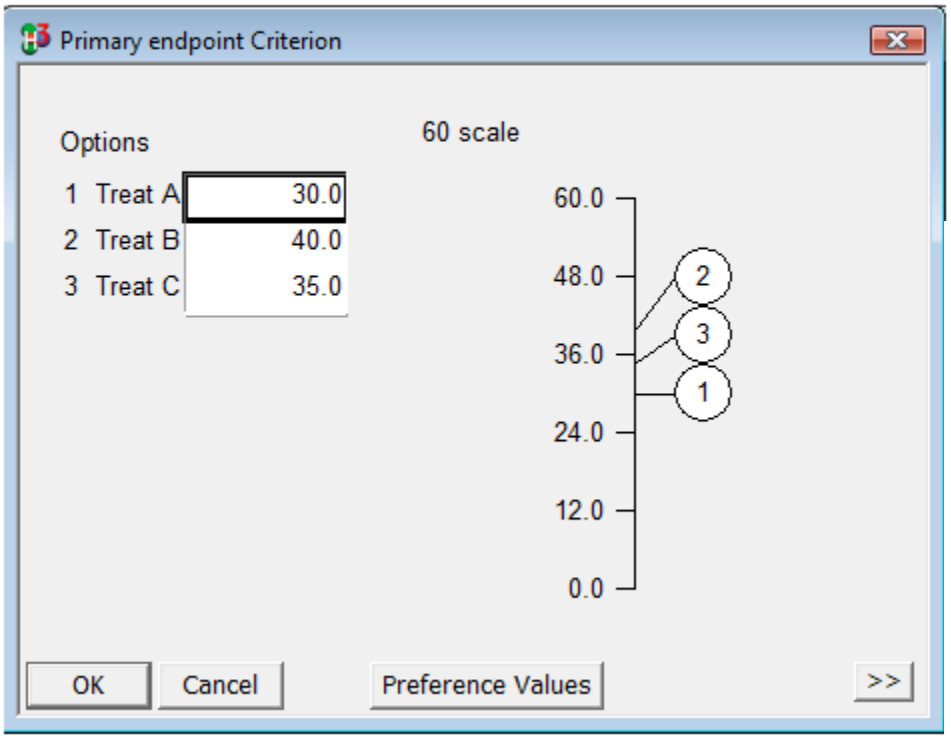
Facilitating the discussion

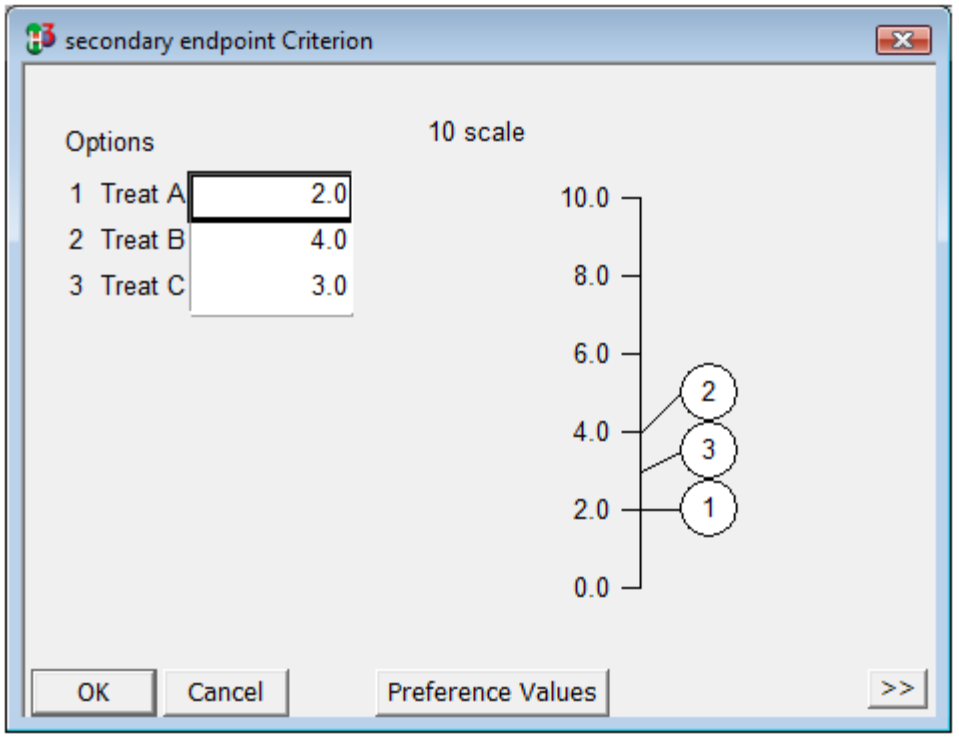
- A new skill to most of us…decision analytics
- Useful to start with the effects table with ranges
- Open clear questions
  - For ranking
    - What is clinically important?
    - Can start with Benefits, then Risks then together
    - How important is the change from the best to worst score for Benefit X vs Benefit Y?

7. Weighting/Ranking discussion

Facilitating the discussion (e.g. HIVIEW [4] type outputs can help)

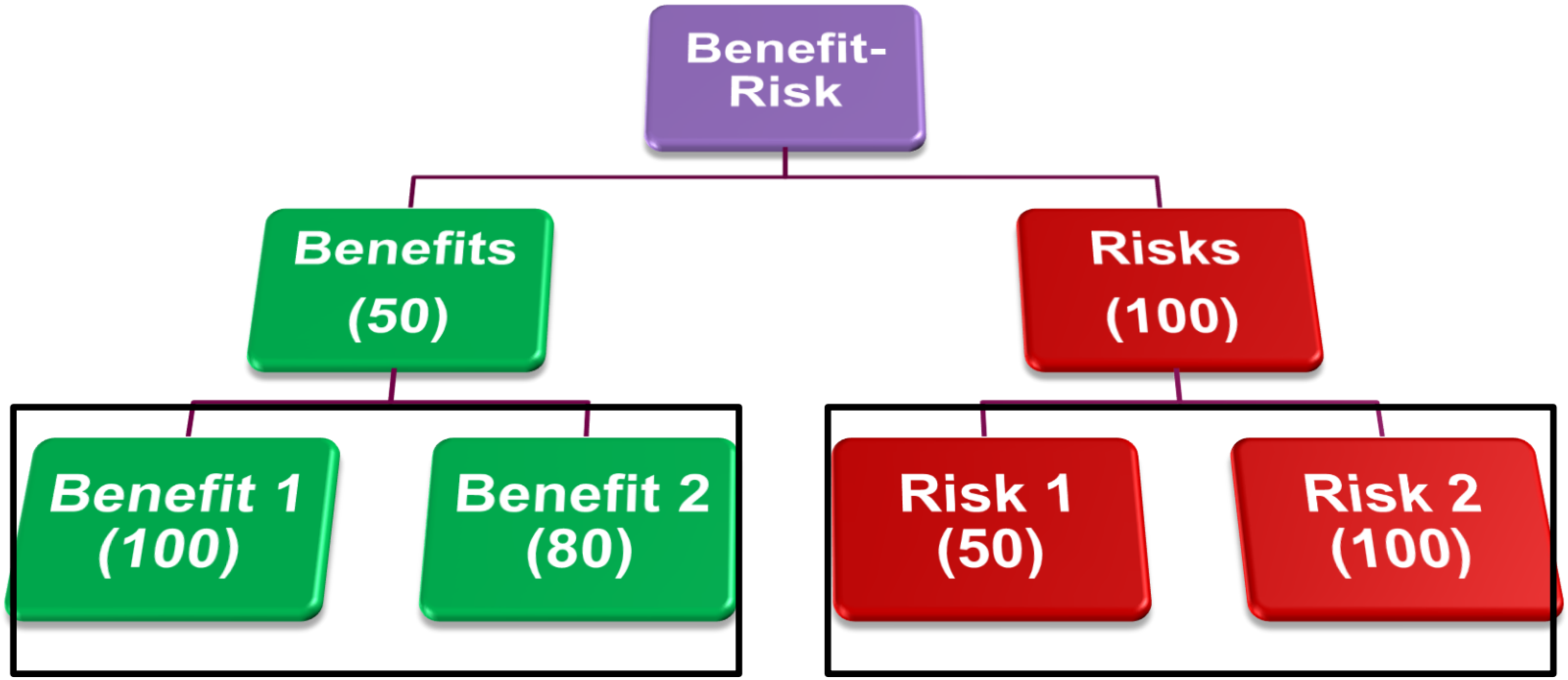
Primary endpoint





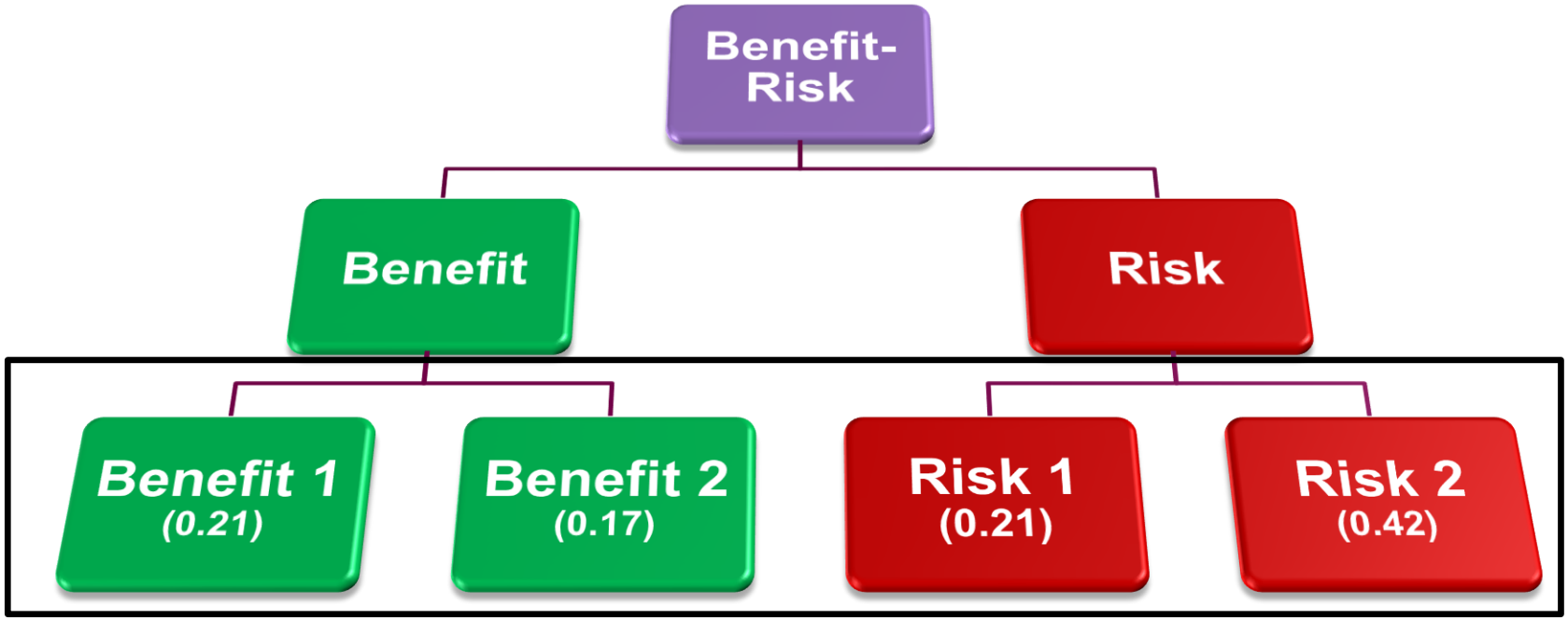
7. Weighting/Ranking discussion

Quantitative weighting



7. Weighting/Ranking discussion

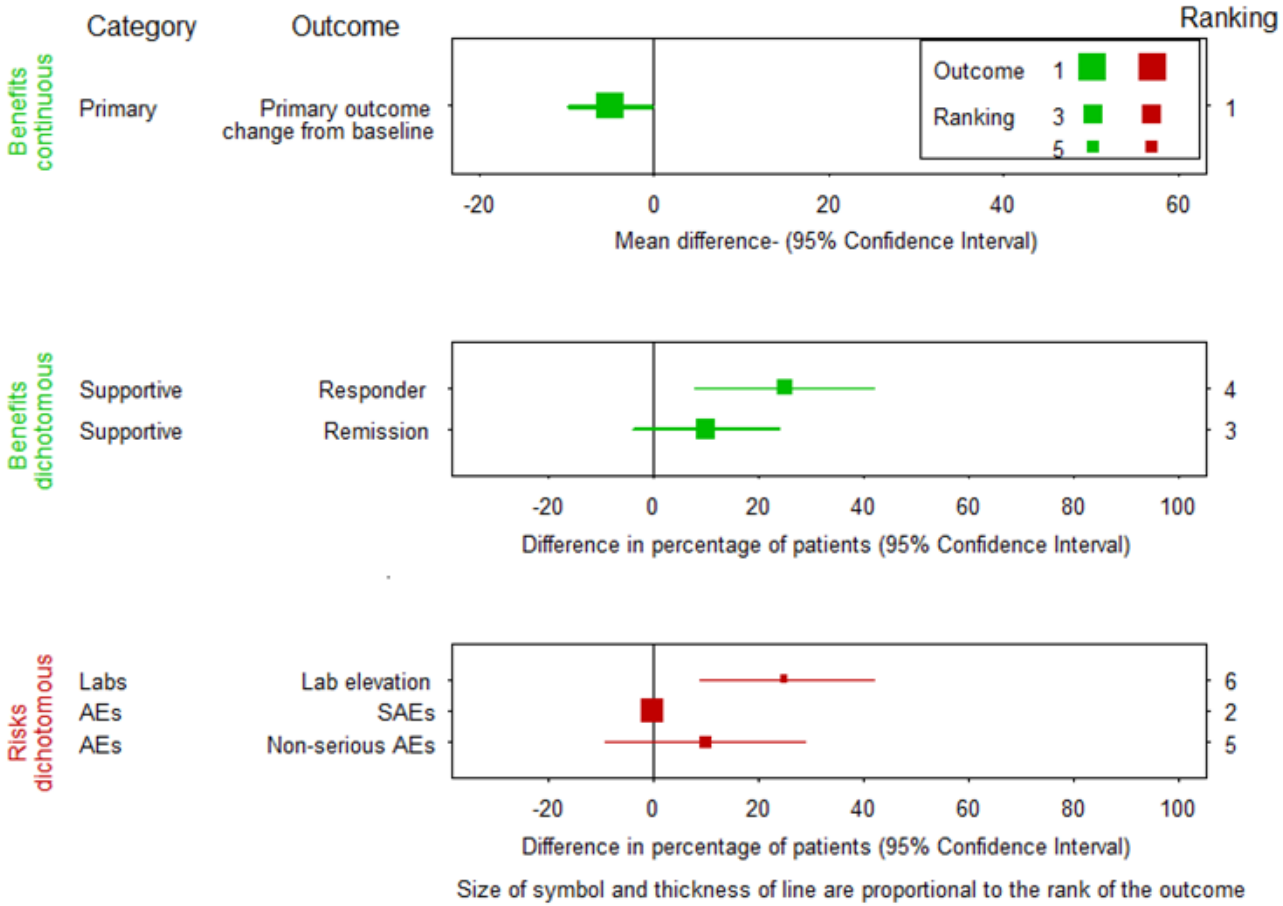
Quantitative weighting



8. Structured Benefit-Risk Forest Plot

- *To present each benefit and risk, treatment effect where appropriate, the ranking/weighting and level of evidence.*
- *Also any key limitations should be included either as footnotes or text.*

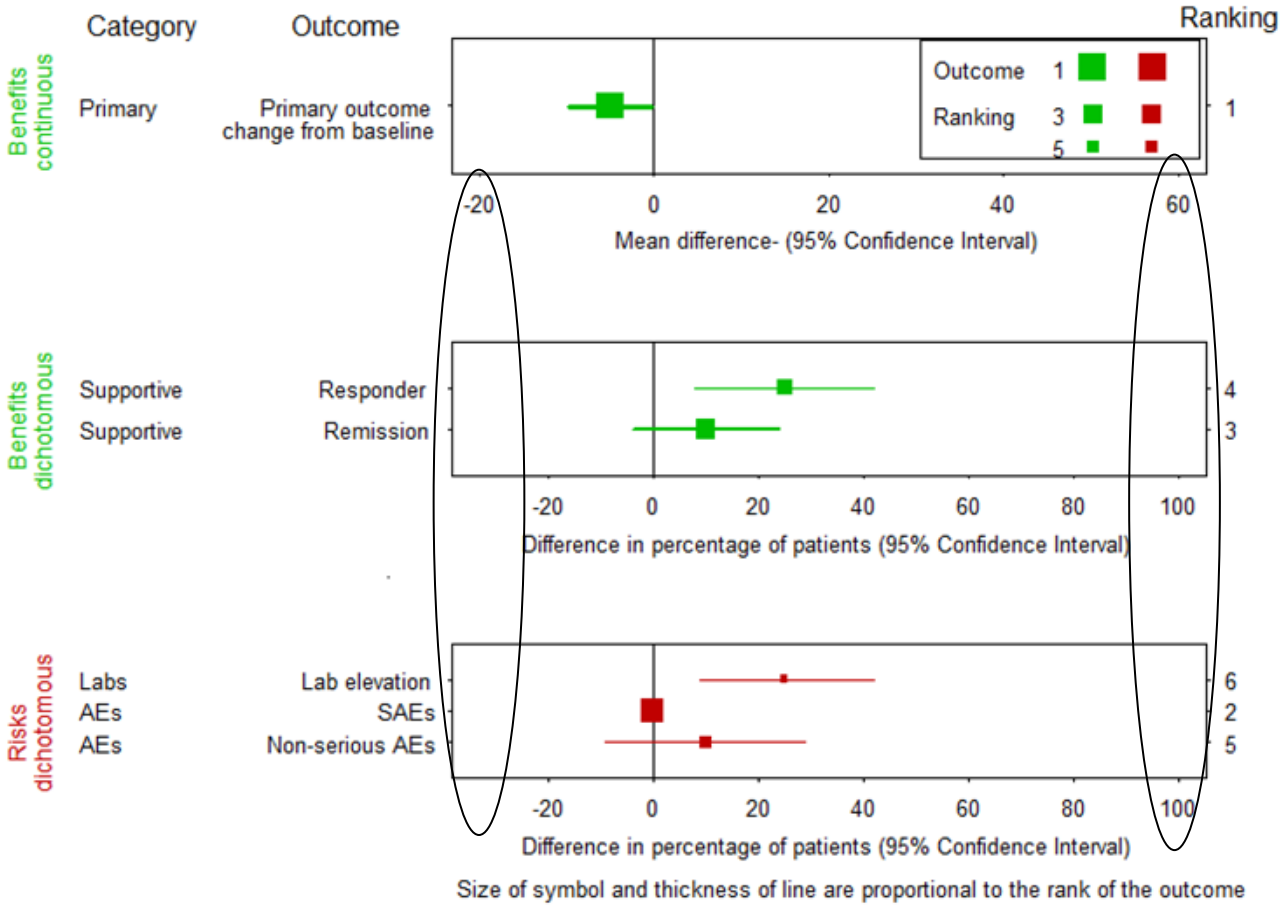
Basic forest plot



Greater numerical difference between active and placebo

Basic forest plot

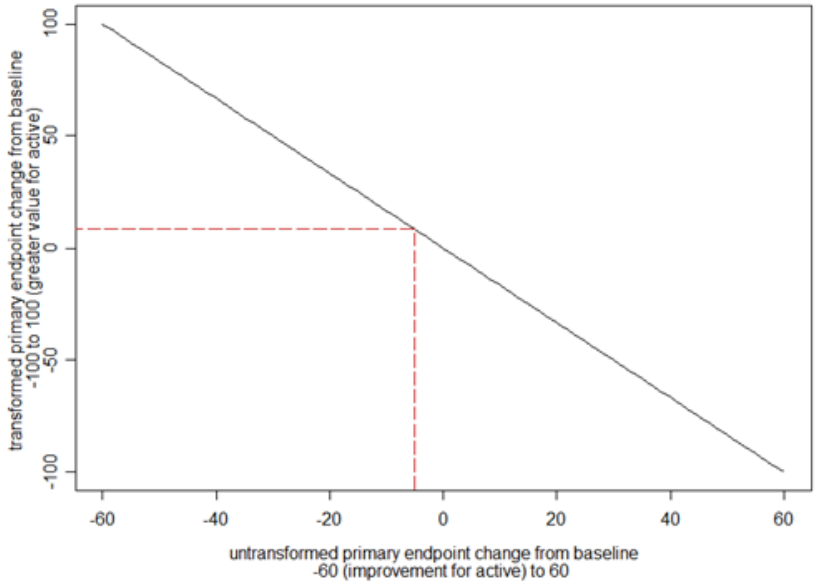
Note comparable ranges are key



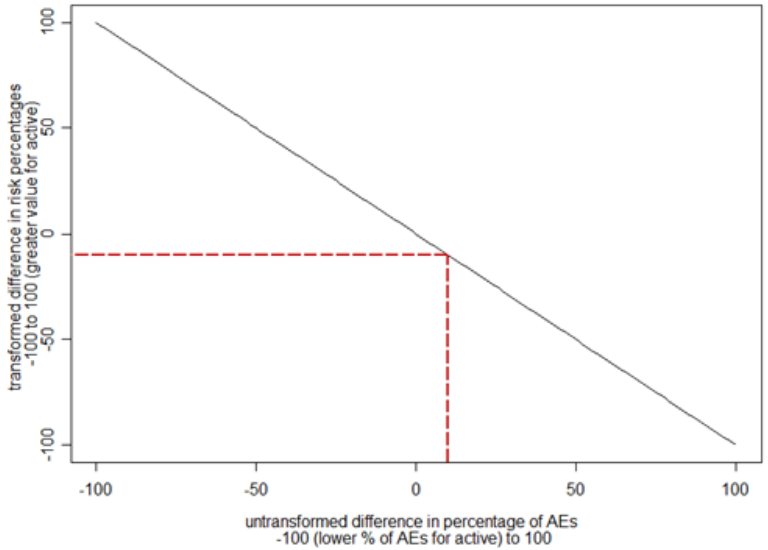
Greater numerical difference between active and placebo

Transforming variables
A potential approach?

Primary endpoint Change from Baseline

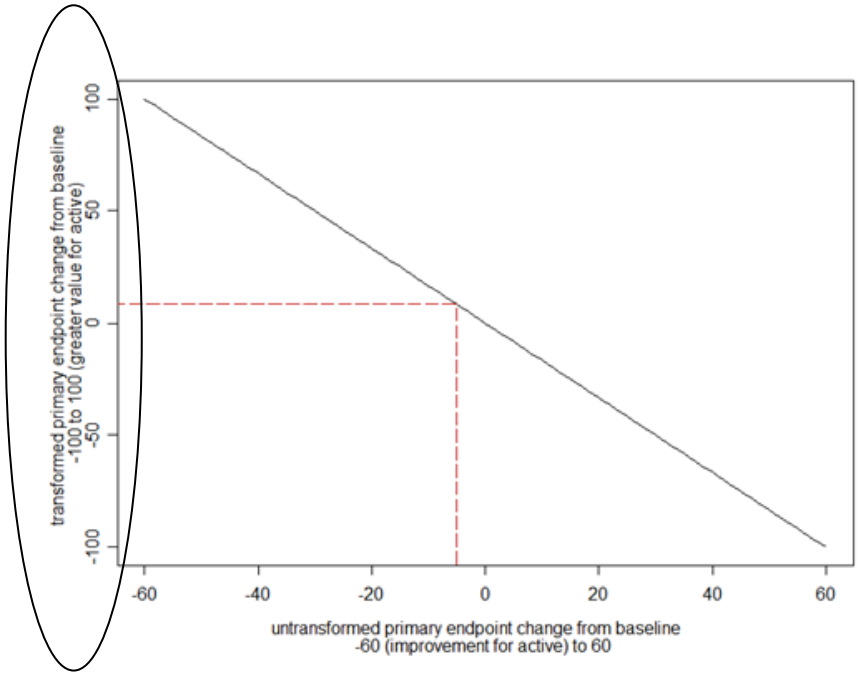


Percentage of AEs

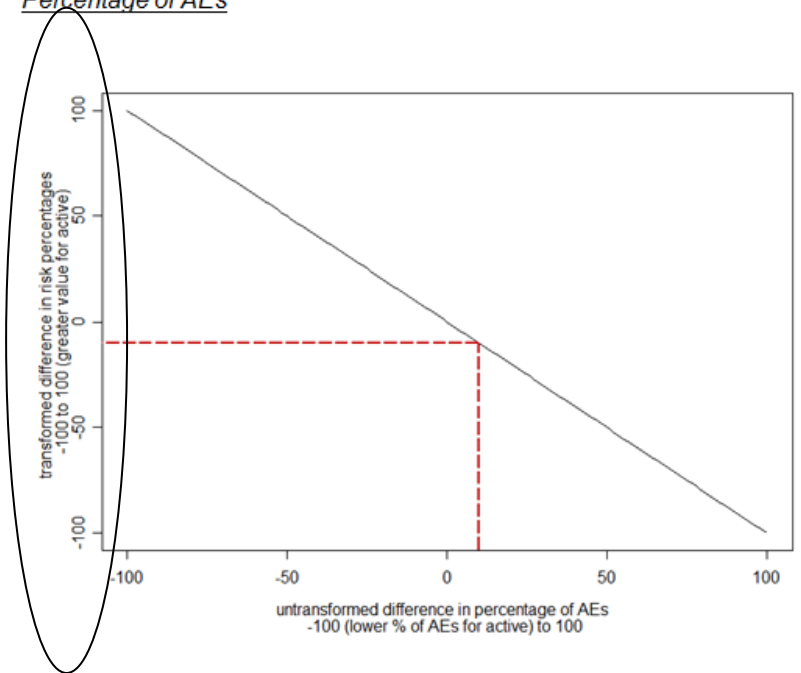


Transforming variables
Again comparable ranges are key

Primary endpoint Change from Baseline



Percentage of AEs



A note on “comparable ranges”

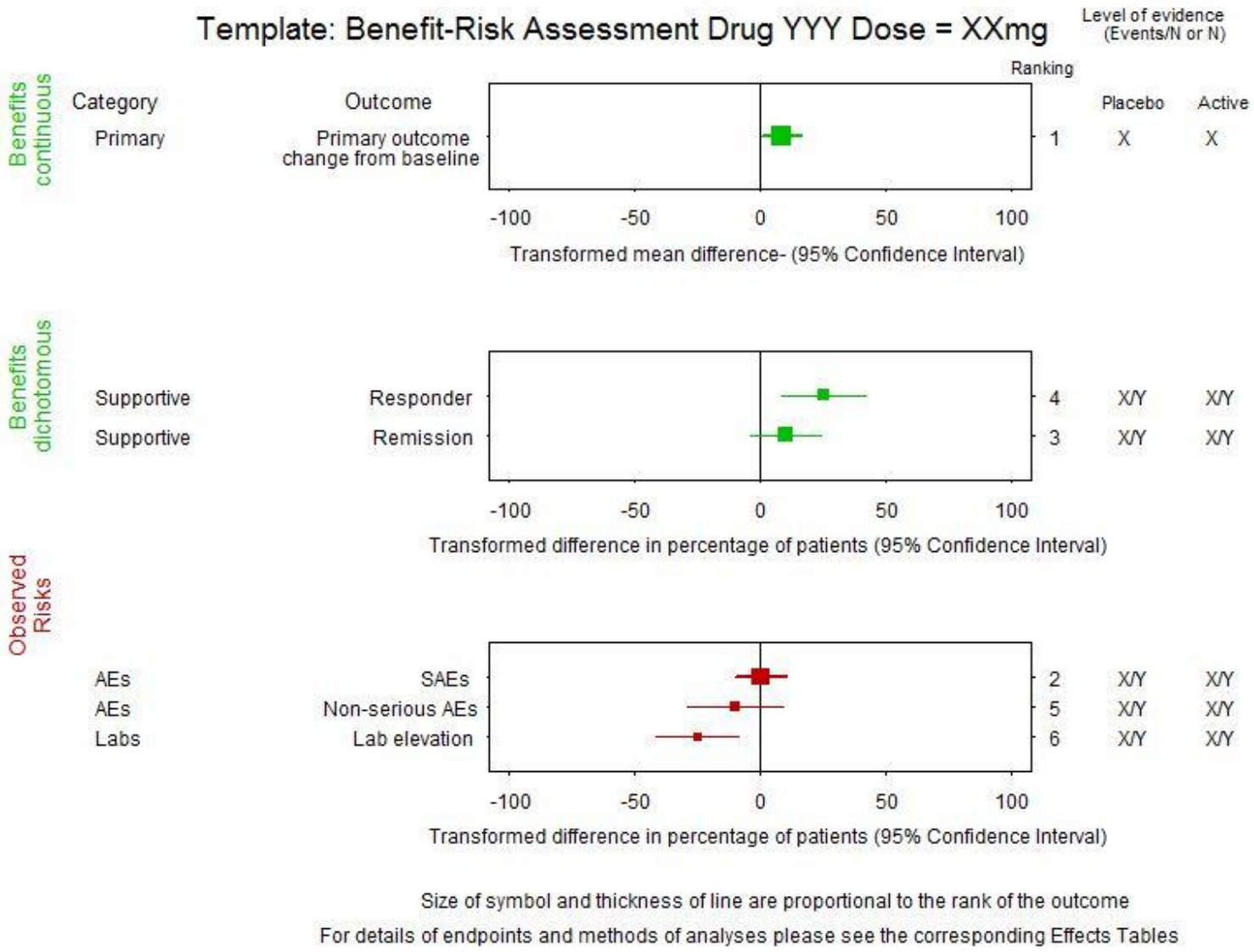
- These are crucial when we have endpoints on different scales

  “How do we compare different outcomes with different ranges?”

- Depending on the ranges chosen, the interpretation of the assessment can change
  - Qualitative through presenting different endpoints on the same table/plot
  - Quantitative as a key part of the algorithm

- Standardisation of what the key endpoints are (e.g. the COMET initiative) and ranges for key endpoints would enable consistency

Forest plot with ranking and level of evidence



Greater value for active vs placebo

Quantitative approaches…..e.g. MCDA

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

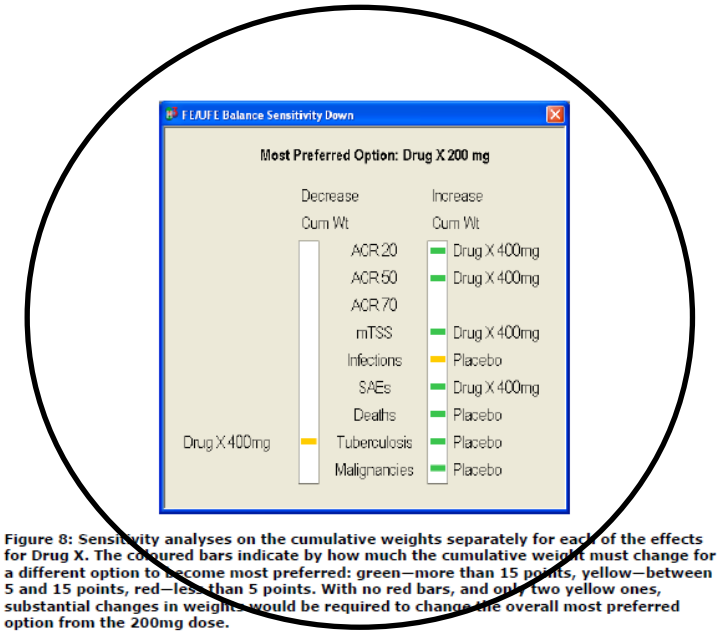


Figure 8: Sensitivity analyses on the cumulative weights separately for each of the effects for Drug X. The coloured bars indicate by how much the cumulative weight must change for a different option to become most preferred: green—more than 15 points, yellow—between 5 and 15 points, red—less than 5 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.

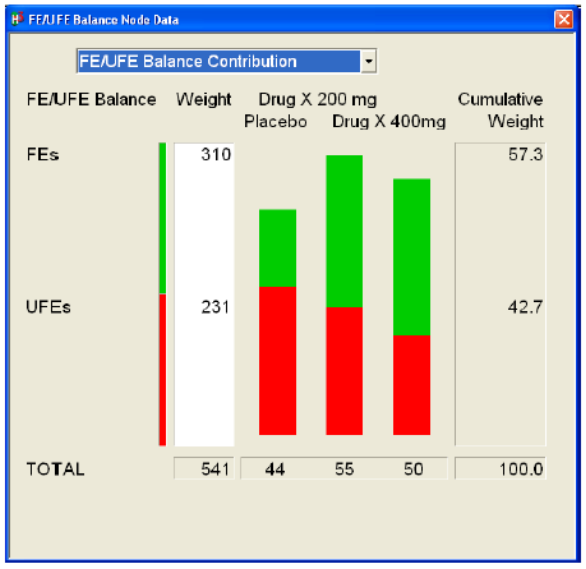


Figure 3: Added-value bar graphs for the favourable and unfavourable effects of Drug X 200mg+MTX, Drug X 400mg + MTX, and for the placebo. Longer green bars indicate more benefit, longer red bars indicate more safety.

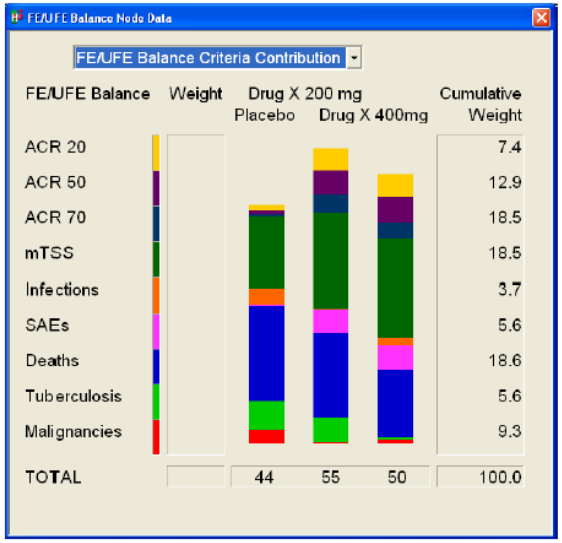
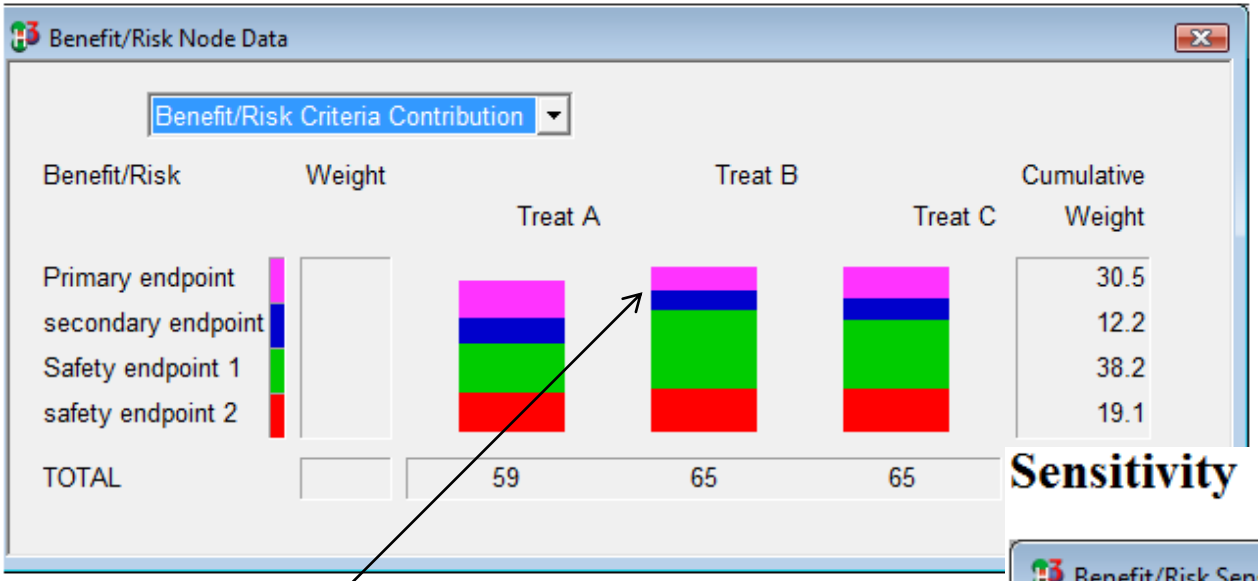


Figure 4: Added-value bar graphs for all effects of Drug X 200mg+MTX, Drug X 400mg + MTX, and for the placebo.

Quantitative approaches…..becomes qualitative in interpretation

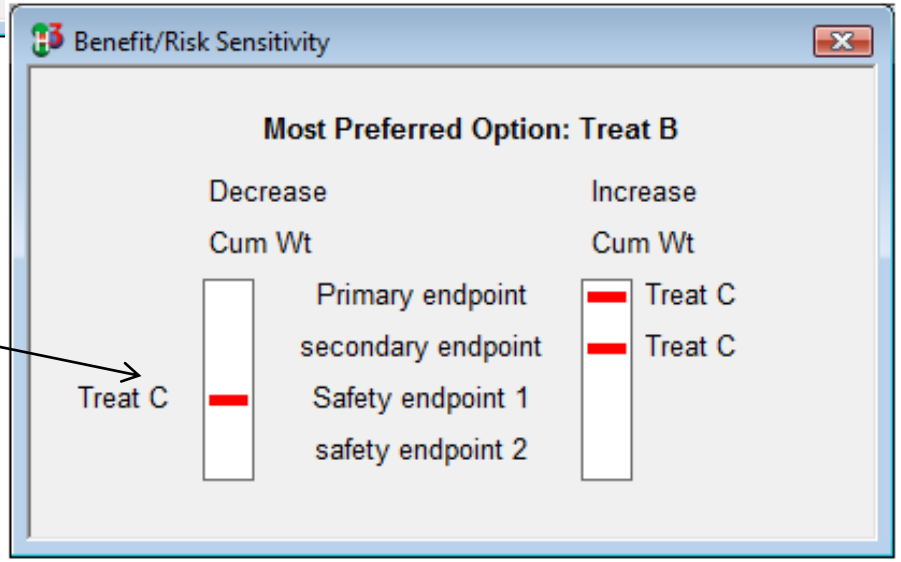
(HIVIEW [4])



Sensitivity

Safety endpoint 1 most influential

Uncertain in assessment



9. Summary

- *Summary of assessment including description of ranking/importance of endpoints and the differences seen*
- *Includes sensitivity of any assessment*
- *Summary of key limitations*
- Used as basis for B-R Statement

Conclusions and learning

Overall

- The BRAT Framework provides a structured way to approach complex decisions on an ongoing basis and provides for transparent and reproducible assessments that can be clearly communicated.
- It takes implicit clinical judgments and makes them explicit.
- There needs to be agreement/further clarification through cross-functional teams (statistics, clinical, regulatory, etc.) on the most robust and defensible methods for data summarization and weighting.
- Further guidance on how this could be incorporated/aligned with current ways of working is needed.

Conclusions and learning

Specific points for each step of the framework:

Define Decision Context(step 1), Identify outcomes (step 2) and Customize framework (step 4)

- It is important to have all key disciplines there to discuss and agree on each step

Conclusions and learning

Specific points for each step of the framework

Identify and extract data (step 3)

•Formal QC of data is needed including the sources of data and which analyses should be included as the most representative. This usually requires more discussion than expected.

•Source data tables should be added as an appendix for completeness.

•Need to better highlight key limitations for example in footnotes or effects tables.

•Adding in an effects table with treatment differences, analyses methods used for the BR display and any sensitivity analyses around them facilitates greater transparency.

•A pooling strategy for assessments with data from multiple studies is key-including a decision of whether it is appropriate to pool data from across the different studies.

Conclusions

Specific points for each step of the framework

Assessing Outcome Importance (step 5)

- Better guidance is needed on how to robustly weight outcomes both qualitatively or quantitatively as well as incorporating variability around any weight chosen.

Conclusions

Specific points for each step of the framework

Display and display key benefit- risk metrics (step 6)

- Transforming outcomes onto the same scale and to make uni-directional seems to be intuitive for teams.
  - A key limitation is where there are no actual ranges defined for an endpoint so the choice of ranges are subjective and could affect the assessment.
  - Consistency for key endpoints where ranges could be agreed via cross-industry agreement would help.
- Useful to add in the actual amount of information used onto the forest plots such as number of subjects and events.
- Need to think about how to demonstrate the level of evidence in the forest plots such as observational vs randomised controlled trial data.
- Need to utilise robust methodology for event summaries especially for low incidence events.
- An assessment of the most appropriate quantitative methodology is needed.

References

[1] BRAT tool
Development of a Framework for Enhancing the Transparency, Reproducibility and Communication of the Benefit–Risk Balance of Medicines; P M Coplan, R A Noel, B S Levitan, J Ferguson and F Mussen: Clinical Pharmacology & Therapeutics (2011) 89 2, 312–315

[2] EMA pilot
http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000314.jsp&mid=WC0b01ac0580223ed6&jsenabled=true

[3] R*egulatory Rapporteur – Vol 9, No 6, June 2012*

[4] Hiview software
http://www.catalyze.co.uk/index.php/software/hiview3/

QUESTIONS/COMMENTS

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