Benefit – Risk Management

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Outline

1. **Need for Comparative Benefit Risk Assessment**
2. **One Approach to Implement CBR Assessment in Product Development**
3. **Challenges to Implementing CBR**
4. **Lessons Learned**

What is Benefit-Risk

- Evaluation of Benefit-Risk is a very common human activity
- Instinctive?
- Principle appears simple
  - Consider benefits
  - Consider risks
  - Weigh up
  - Act accordingly
- However becomes complicated
  - Individual v Group
  - Multiple risks, complexity, frequency, severity
  - Indirect gain, criteria for benefit
  - Multiple stakeholders, each with own interpretations and considerations
- Difficult to produce absolute values on apparently simple decisions

What is 'Benefit'?

- `benefit' originates from Latin `**bene factum**' and means a 'good deed' or 'good achievement'

- Definition:
  - 1. a. Something that promotes or enhances well-being; an advantage: The field trip was of great benefit to the students.
  - b. Help; aid.
  - 2. A payment made or an entitlement available in accordance with a wage agreement, an insurance policy, or a public assistance program.
  - 3. A public entertainment, performance, or social event held to raise funds for a person or cause.
  - 4. Archaic A kindly deed.
- Benefit is a **quantity**
- Often subjective, often a range of 'success'

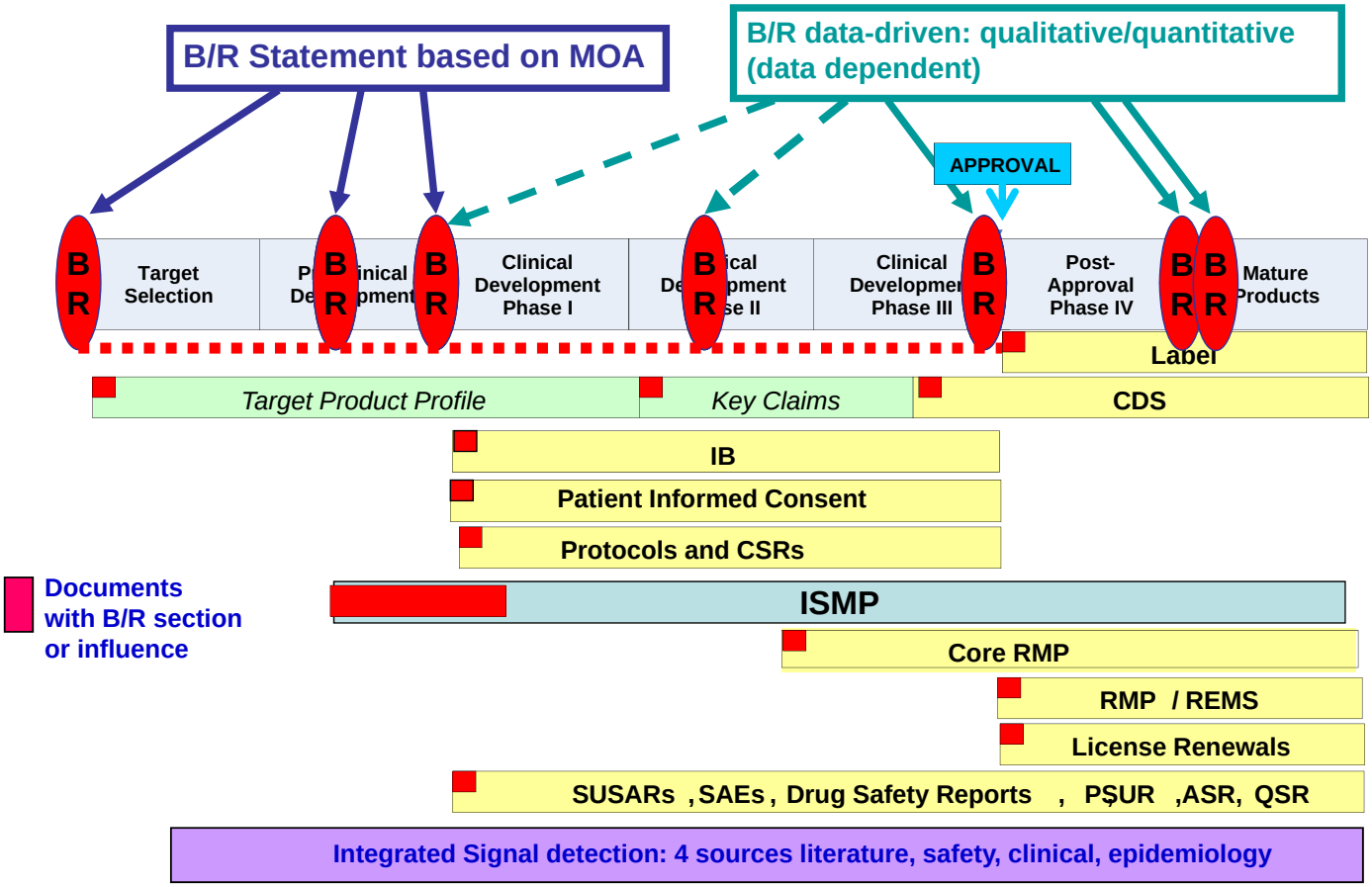
What is ‘Risk’?

- Origin? French: risque, Italian risco (mod. rischio)
- Definition of ‘Risk’
  - 1. **The possibility of suffering harm or loss**; danger.
  - 2. A factor, thing, element, or course involving uncertain danger; a hazard: "the usual risks of the desert: rattlesnakes, the heat, and lack of water" (Frank Clancy).
  - 3. a. The danger or probability of loss to an insurer.
  - b. The amount that an insurance company stands to lose.
  - 4. a. The variability of returns from an investment.
  - b. The chance of non payment of a debt.
  - 5. One considered with respect to the possibility of loss: a poor risk.
- Risk is a **probability** of an individual developing an adverse event (**Hazard**) in a given period of time
- Probability will depend on multiple other factors

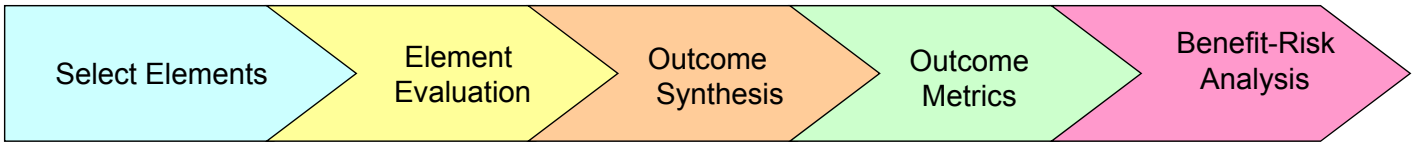
Ideal situation

- Ideal: ***Benefit Risk Ratio for drug X is 23.45 and is therefore strongly positive***

- Is it possible?
- Is it naive to believe that Benefit (a subjective quantity) and a Risk (a set of probabilities) can ever be connected?
- Benefit-Risk **Analysis**, is an ‘evaluation’
  - It is too early in it’s concept to produce absolute terms (though this may be possible in some circumstances)
  - Any strategy for designing Benefit-Risk processes must take this into account and be flexible enough to evolve with the times



So where and when to start?



- How to define benefit?
- How to define risk?
- How to capture uncertainty?

- How to elicit preferences?
- What perspective (s) to consider?

- What methods to use? Statistical tools, Decision trees, Markov models, Discrete event simulation

- What metrics to use? MCDA, INB, MAR, QALYs/RVALYs
- GBR, Q-TWiST

- How to communicate benefit-risk analysis results?

- When in the development lifecycle should benefit-risk analyses be initiated?
- Do we harmonise them, for a product, for all products?
- What products should be prioritised?
- Where should benefit-risk analysis results be communicated?
- Different Benefit Risk Analyses for different reasons, different countries?
- Concept of a Core Benefit Risk Analysis?

Definition and Purpose of CBR Assessment

- **Definition:** An evaluation of the balance of "observed benefits and harms, as well as the uncertainties and risks" associated with a particular product.
- (EMEA Working Group on Benefit Risk Assessment)

- **Purpose:** to *facilitate decision-making* in the development and/or commercialization of a product.

  (Represents only one perspective! Could apply equally to consumer decision making)

One Benefit-Risk Analysis, But Different Results

- Patients perception
  - May be prepared to take on more risk
  - Time: evaluation - experience
- Prescribers perception
  - Key player in the evaluation of the known benefits to the specific risks for an individual patient
  - Benefit Risk may be easier on a patient, by patient basis
  - May be reason why there is a perception that Generalised B-R should be simple
- Regulatory Authority perception
  - Consideration for a wider population (may be still limited to their region)
  - Cultural considerations
- Health Authority (payer)
  - Finance becomes a component
- Public perception
- Legal interpretation

Regulatory Perspective on CBR Assessment

- *It remains to be seen whether, and in what circumstances, quantitative decision analysis will prove useful, but it is already clear that quantitative approaches—estimated event rates and outcomes, number needed to treat or harm—are useful and revealing about risk–benefit analyses. However, many other factors, as described above, are critical and difficult to incorporate into any single analysis.*

- *Even with the best data available, it seems likely that in many cases, perhaps most, conclusions will turn on qualitative judgments, which are important to reveal and*
- *discuss but are not easily scaled. Perhaps most difficult is the common problem of*
- *weighing a very serious risk with benefits other than survival that are broadly experienced.*

- -R. Temple *Clin Pharm Ther* 2007

Industry Perspective on CBR Assessment

Tradeoffs are based on clinical judgment or past experience, and outcomes may vary widely based on different assumptions made by clinicians or members of the team. Teams tend to be optimistic in expectations or be champions of their drug. In addition, team members may prefer the approach of 'We'll know it when we see it' rather than committing to specific criteria. The discussions within a team of what constitutes a 'winning' profile are crucial in exposing differences in expectations…provides a basis for more transparency and facilitates the debate on the importance of different assumptions.

"Assessment of the value of different attributes is often part of a target product profile that may be generated by other parts of the organization and may be done early in drug development before the performance of the compound is understood.

Daniele Ouellet, Director, GSK Clin Pharm Modeling & Simulation,
Expert Opin. Drug Saf 2010. 9:289-300

Patient Perspective on CBR Assessment

The New York Times
Well
Tara Parker-Pope on Health

DECEMBER 14, 2009, 5:04 PM

When Lowering the Odds of Cancer Isn't Enough

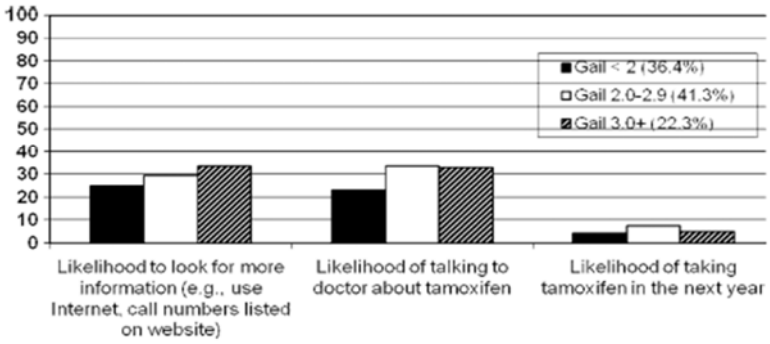
By TARA PARKER-POPE

If someone invented a pill to cut a cancer risk in half, would you take it?

Who wouldn't?

Apparently the answer is millions of women — people like Cindy Birkhold of Sarasota, Fla.

Fig. 2 Percent of women expressing interest in tamoxifen by Gail score



[Some] Areas Where Decision Making Could Improve?

Determining whether benefits outweigh risks given multiple outcomes:

- Piecemeal integration of individual outcomes. Arbitrary weighting.

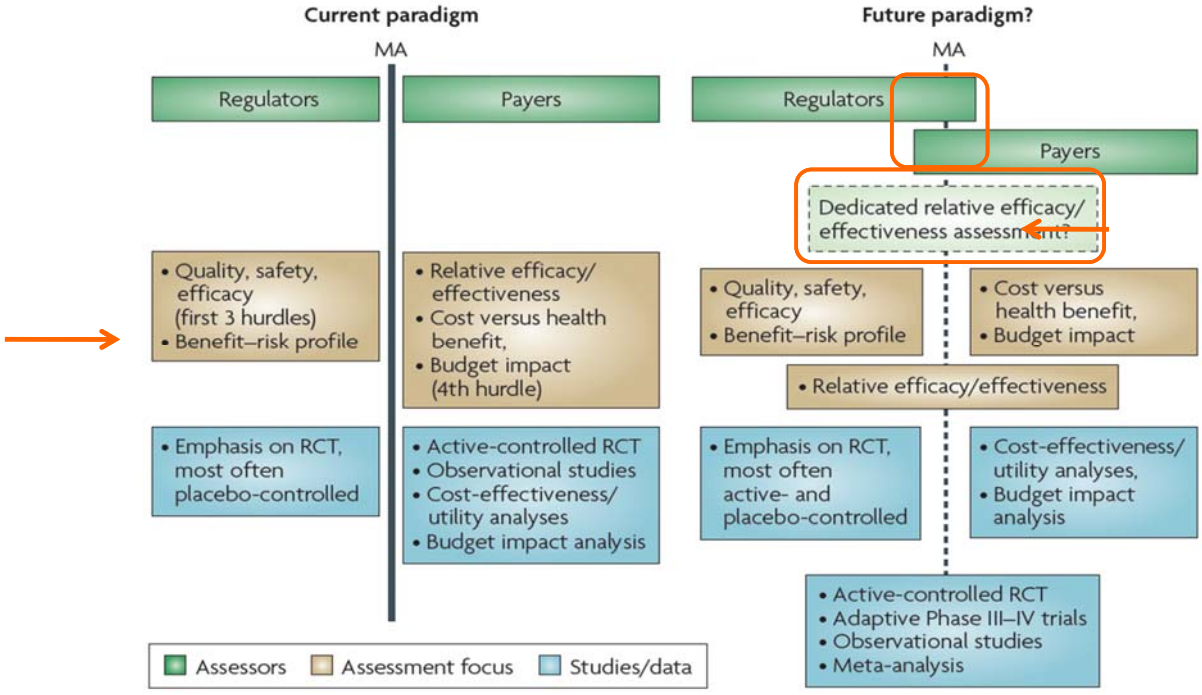
Measuring and translating uncertainty for decision-making:

- Confidence intervals for an endpoint don't describe decision uncertainty.
- We establish statistical significance…what of clinical relevance? (external validity of outcome measures/endpoints).
- Subjective interpretation of uncertainty, without valuations from consumers.

Lack of organizational processes to ensure consistent, inclusive,

Changing Interface between Different Decision Makers (e.g., Payers, Regulators)

The anticipated evolution of relative efficacy assessment



Eichler et al. *Nature Rev Drug Disc* 2010. 9:277-291

EU vs US: Different Landscape May Result in Slower US Uptake to New approaches in CBR

- Politics and the fractured healthcare system in US continues to destabilize the potential link between Payer and Regulatory evidence requirements.
- Single payer markets such as those in EU appear to be weighing more heavily on Regulator's minds (Eichler et al 2010).
- Both EU and US are becoming more receptive to observational data in regulatory decisions

Why are Better Methods of CBR Needed in Drug Development Today?

"Assessment of the value of different attributes is often part of a target product profile that may be generated by other parts of the organization and may be done early in drug development before the performance of the compound is understood.

"Presently, CBR is based on clinical judgment or past experience, and outcomes may vary widely based on different assumptions made by clinicians or members of the team.."

"Teams tend to be optimistic in expectations or be champions of their drug and may prefer the approach of 'We'll know it when we see it' rather than committing to specific criteria.

Therefore:
"The discussions within a team of what constitutes a 'winning' profile are crucial in exposing differences in expectations…provides a basis for more transparency and facilitates the debate on the importance of different assumptions."

D. Ouellet (GSK, Dir. Clin Pharm), *Expert Opin. Drug Saf* 2010. 9:289-300

Recent Developments in CBR Assessment

1998
- CIOMS IV report highlights inadequacy of BR assessment).

2006 – 2008
- FDA, EMA, Health Canada initiate dialog, scope the problem and evaluate options for improvement
  - Series of meetings with stakeholders
  - EMA opinion paper on possible methods

2008 – 2009
- EMA, FDA solicit research proposals to assess BR methodologies.
- **EMA modifies BR assessment section of EPAR template…more explicit. Improving CBR not an option.**

2010
- FDA unveils a qualitative CBR "grid" framework.
- EMA (Lönngren and Eichler) endorsing CBR outcomes models
- CHMP exploring consensus-driven methods (2010 white paper).

2011
- FDA drafting 5-year plan to modernize CBR assessment
- EMA Pharma package: CBR to be included in RMP, PSUR, PASS/PAES

Traditional CBR Assessment

Primary Efficacy Endpoint	Drug X	Pbo
% with >10% LDL reduction	20%*	5%
% with >5% LDL reduction	40%*	7%
*$p < 0.05$		

25 tables later…

Serious AEs Reported by >2 patients	Drug X	Pbo
Gastrointestinal	5%	2%
Rhabdomyolysis	0.8%	0%

"Ad Comm Briefing Document"

Traditional Benefit-Risk Statement

In summary, the benefits of Drug X in treating hypercholersterolemia has been demonstrated.

The overall benefit/risk assessment of Drug X in patients with hypercholesterolemia is favorable. Drug X provides a new therapeutic option for patients.

Opportunities for Improvement in CBR Assessment

Integrated not separate display of summary efficacy and safety data (Table 1…Table 26?).

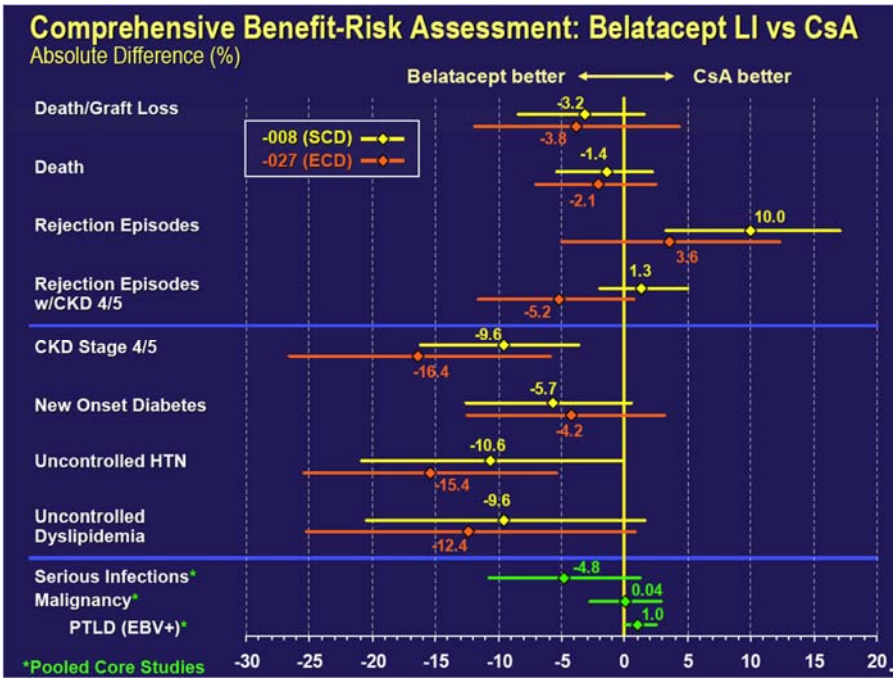
Measures of uncertainty?

Display of comparative effects (additive or multiplicative)?

Translation of observed treatment effects into clinical terms?

Clear rationale: why observed efficacy offsets harms?

New CBR:
ex- belatacept for kidney transplantation

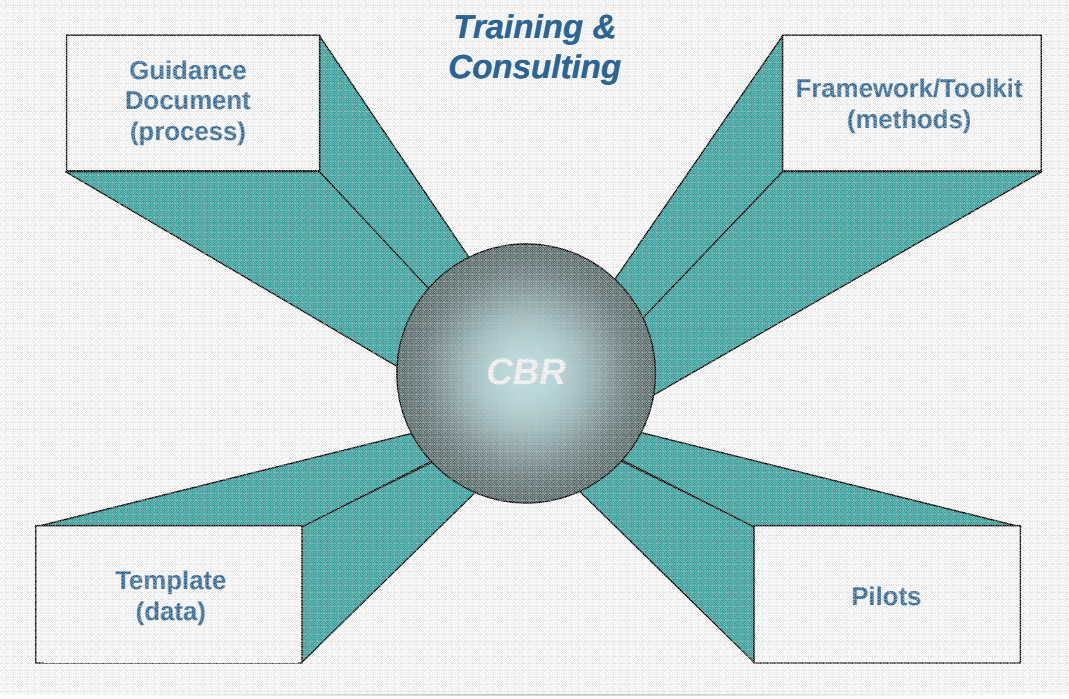


FDA AdComm Feedback

"Slide 77 …was particularly informative, summarizing the net benefit and risk point estimates using absolute risk."
(p.236-237)

"I voted yes. That's based on, as I said before, the totality of the information, in particular, the benefit relative to the survival of the graft and the patient, as demonstrated by both sponsor and the FDA, and the potential benefits relative to cardiovascular and metabolic endpoints." (p.391)

Building Comparative Benefit Risk into Development



Roche/GNE CBR Working Group: Moving from Problem to Solution

Problem	• Although BR assessments are brought to governance bodies such as DRC, assessments are conducted on a situational basis and there is not specified guidance or method around CBR. The conclusions about BR tradeoffs are therefore not always transparent or systematically reached.
Solution	• Increase effective communication and collaboration among core and supporting functions to make more informed decisions, by developing a more systematic and integrated approach to CBR assessment. • To develop Guidance, Template, and Toolkit alongside pilot examples, so as to provide an understanding of the challenges and opportunities for conducting CBR.

Develop a Toolkit: Framework & Quantitative Methods

A Framework for CBR Assessment

- Step 1: Perspective
- Step 2: Identify Elements
- Step 3: Create the Framework
- Step 4: Modify the Elements, The Framework and Valuations
- Step 5: Weigh Elements within the Framework
- Step 6: Quantify and interpret key BR Metrics

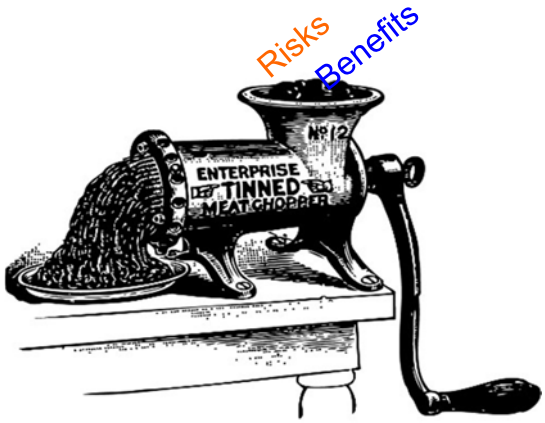
Quantitative Measures for CBR Assessment

- Models for single clinical trials (e,g, NNT/NNH)
- Multi-attribute models (decision analytic models)
- Health outcome, QALY-based modeling
- Conjoint Analysis
- Models for specific products or class of products (e.g., Q-TWiST)

New Approaches to CBR Assessment to Facilitate Decision Making

- Start with a qualitative assessment to figure out what ingredients we have and then build upon it when appropriate with more sophisticated assessments.
- Identify approaches which could facilitate both HTA and CBR assessments.

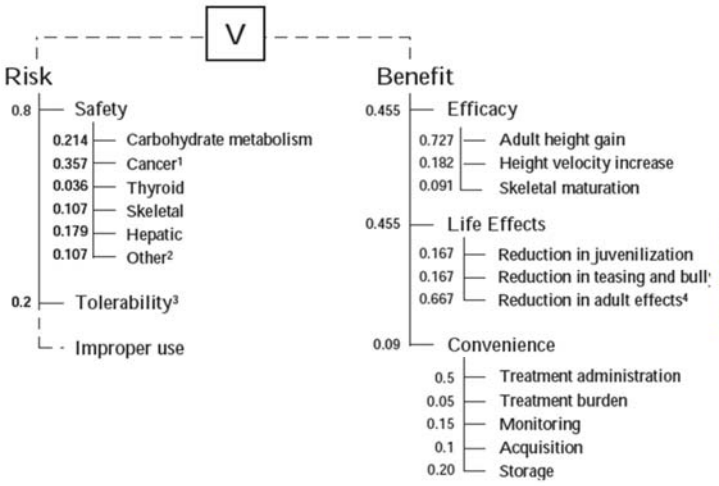
What have we got?



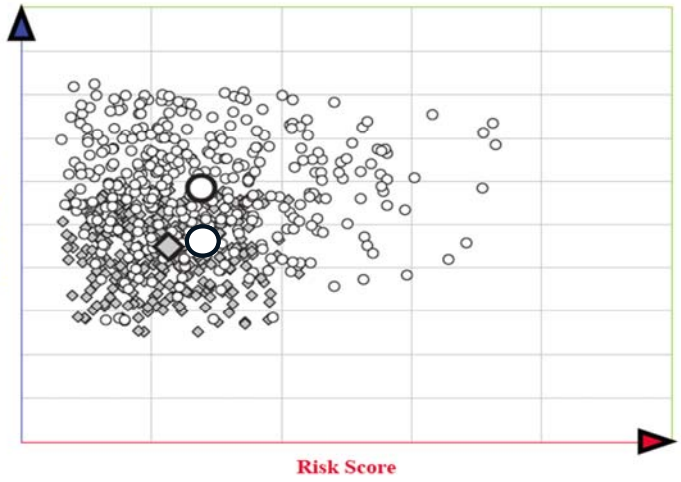
CBR Assessment

Use of MCDA as a Model to Identify Key Benefits and Risks

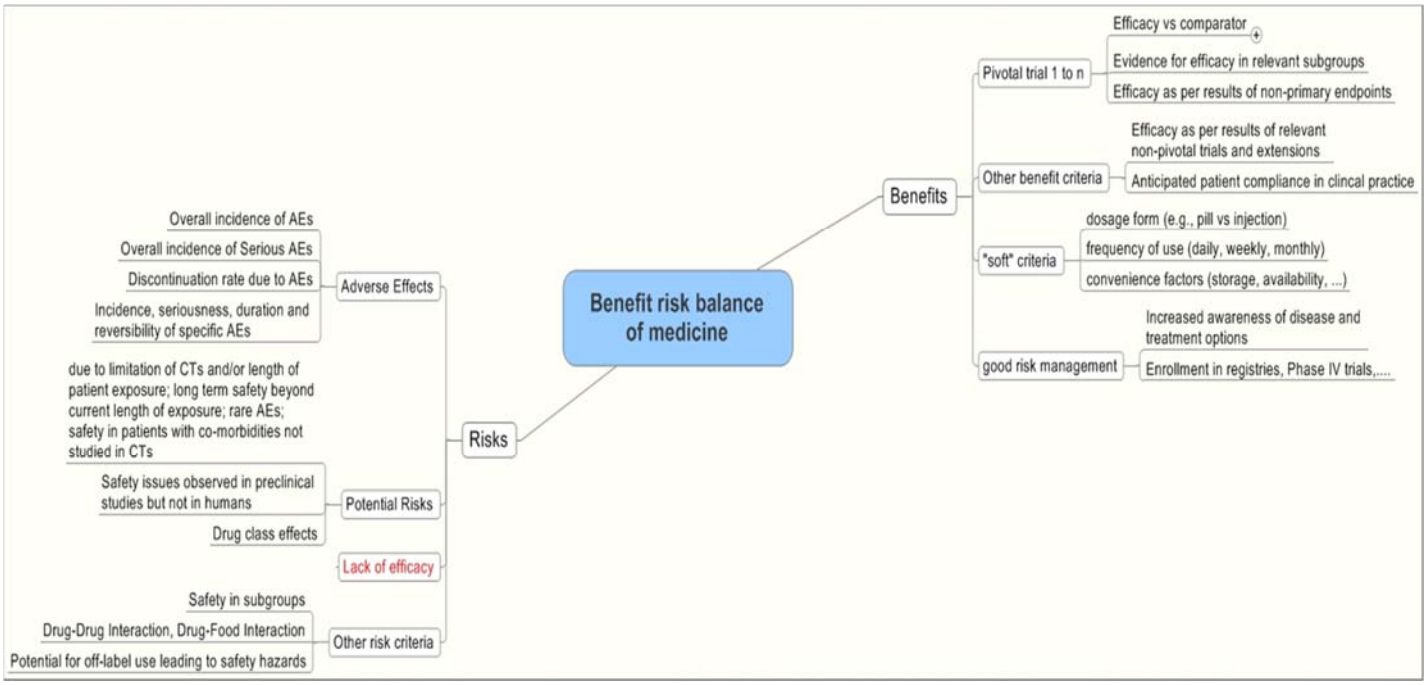
Value tree: Identify key features of CBR and weight them: could facilitate HTA or Regulatory processes.



Risk-benefit plane…cost-benefit plane?

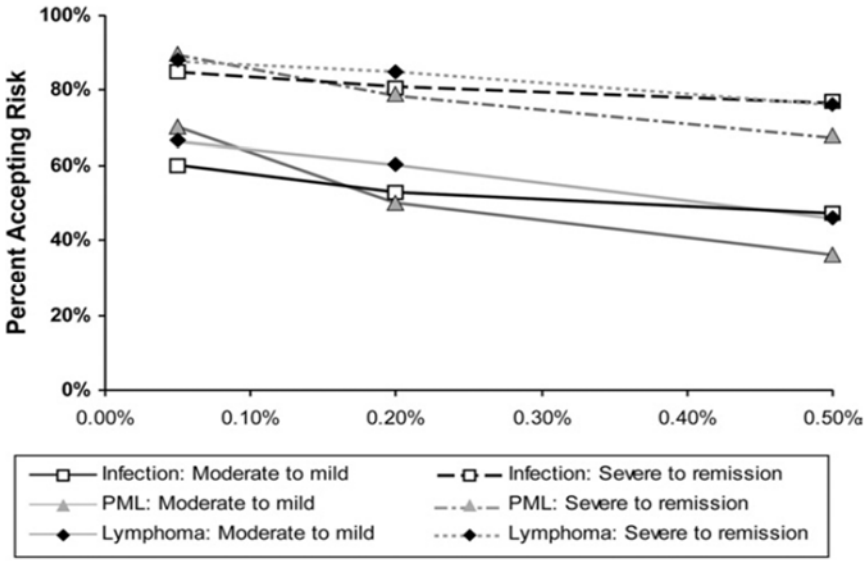


Key B/R Factors around time of approval



Developing Value Propositions for Regulatory, HTA, and Internal Decisions: Understanding Consumer Preferences

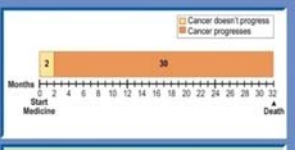
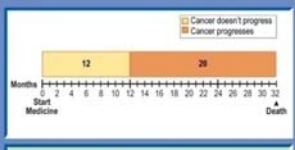
Example: Weighing treatment benefit against harms in the treatment of Crohn's disease



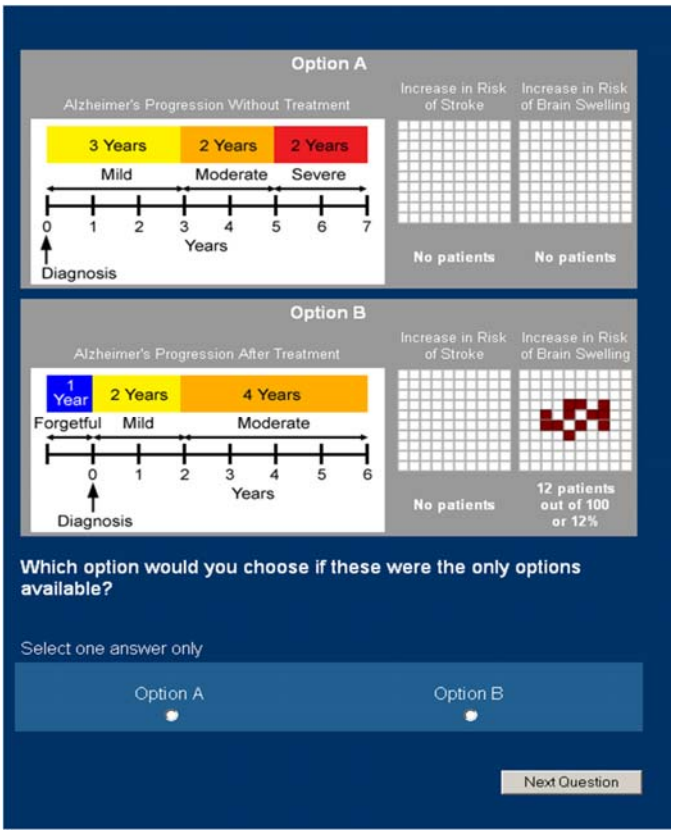
(Johnson FR et al. *Gastroenterol* 2007. 133:769-779)

Example of a Trade-off Question - Renal Cancer

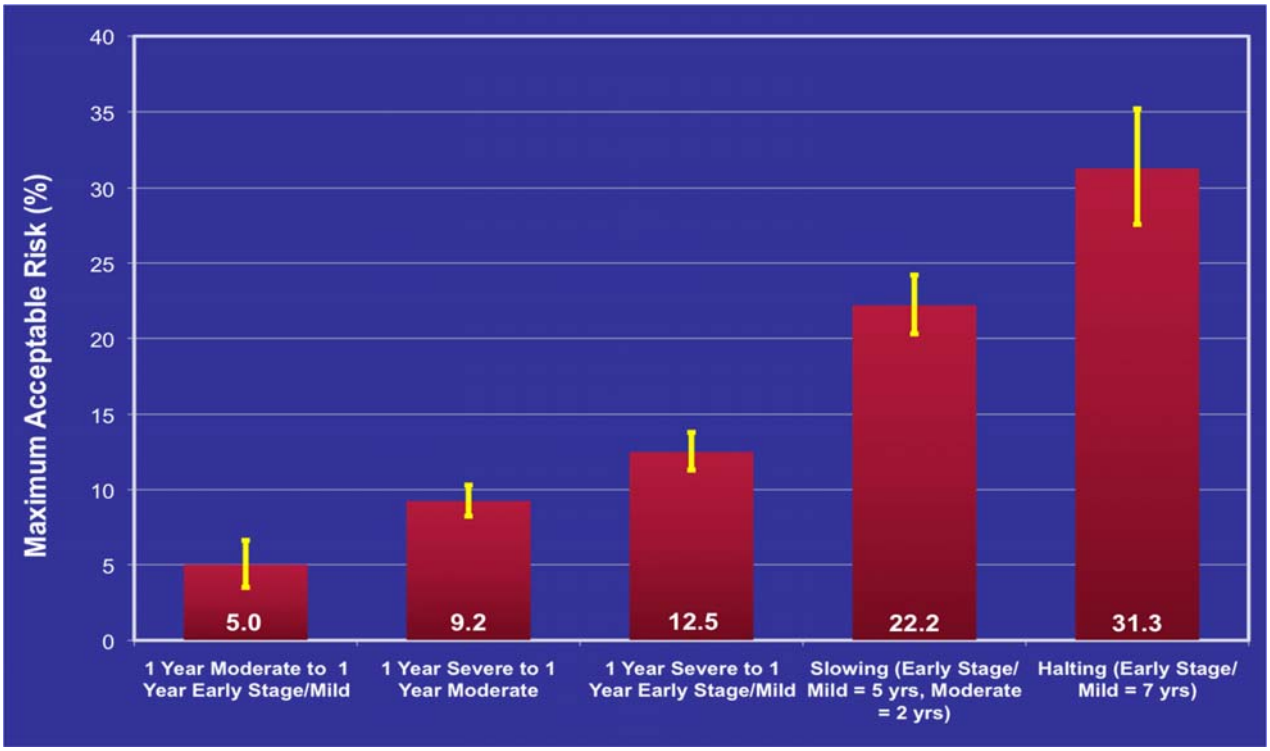
Roche

	Medicine Features	Medicine A	Medicine B
Efficacy	How long you will live after starting to take this medicine and how long the medicine will keep the cancer from getting worse		
Side Effects	Feeling tired	Moderate	Moderate
	Diarrhea	Moderate	Moderate
	Redness and sores on your hands and feet	Moderate	Severe
	Sores in your mouth or throat	Mild-to-moderate	Mild-to-moderate
Serious Adverse-Event Risks	Chance of liver failure	3 people out of 1,000 (0.3%)	No Chance
	Chance of getting a blood clot	30 people out of 1,000 (3.0%)	No Chance
	Which medicine would you choose if these were the only options available?	**Medicine A** ○	**Medicine B** ○

Benefit-Risk Tradeoff Question



Risk Tolerance for AD Disease Modification



Hauber, et al. *Alzheimer's Disease and Associated Disorders, 2009*

Provide Guidance to Provide Process Context

I. Introduction
II. Purpose and Benefits of Structured CBR
III. Assessment
    a. Planning a CBR Assessment
        b. Timing
        c. Responsibility and Accountability
        d. Governance, Interactions, and Decision Making
        e. Engaging Stakeholders
        f. Use of a Template
        g. Data Sources
        h. Use of CBR in Other Documents
        i. Storage and Documentation
    j. Plan for Required Resources: Time, FTE, Costs
IV. Glossary
V. Appendix

Conduct Pilots to Improve Toolkit and Guidance

I. Using the Framework with molecules in different diseases:
   i. Identifying/prioritizing relevant attributes of CBR
   ii. Data tabulation
   iii. Data visualization

II. Conjoint Analysis for **Postmarketing** Purposes
   i. Drug-specific: max acceptable risk, min acceptable benefit

III. Conjoint Analysis for **Premarketing** Purposes
   i. Disease-specific: endpoint identification
   ii. Outcomes modeling: TBD

CBR Is Easier Said Than Done

I. Creating internal awareness of the value propositions

II. Gaining management support to resource activities around core document deliverables

III. "Not in my backyard" attitude from molecule teams
   i. Seen as a potential delay to deadlines
   ii. You might distract project teams

So…"what's in it for me?"

☺A structured approach to understanding and describing the comparative BR profile of a product or set of products would uphold our collective goal to ensure that products we commercialize are ultimately found by patients and clinicians to have favorable comparative BR tradeoffs.

- Greater likelihood of satisfying regulatory approval requirements if new therapeutics provide "value" to patients/clinicians
- Strive toward our goal: "First-in-class, best-in-class"
- Improved resource allocation
- More informative TPP claims:
  - e.g., "Our drug is within the safety margins patients appear willing to accept when given the choice between our drug and drug X"
  - vs., "Our drug is no less safe than drug X"

"What's in it for me"…(continued)

☺By virtue of a structured approach, the **thought process** involved in assessing the BR tradeoffs leads to more productive and efficient communication and collaboration:

1. **Cross-functional** communication and collaboration
   - Constructing a robust BR model/analysis requires understanding of assumptions and their impact on the validity and interpretability of findings…bringing key functions together.

2. **Within franchise** and **team-committee** communication/collaboration
   - Franchise-wide assessment permits consistency across DSTs of a therapeutic area.
   - More explicit interpretation of results for DRC…e.g., RCT results relative to what patients and clinicians value?

Lessons Learned

I. **Know what in the pipeline might make good case studies:**
   i. First in indication/class compounds
   ii. Molecules with a complex CBR profile
   iii. Disease areas with changing regulatory landscape

II. **Have a strong case for how you might help molecule teams**

III. **Know who to involve:**
   i. Regulatory, Safety, Biometrics, Pharmacoepidemiology, Clinical (your *toughest* partner)

IV. **Find less obvious partners, involve them, create champions:**
   i. Early development functions (like tox): they constantly make candidate selections and grapple with BR in doing so.
   ii. Commercial functions (like health economics): develop value propositions for molecules and want a clear understanding of CBR.

And don’ t forget that risk tolerance and the view of BR are prone to change over time

Acknowledgements

Thanks for providing time and expertise

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We Innovate Healthcare