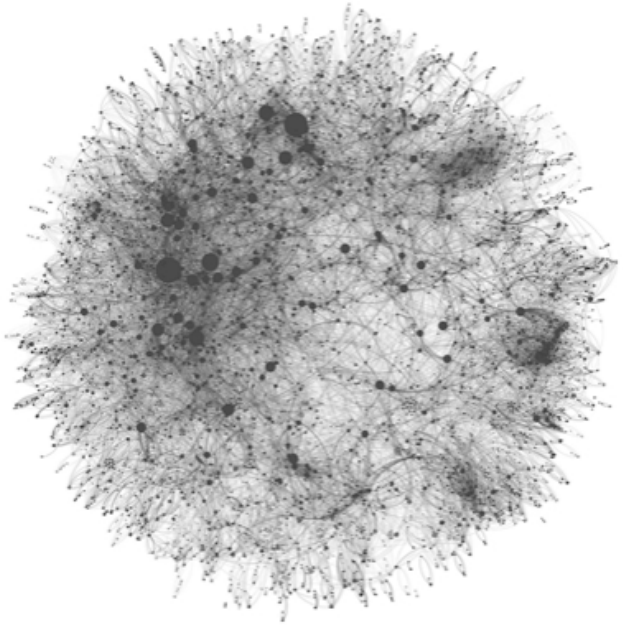
Thoughts on Evidentiary Criteria for Biomarker Qualification: A "Decision Science" Perspective

FDA/CDER/OSP/OPSA

July 2018



The material presented here are the views of presenters and do NOT necessarily reflect agency's position.

Three topics to cover

1. What is decision science?
2. How is decision science relevant to evidentiary criteria for biomarker qualification framework?
3. Has decision science been utilized in other areas in healthcare?

What is decision science?

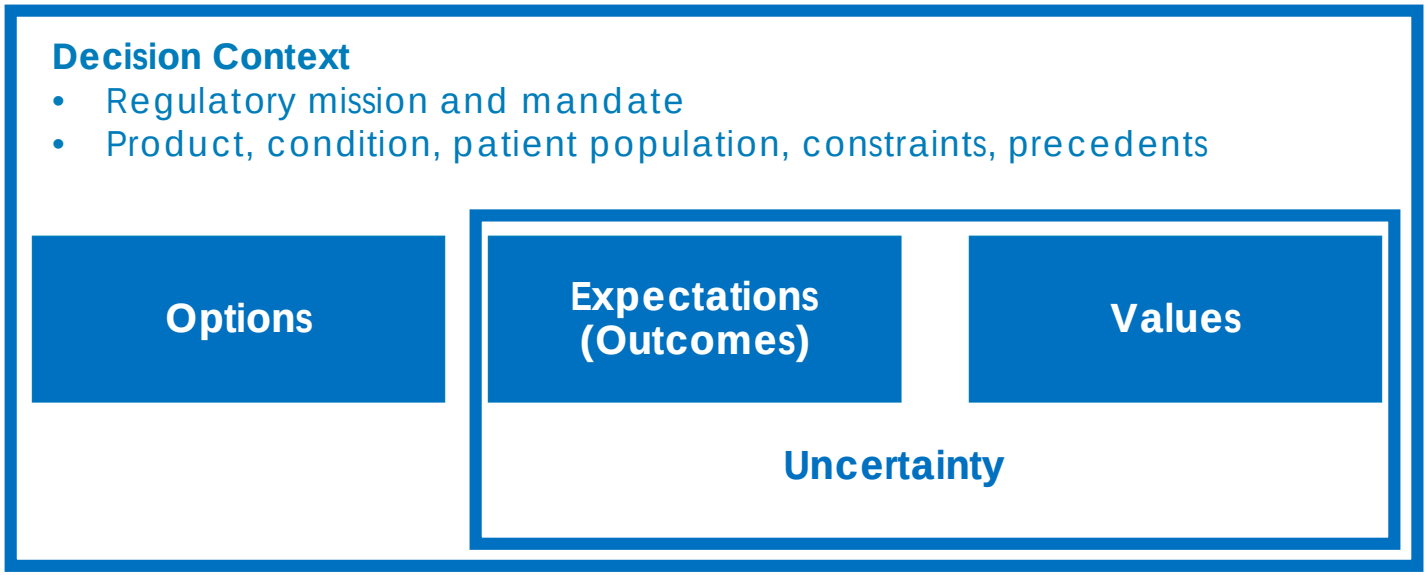
Developing and applying approaches, methods and tools to inform decision making by individuals or organizations

First things first

- What is the decision to be made?
  - Use of biomarkers as a surrogate endpoint in lieu of clinical outcome to support a particular regulatory decision?

- Who is the decision maker?
  - Regulatory decision of benefit –risk tradeoff has to be disease specific

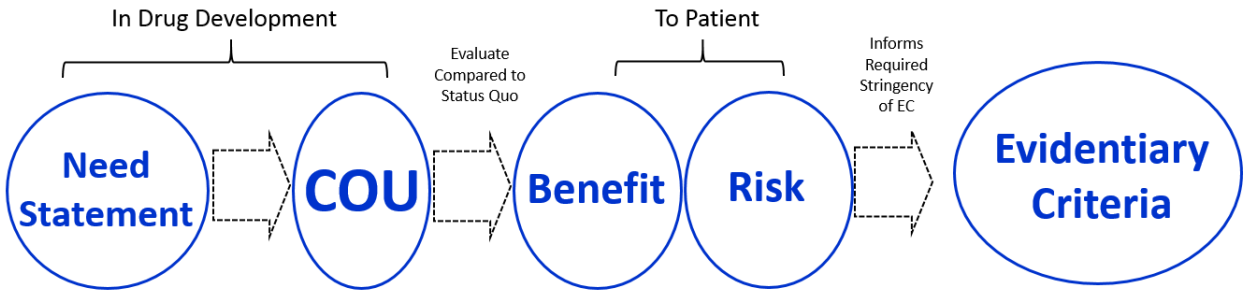
Fundamental elements of a decision



Our job as analysts is to help decision maker, structure the decision and break it down to these elements

How is decision science relevant to evidentiary criteria for biomarker qualification framework?

Evidentiary Criteria Framework



- *Knowledge gap?*
- *Drug development need?*

- *Class of Biomarker?*
- *What is the question the biomarker is addressing?*

- *Improved sensitivity*
- *Improved selectivity*
- *Mechanistic context*

- *Consequence of false positive*
- *Consequence of false negative*

- *Characterization of Relationship Between the Biomarker and Clinical Outcome*
- *Biological Rationale for Use of Biomarker (If Known)*
- *Type of Data and Study Design (i.e. Prospective, Retrospective, etc.)*
- *Independent Data Sets for Qualification*
- *Comparison to current standard*
- *Assay performance*
- *Statistical Methods to Use*

Thoughts on the attributes of this evidentiary criteria framework

- The main question here seems to be about uncertainty
  - How much risk of being wrong and various uncertainties are acceptable, and that is exactly why decision context matters
  - How bad is the expected loss given the status quo, so how much uncertainty are we willing to take for it?

A potential approach to inform decision-making on biomarker qualification

A: Establish the decision context for biomarker qualification

- When: Early in the qualification process (e.g., Letter of Intent)
- Why: Context informs FDA's judgments about tolerance for uncertainty
- Decision context is distinct from Context of Use

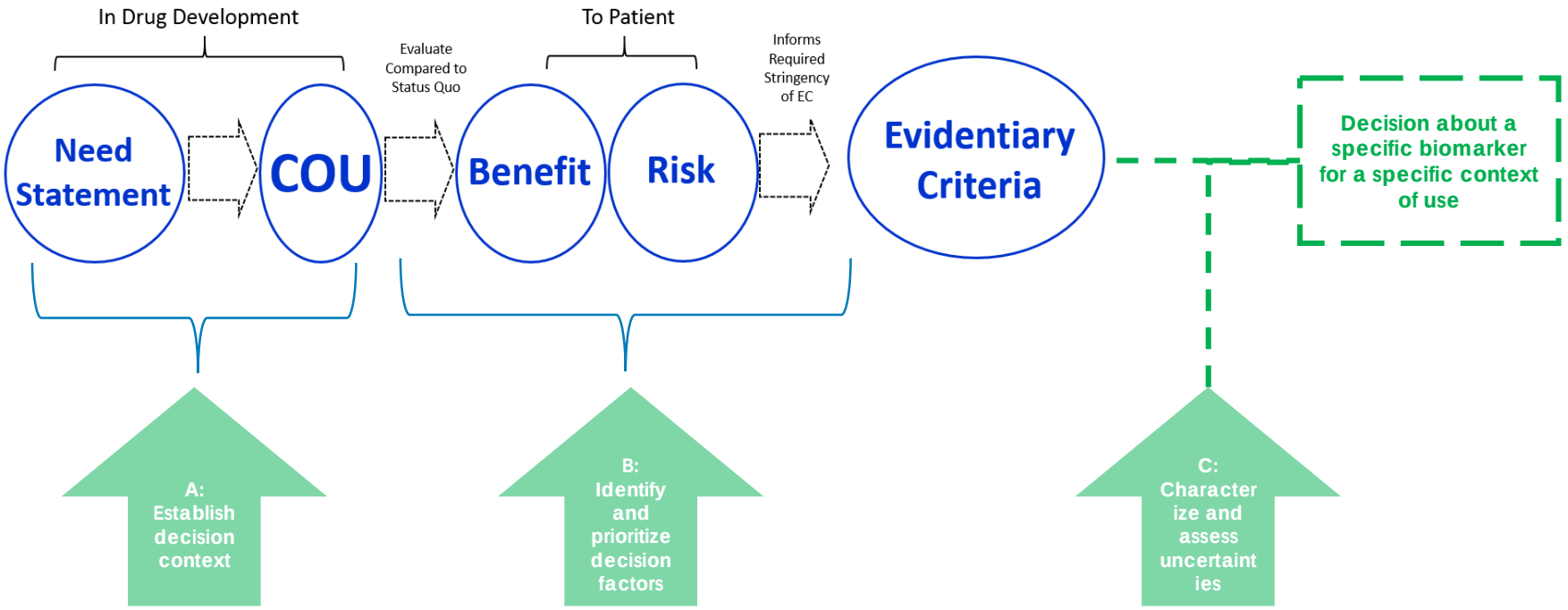
B: Translate decision context into specific evidentiary criteria

- When: Upon early discussion of study design
- Why: Informs FDA's judgments about how evidence will be assessed and factored into decision making

C: Assess the resulting evidence and uncertainties against the criteria

- When: Upon submission of evidence
- Why: Systematic (quantitative) assessments inform FDA's judgments about the totality of evidence, within the decision context

How could it fit to the biomarker framework?



FDA's Benefit-Risk Framework

Benefit-Risk Framework overview

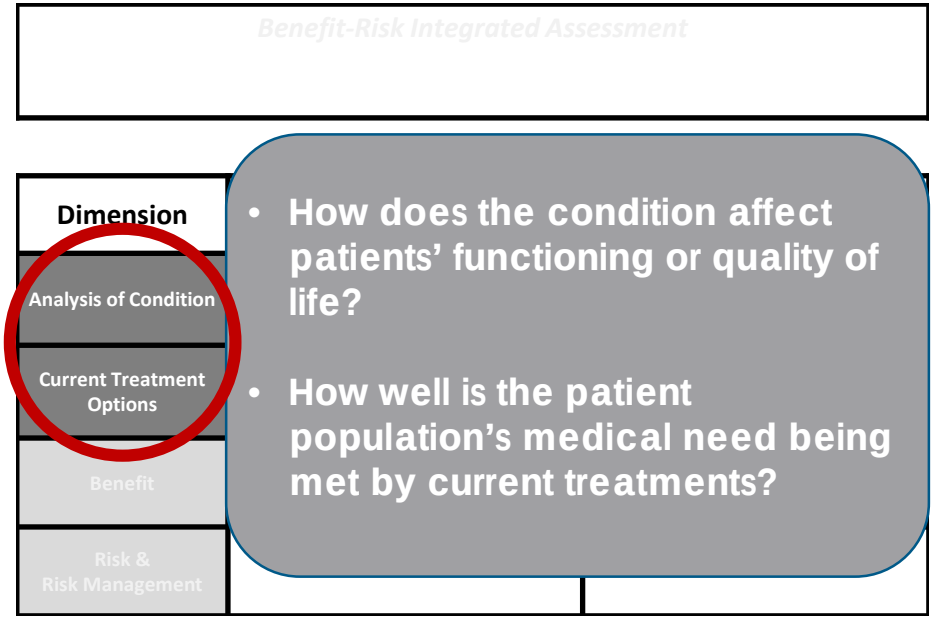
Benefit-Risk Integrated Assessment		

Benefit-Risk Dimensions

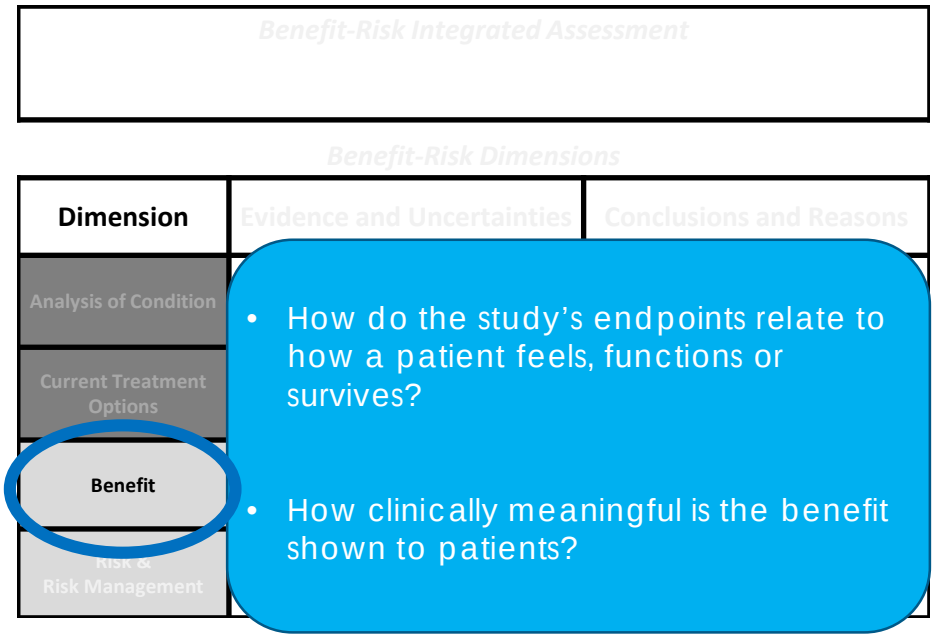
Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk & Risk Management		

- FDA determined that a structured qualitative approach best fit its needs
- Reflects reality: B-R assessment is a qualitative exercise
- More rigorously communicates the basis for decisions
- Flexible to accommodate supporting quantitative analyses

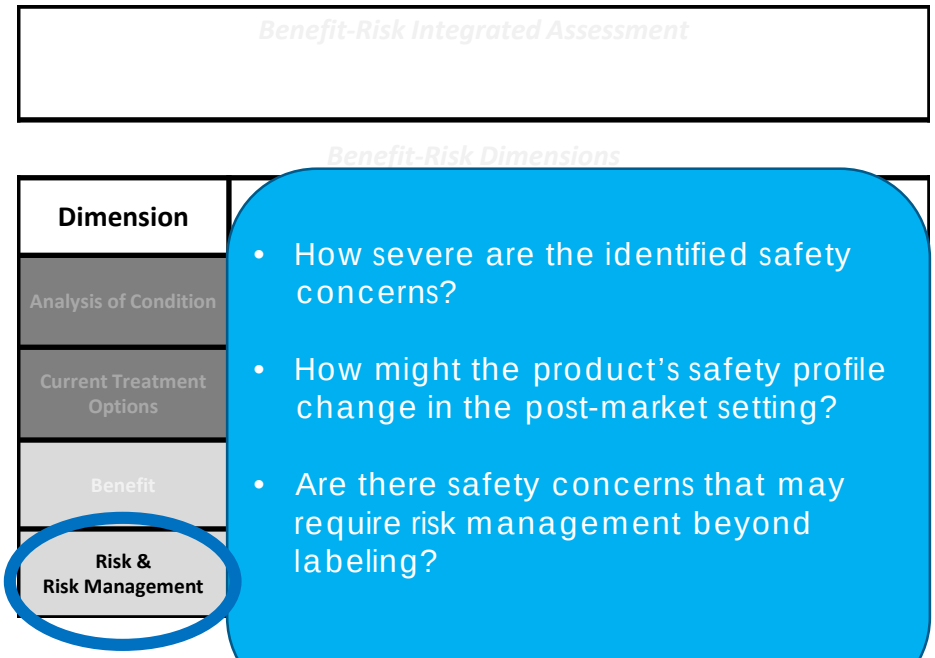
Sample Framework Questions



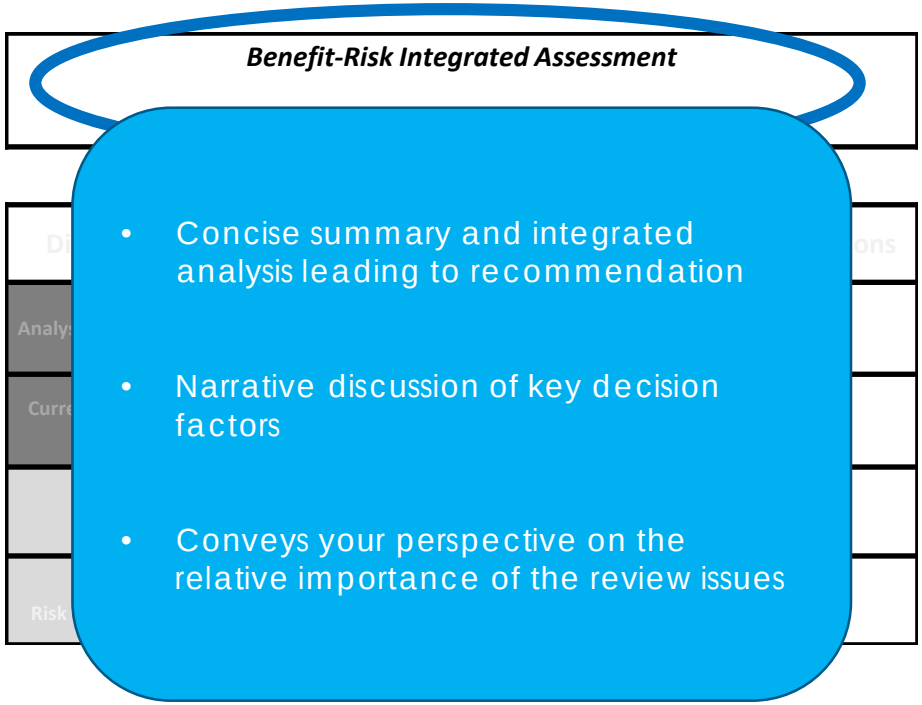
Sample Framework Questions



Sample Framework Questions



Providing an Integrated Narrative



Thoughts on the Benefit-Risk Framework

- To move to any form of a quantitative approach, a first step is characterization of elements of benefits (and risks)

- This breaks down the parameters of the problem to smaller "bite-sized" elements that are easier to assess
  - Either observable data is available
  - Or experts are more comfortable and confident to provide estimates

Quantifying Benefit & Risk

A Fundamental Challenge

- "our current inability to specifically quantitate benefit, risk or value of individual data sources prevents a direct, strictly-quantitative link from benefit and risk to the amount of evidence needed to qualify biomarker"…

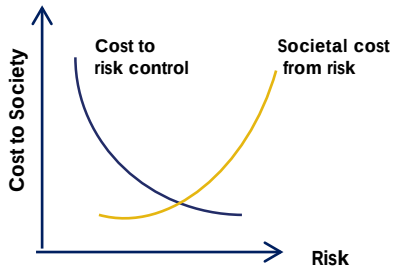
(Framework for defining evidentiary criteria for biomarker qualification, 2016, page 23)

Quantification of benefit and risk

- What might be helpful?
  - Decision making under uncertainty techniques
  - Relevant examples in healthcare

Decision making and uncertainty (1)

- One categorization of methods is
  - Economic Techniques
    - Decision relies on the economic viability
    - Methods include:
      - Cost benefit analysis
      - Value of money
      - Cost-Effectiveness analysis
        - Williams et al (2006)
          - "limited practicality given the difficulty of measuring "cost" defined as societal harm"
      - Risk-Effectiveness analysis

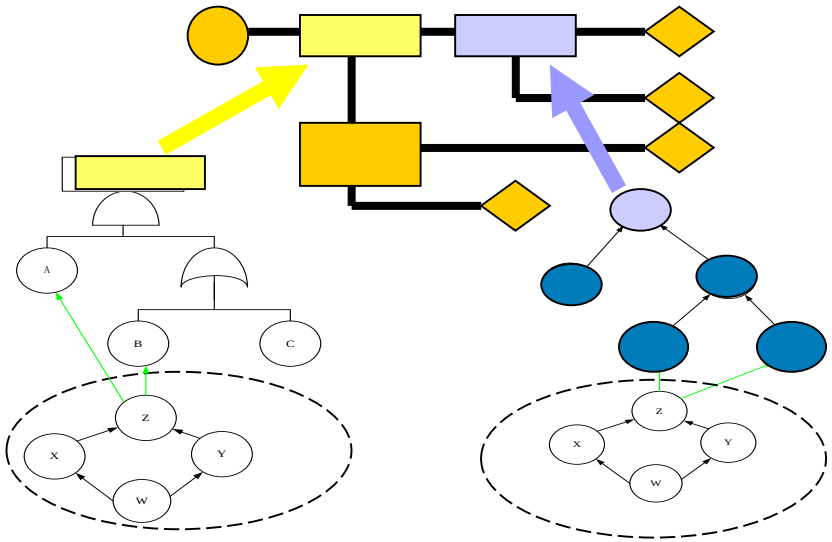


- Reference: Risk analysis in engineering, M. Modarres, 2006

Decision making and uncertainty (2)

- Non-economic Techniques
  - Useful in cases involving multiple factors and tradeoffs
  - Methods include
    - "Probability of exceedance" method
      - If you can set an acceptance criteria for frequency, or consequences
    - Structured value analysis
      - Value functions for cost, risk , time, … parameters and assign importance weights (determined by SMEs)
    - Analytical hierarchy process
      - Systematically prioritizing between multiple criteria (pairwise comparison)
      - Multi criteria decision analysis (MCDA)
    - Decision tree analysis

In decision analysis, we break down complex decisions into smaller, measurable components



- Probabilistic risk assessment procedures guide for NASA managers and practitioners, NASA, 2011
- System and Methods for Assessing Risk Using Hybrid Causal Logic, A. Mosleh, 2010 (Patent)

What if we don't have enough data (observations)?

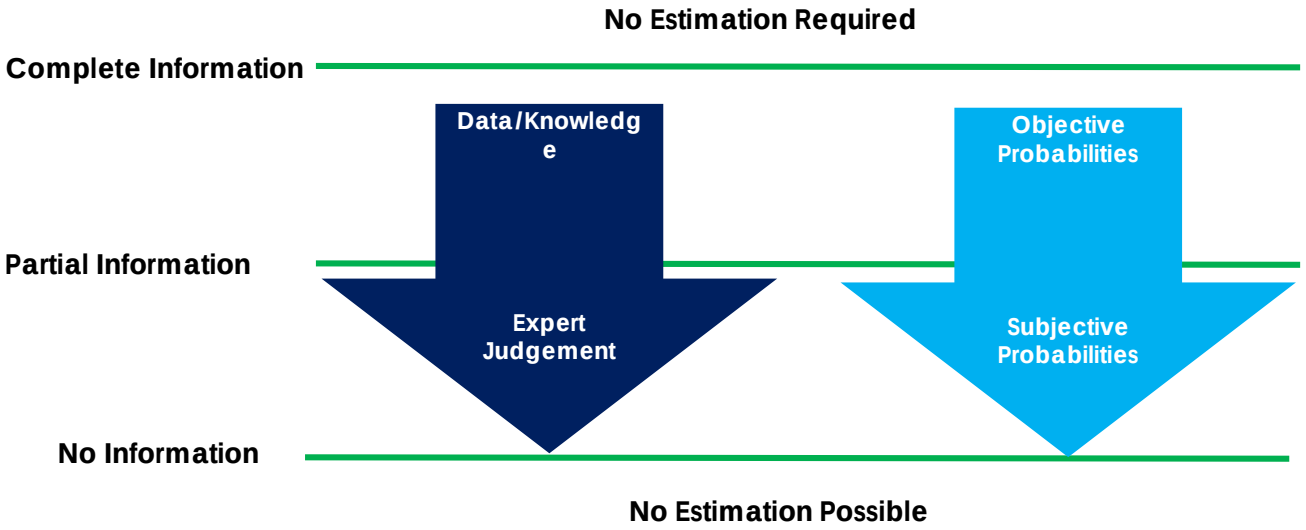
- Subjective information/data might help
- We can study methods to elicit experts' quantified judgments within this framework
  - *How do you quantify the value of a clinical outcome versus a surrogate endpoint?*
- Expert elicitation is common practice in other safety sensitive organizations where data is scarce or unavailable
  - Aerospace (e.g. NASA) and Nuclear industry (e.g. NRC) have extensively researched, published and used expert elicitation

Expert elicitation is common in other technical fields

- Severe Accident Analysis (NUREG-1150, 1990)
  - Elicited probabilities and consequences in risk studies of accidents where operational data was unavailable
- Seismic Hazard Analysis (1988)
- Expert judgment elicitation and calibration methodology for risk analysis in conceptual vehicle design (NASA, 2004)

- Branch technical position on the use of expert elicitation in the high-level radioactive waste program, NRC, 1996
-Use of expert elicitation at the USNRC. R. Frye, 2013

Objective and subjective information

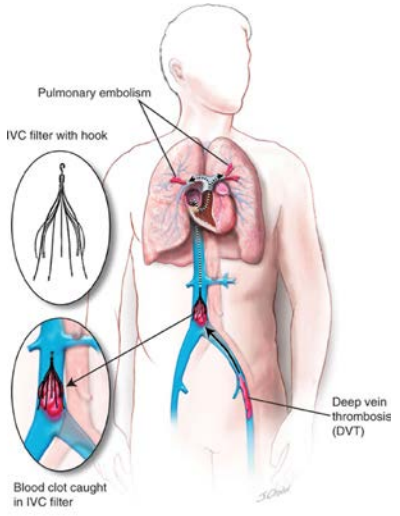


Content and concept taken from: "Expert Elicitation of a Maximum Duration Using Risk Scenarios", 2014, Nasa Cost Symposium, NASA Langley Research Center

Has decision science been utilized in other areas in healthcare?

Example 1: IVC filter removal decison

- Retrievable filters used preventively in patients without pulmonary embolism (PE) but at transient risk
- Device is often not removed after decline in PE risk
- Decision analysis method is used to assess benefit and risk of retrievable filters as a function of time in situ



Decision analysis of retrievable inferior vena cava filters in patients without pulmonary embolism, Jose Pablo Morales, MD, Xuefeng Li, PhD, Telba Z. Irony, PhD, Nicole G. Ibrahim, PhD, Megan Moynahan, MS, and Kenneth J. Cavanaugh Jr, PhD, Journal of Vascular Surgery, 2013

Background

- IVC filter use in the US continues to increase.
- Non-retrievable practices

- Postmarket adverse event reports suggest that the number of filter-related events has risen over the past decade
  - The most common adverse events associated with IVC filters include:
    - IVC thrombosis,
    - deep vein thrombosis (DVT),
    - access site thrombosis,
    - filter migration/embolization,
    - caval penetration, and
    - filter fracture

- Unknown Public Health Impact

Decision analysis model

- A decision analysis model was developed to assess the risk/benefit profile of IVC filter use over the potential life of the implant
  - Emphasis was placed on the off-label prophylactic use of these devices once they had already been implanted as per clinician judgement (e.g. as part of trauma care or bariatric and orthopedic surgery)

- What is the time on which the risk on having the device *in-situ* outweigh the benefits?

Decision context

- If/When Should the IVC Filter Be Removed

- No controlled study to address
  - device related AE may vary with time
  - continued impact of implant duration

- A quantitative decision analysis has been used as an alternative

Definition of benefits/risks

- Risk Score at time *t* for a specific adverse event (AE) is defined as the cumulative occurrence rate from time *0* to *t* times the Weight.

$$RS_{AE}(t) = Weight_{AE} \times \int_0^t OR_{AE}(s)ds$$

- Net Risk Score:

$$NRS(t) = RS_{in-situ}(t) - RS_{no-filter}(t) - RS_{removal}(t)$$

- Turning point: the time the Net Risk Score starts to increase.

Method and Data for Estimating Risk

- Use of quantitative decision analysis model to analyze the time dependent, relative risks of
  - Implant
  - Retrieval
  - Or continued implantation

- Data from 19 clinical studies and expert judgement

Occurrence rates: point estimates

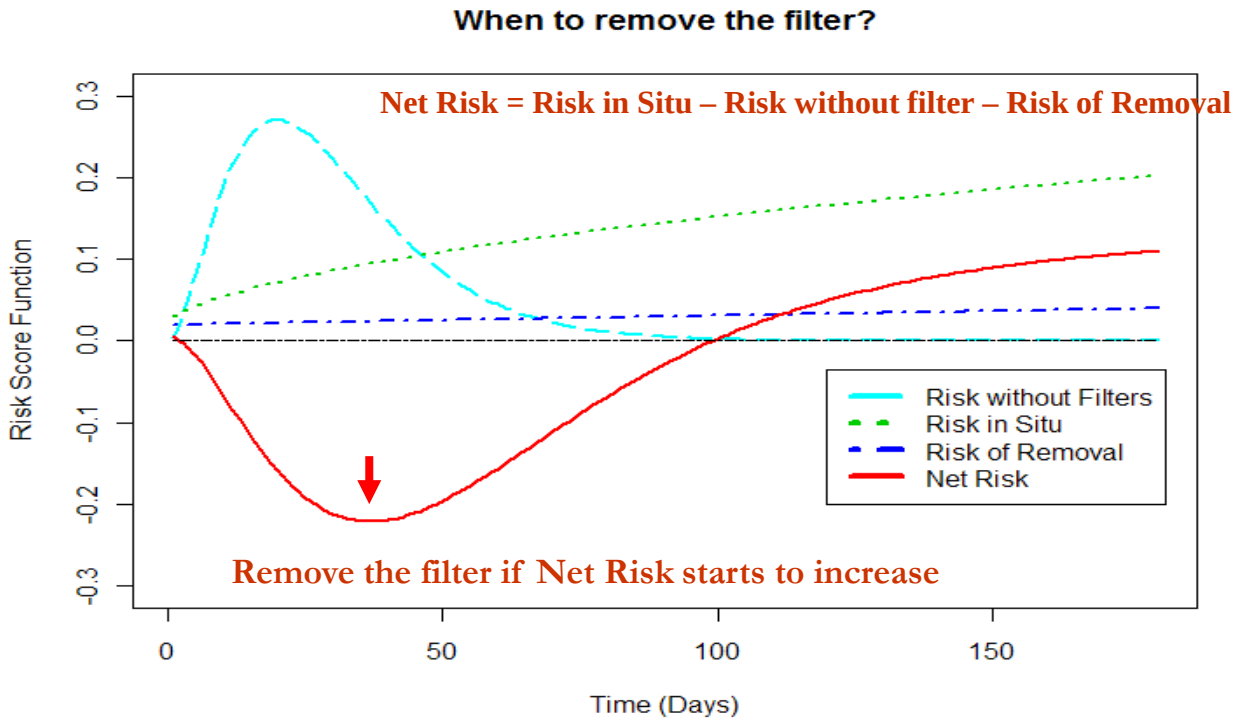
	Rate of Occurrence		
Adverse Event	**0 to 30 days**	**31 days to 6 months**	**6 months to 2 years**
Death	0%	0%	0%
Recurrent PE	4%	1%	0%
Occlusion	0.20%	1%	2%
Filter Emboli	0.10%	0.50%	1%
Migration	0.10%	0.50%	2%
Penetration	0.10%	0.50%	1.50%
Fracture	0.10%	0.50%	1%
DVT	0.50%	2.00%	6%
Retrieval Complication	3%	3%	4%

Risks and weights (severity)

- Risks
  - Risk without filters (Benefit of filters)
  - Risk in Situ
  - Risk of removal
- Weights
  - Relative severity
  - Measure all risks in the same scale
  - Worst case: 10

		Severity of Consequences	
	Adverse Event	Weight (Ranges)	Wright (point Estimate)
Risk w/o filters	Death	10	10
	Recurrent PE	7-9	8
Risk in Situ	Occlusion	4-6	5
	Filter Emboli	7-9	8
	Migration	2-4	6
	Penetration	5-7	3
	Fracture	3-5	4
	DVT	4-6	5
Risk of Removal	Retrieval Complication	2-4	3

Results


When to remove the filter?
Net Risk = Risk in Situ – Risk without filter – Risk of Removal
Risk without Filters
Risk in Situ
Risk of Removal
Net Risk
Remove the filter if Net Risk starts to increase
Risk Score Function
-0.3
-0.2
-0.1
0.0
0.1
0.2
0.3
0
50
100
150
Time (Days)

Conclusions

- Quantitative decision analysis suggests that if the patient's transient risk for PE has passed, the risk-benefit profile begins to favor removal between 1 and 2 months.

- While there are limitations in the analysis, particularly related to the paucity of patient data for prophylactic use, the analysis supports the recommendations of the FDA and the clinical community:
  - filter removal should be considered for individual patients whose transient increased risk of PE has diminished.

Example 2: MCDA for Diabetes Type 2 Treatment Decision Making*

- Goal of the study: Using multicriteria decision analysis (specifically Analytical Hierarchy Process(AHP)) in decision-making for type-2 diabetes medication

- Method of the study: Expert elicitation with nine diabetes experts, to rank add-on (to metformin) therapies
  - Treatment alternatives are compared relative to eight outcomes and relative importance of different outcomes

Treatment alternatives

- Pioglitazone
- Sulfonylureas
- Sitagliptin
- Exenatide
- Metformin

Outcomes

- Reduce HbA1c (benefit)
- Risk of fracture (harm)
- Weight gain (harm)
- GI symptoms (harm)
- Sever hypoglycemia (harm)
- CHF risk (harm)
- Acute pancreatitis (harm)
- Risk of bladder cancer (harm)

* Maruthur, et al., Use of the analytic hierarchy process for medication decision making in type 2 diabetes, 2015

Background

- 11 additional classes of add-on medication to metformin are available
- Treatment-related benefits and harms may not be fully known at the time of approval
- Patients, providers and regulatory decision makers view importance of treatment related outcomes differently
  - Likelihood of these outcomes and their importance from each stakeholder's view point should be considered
- A quantitative framework which integrates evidence on treatment related benefits and harms with preferences on trade-offs between benefit and risks is necessary to support treatment decision

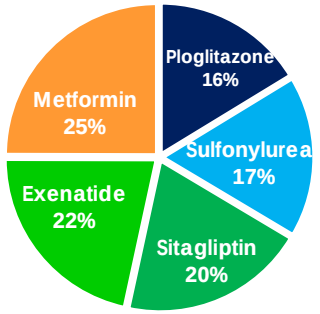
Results

- Experts are asked to weigh their preference for maximizing benefits versus minimizing harms for metformin monotherapy and non- insulin add-on agents
  - The process yields experts' prioritization of harms as well

Global priority scores of objectives

Objective Global Priority Score	%
Maximizing benefits	54.83
Reduce HbA1c	54.83
Minimizing harms	45.17
Minimizing non-serious harms	14.79
Risk of fracture	2.57
Weight gain	7.65
GI symptoms	4.57
Minimizing serious harms	30.38
Severe hypoglycemia	14.01
CHF risk	7.96
Acute pancreatitis	4.46
Risk of bladder cancer	3.95

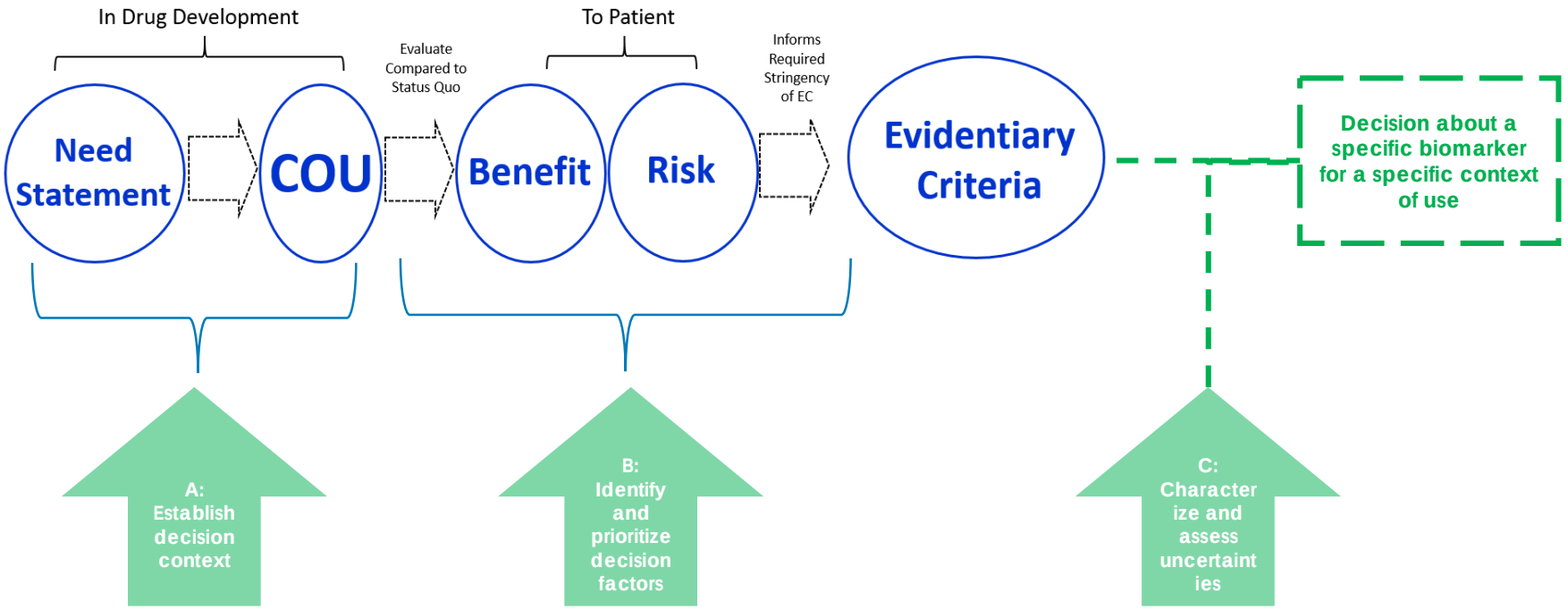
Priority score for treatment alternatives%



Decision science adds value by helping experts and decision makers **focus their efforts on what matters most** to the decision at hand

- Make sense of the decision problem
- Articulate goals and priorities
- Justify evidence requirements
- Focus deliberation on decision-relevant issues
- Clarify areas of agreement and disagreement
- Explore uncertainty and its implications
- Help communicate to a broader audience
- Help with consistent and transparent decision making

How could it fit to the biomarker framework?



Appendix: A potential approach to inform regulatory decisions on biomarkers

A potential approach to inform regulatory decisions on biomarkers

Ideally, upon LOI submission or similar early engagement on proposed biomarker

A Establish the decision context

- Assess state of drug development in disease area or population
- Articulate current **benefit-risk framework** for drug development
- Identify key consideration on the potential use of biomarker to inform regulatory decisions

Context informs FDA's judgments about tolerance for uncertainty about DDT's relevance and performance

Ideally, upon early discussions on study design

B Translate decision context into evidentiary criteria

- Identify discrete, measurable factors that will have the most bearing on FDA's decision-making
- For each factor, determine the *type* and *level* of evidence that will best support acceptance of the biomarker in context of use

Evidentiary goals informs FDA's judgments about how evidence will be assessed and factored into decision making

Upon submission of evidence

C Assess the resulting evidence and uncertainties against the criteria

- Characterize and assess the quality of the evidence and the attendant uncertainties
- Map the evidence and uncertainties against the established evidentiary criteria
- Assess the sensitivity of decision making to uncertainty in the evidence
- Determine whether additional information may be necessary

Systematic assessment informs FDA's judgments about the totality of evidence, within the decision context