Structured Benefit-Risk Optimization (BRO)

State-of-the-art and Role of Fully Quantitative Decision Support Tools

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These are my views not necessarily those of companies, academics or regulators that I am or have been affiliated or worked with.

Topics

- evolution of *structured* benefit-risk
- state-of-the-art
- value of frames
- implications

In the Eye of the Beholder

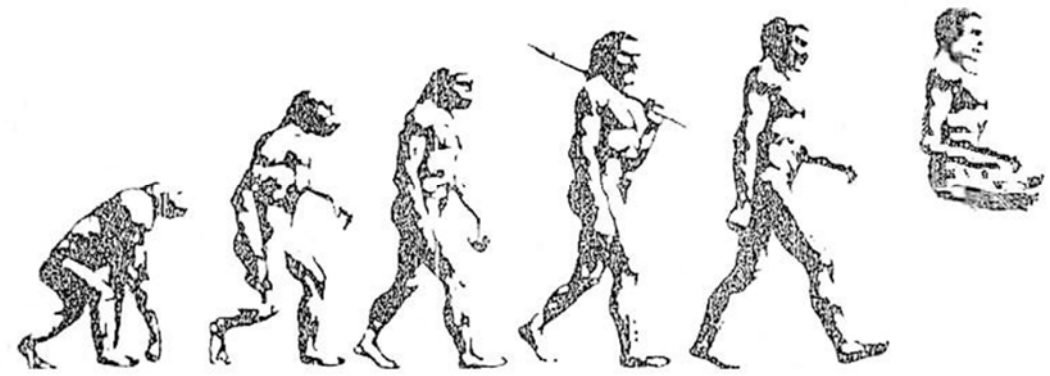
- Cardiologist
- pharmaceuticals, non vaccine biologics (including Tysabri) and vaccines
- PhRMA Risk Management Steering Committee
- past Vice-chair PhRMA Benefit-Risk Action Team (BRAT) and current core member
- member Next Steps Working Group (NSWG) - EMA, FDA, Health Canada, Academia & Industry

Not a 'Quant' but ...

- Clinical Epidemiology (McMaster with Sackett *et al*)
- Biometrics (Cedars-Sinai)
- research in expert systems
- developed static & dynamic statistical predictions models for use in expert systems (e.g., Rand Corporation - Kalman filters)

Evolution of Benefit-Risk Balance

… to benefit-risk optimization



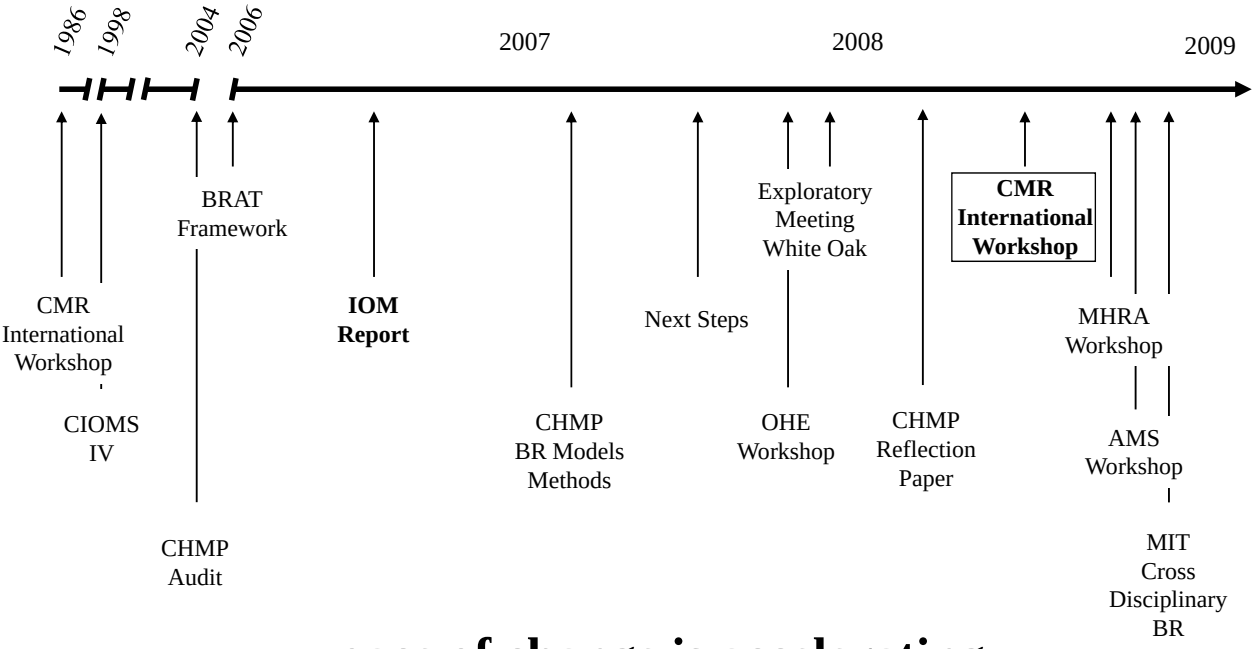
BRM-2011 *

BRO *

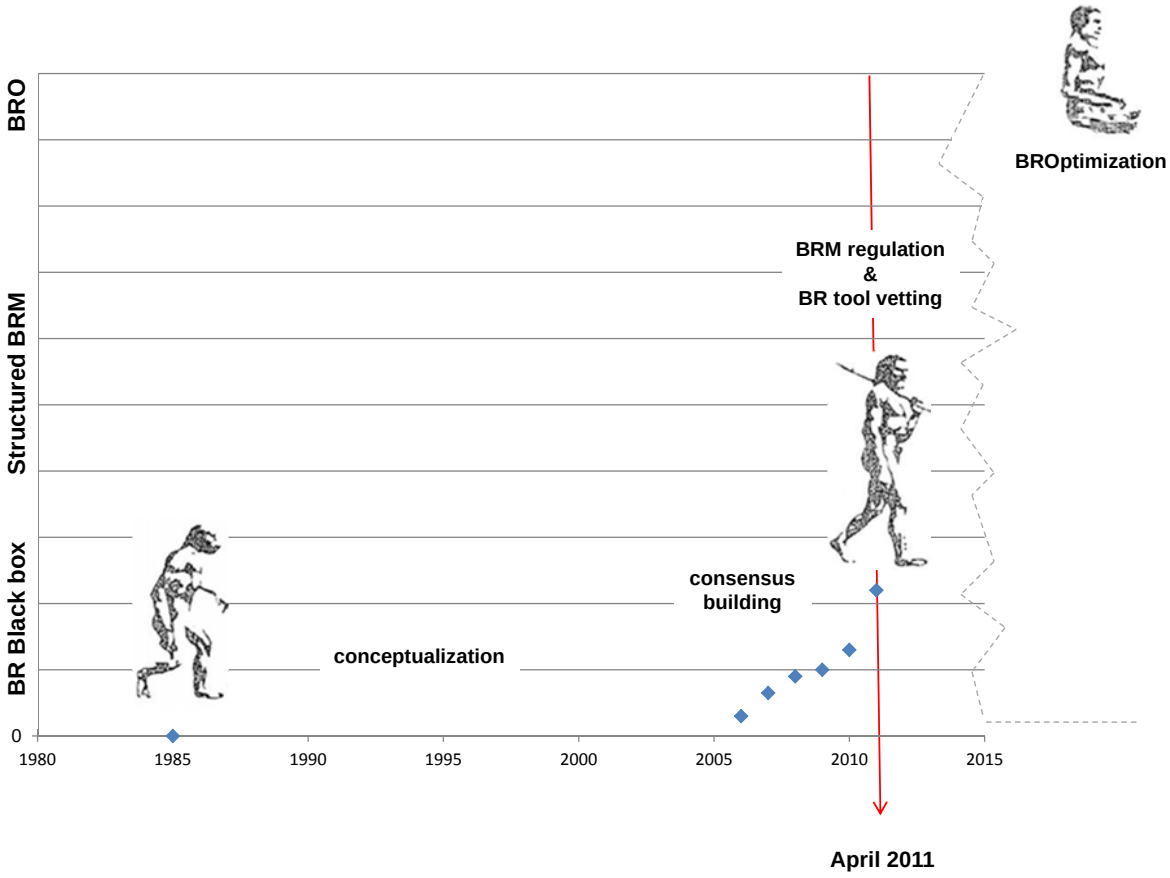
* BRM Benefit Risk Management BRO Benefit Risk Optimization

A Brief History of BR & Frames

An Idea that is Gaining Traction



… pace of change is accelerating



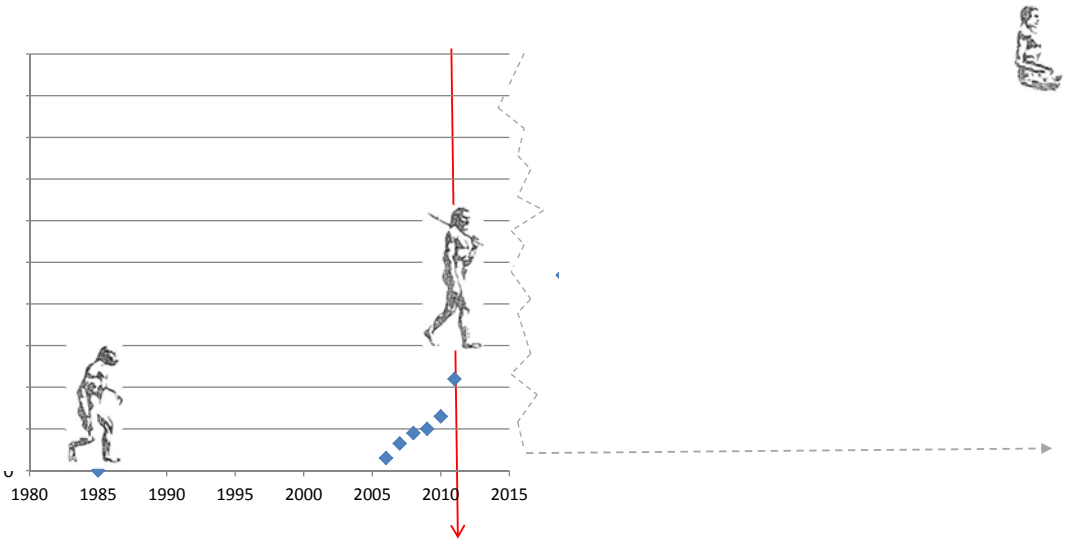
Key Point

If you only remember one thing ...

Structured BR is here to stay!

And we have re-engineered clinical safety at NVD with this in mind

.. but like signaling, refinement will take time



April 2011

"The longest journey begins with a single step" *

*** Tao Tsu**

State-of-the-Art

Benefit & Risk (BR)

Two Sides of the Same Coin

We accept the possibility of harms in return for the possible benefits that outweigh them.

The Key Question

What is acceptable risk
given expected benefits?

Asymmetry of the Risk Management System

Risk Management

What happen*ed* to benefit?

Risk Management Guidances

framework for risk management	√
need to balance benefit & risk	√
framework for balancing benefit & risk	X
guidance on balancing benefit & risk	X

Regulations

- require demonstration of efficacy and safety
- refer to but do not define positive or negative benefit-risk balance
- do not specify methods for making benefit-risk assessments
- leave it to the prescriber and patient to determine BR balance

…is the current system ideal?

Risk Management

What's happen*ing* to benefit?

Balance appears to be changing

… but not at the expense of risk

There are *no accepted* general *methods* for *deriving* a ‘‘*benefit-risk ratio*’’ or another composite metric, *or* for *using such measures* to *compare* relative *merits* of *alternative treatments*. *

*** CIOMS 1998**

Today’s BR Balance

A heuristic approach to decision-making

- educated impression
- based on *implicit* probabilities & values
- *inscrutable*, *subjective*, piecemeal, integration & weighting of evidence that is not standardized or reproducible

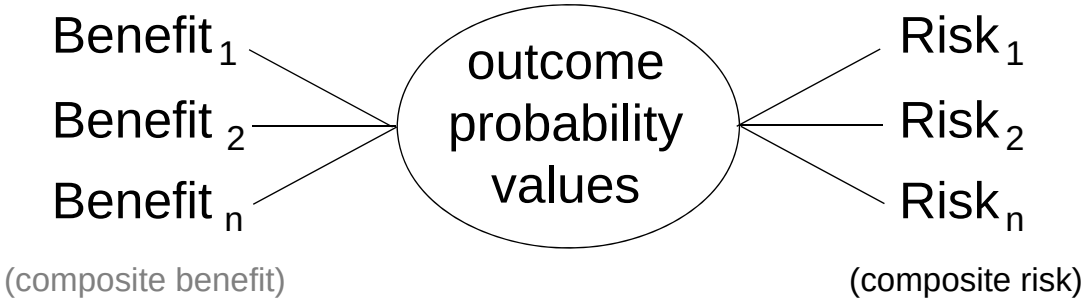
Regulatory Implications

Subjectivity may contribute to different actions across regulatory jurisdictions

The Fundamental Problem

Benefit-Risk ‘String Theory’

- outcomes
- probabilities
- values (*perceptions*)



(composite benefit) (composite risk)

Common Scale

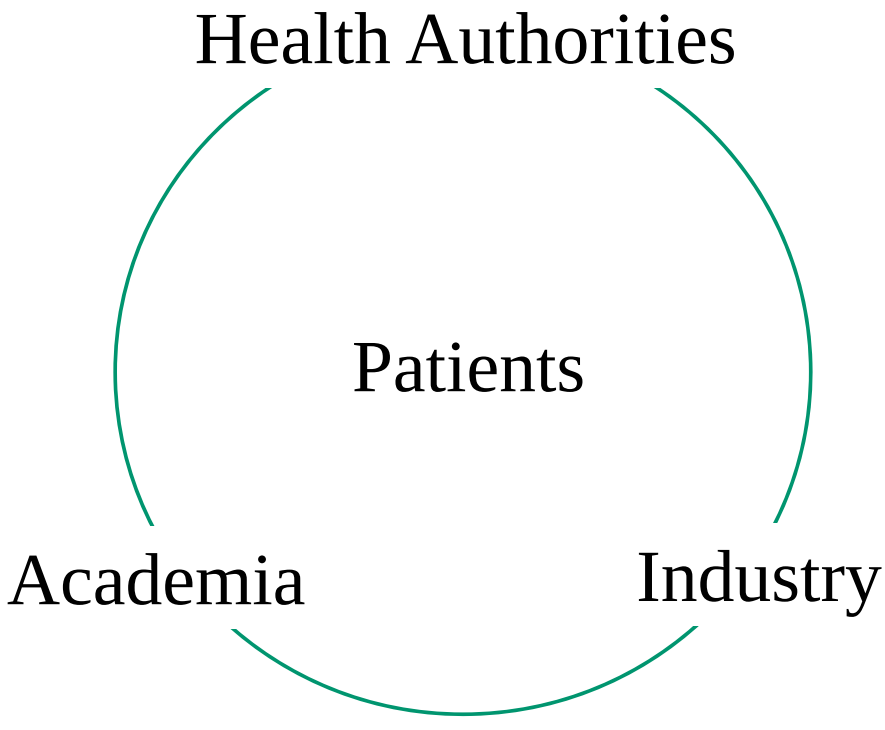
Apples & **Cranberries** → **Cran-Apple**

risks

benefits

common scale

Stakeholder Perspectives



Industry View

Company Perspectives *

- BR means different things to different people (industry & HAs)
- in general, companies use BR to inform internal discussions about TPP, label & study design
- companies engage HAs in formal discussions of BR on limited, case-by-case basis but
- few companies use explicit BR framework during approval discussions
- however, formal HA BR requirements rapidly increasing (re: E2c)

*** 2011 PhRMA-Boston Collaborative Group Survey**

Company Challenges

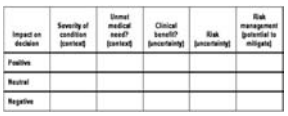
- BR decisions lack clarity
  - no standards for balancing BR
  - regulatory decisions lack structure & transparency
- approach to BR at HAs
  - separate evaluation of efficacy and safety NOT joint balancing of benefits and risks
  - disproportionately focused on risk particularly post-approval where little if any opportunity to refine benefit profile

What Companies Seek

- more balanced weighting of benefits and risks
- *most of all*, seek common BR framework that promotes standards & transparency resulting in consistent & predictable HA decision-making/communication

Health Authority Views

Recognizing need for systematic B-R assessments, regulators are developing B-R frameworks

Framework	Characteristics	Background	Status and next steps
FDA 	• Qualitative 'grid' identifying key issues for B-R deliberations • Intended to be used for retrospective explanation of decisions	• Developed with the goal of improving transparency in decision making • Unclear if FDA intent is to apply during approval process or use post-hoc as communication tool only	• Internally piloting framework • Next steps unknown • No roadmap released to date
EMA 	• "Four-fold qualitative model" to improve review quality • Evaluates: – Favorable and unfavorable events – Uncertainty of favorable and unfavorable effects	• Introduced in 2008 • EMA Road Map to 2015 positions B-R as part of EMA's efforts to improve the quality of scientific reviews, proposes shift from risk management plans to "benefit/risk management plans"	• CHMP Assessment Templates have included a list of B-R criteria since Oct. 2009 • B/R Methodology Project (target completion 2011) aims to adapt or develop tools for B-R assessment
CASS[1] 	• Qualitative framework to support regulatory decision making in CASS countries	• Commissioned in 2008 • Led by Centre for Medicines Research (Stuart Walker)	• Currently being piloted

1. CASS denotes the Canada, Australia, Switzerland, and Singapore initiative to develop a B-R framework

FDA Update

- PDUFA re-authorization:
  - agreement on proposal includes: a "*patient-focused approach*" to *benefit-risk assessment* in drug development
- CDER is piloting a new benefit-risk framework
  - will become basis of NDA's medical review executive summary
  - intuitive-type of benefit-risk framework
  - person on the street or a MD could look at & understand
  - doesn't have a lot of equations or math in it

EMA Update

- IMI Protect
  - Develop methods to strengthen BR monitoring
  - enhance early detection/assessment ADRs from diverse sources
  - enable the integration/presentation of BR data
- EMA Benefit-Risk Assessment Project
  - development/testing
  - tools/processes for balancing multiple benefits and risks to inform regulatory decisions
- ICH E2C
  - proposal to make PSUR the primary tool for implementing regulatory requirement for structured benefit risk

Health Canada

- 'Technical Discussions on Regulatory Modernization’
- series of 3 multi-day public meetings
- validate proposed activities for regulation throughout product life-cycle
- structured benefit-risk a central theme with emphasis on role in re-authorization

AFSSAPS Update

- AFSSAPS Reform Initiative
- improve assessment of patient benefits
- emphasis on a drug’s “added therapeutic value” over existing therapies as a factor in approval

State-of-the-Art

Academia's View

e.g., MIT-CBI NEWDIGS

State-of-the-Art

Patient's View

Value of Frames

Decision-Making

Key point

must learn to walk before you can run

or

must learn to frame before you can make the quantum leap’

Decision Framework

A working Definition

A system used to coordinate a collective thought process, carefully managed to clearly delineate a meaningful and tractable problem, in unambiguous and actionable terms, leading to explicit decisions that can be measured, revisited and revised.

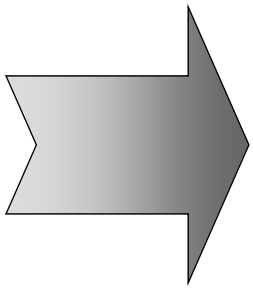
Key Point

Blueprint for making &
Rosetta Stone for deciphering
BR decisions.

… sharing ideas through structured dialogue

Value of a BR Framework

- structure
- standardization
- simplification



- transparency
- predictability
- feasibility

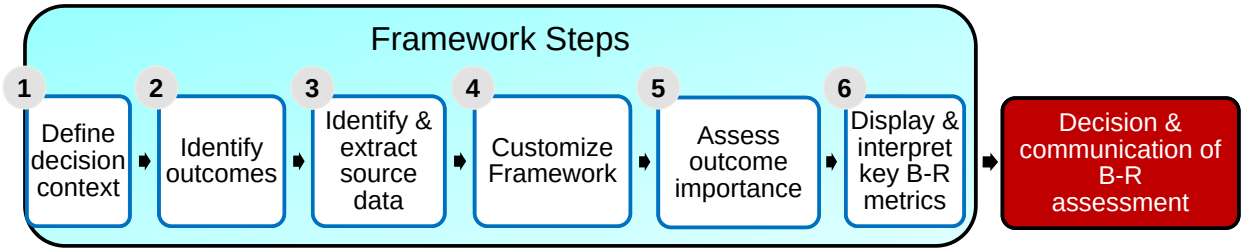
Framing's Value Proposition

- organize all relevant inputs to the decision
- justify data reduction
- simplify data synthesis
- characterize gaps in knowledge & uncertainty
- explicitly characterize & record BR decisions
- revisit/review and learn
- Build consensus and promote share understanding across multiple stakeholders

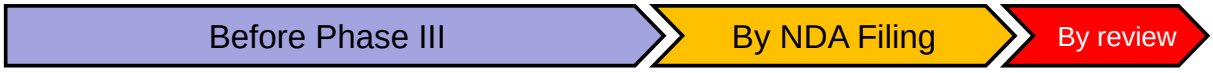
BRAT Framework[1,2]

1. Coplan PM, Noel RA, Levitan BS, Ferguson J, Mussen F. Development of a framework for enhancing the transparency, reproducibility and communication of the benefit-risk balance of medicines. Clinical Pharmacology & Therapeutics 2011; 89: 312-315
2. Levitan BS, Andrews EB, Gilsenan A, Ferguson J, Noel RA, Coplan PM, Mussen F. Application of the BRAT framework to case studies: observations and insights. Clinical Pharmacology & Therapeutics 2011; 89: 217-224

Six steps in the BRAT Framework



Example application: Late development



Framework can be applied at any stage during development or post-approval

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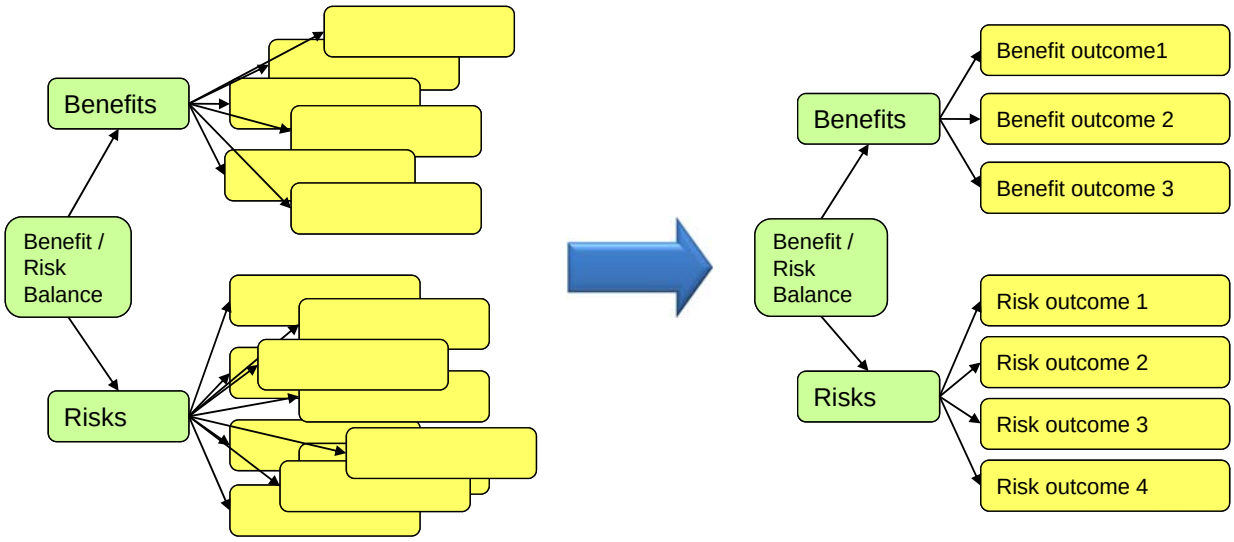
Framework Process – Value Tree

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



Framework can serve as basis for discussion with health authorities to prospectively frame the benefit-risk assessment

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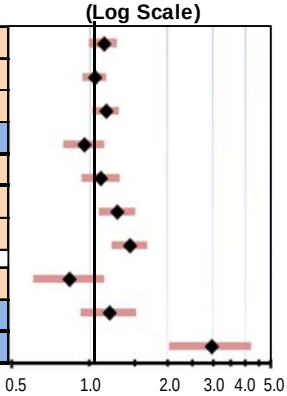
Key Benefit-Risk Summary Table Triptans in Migraine

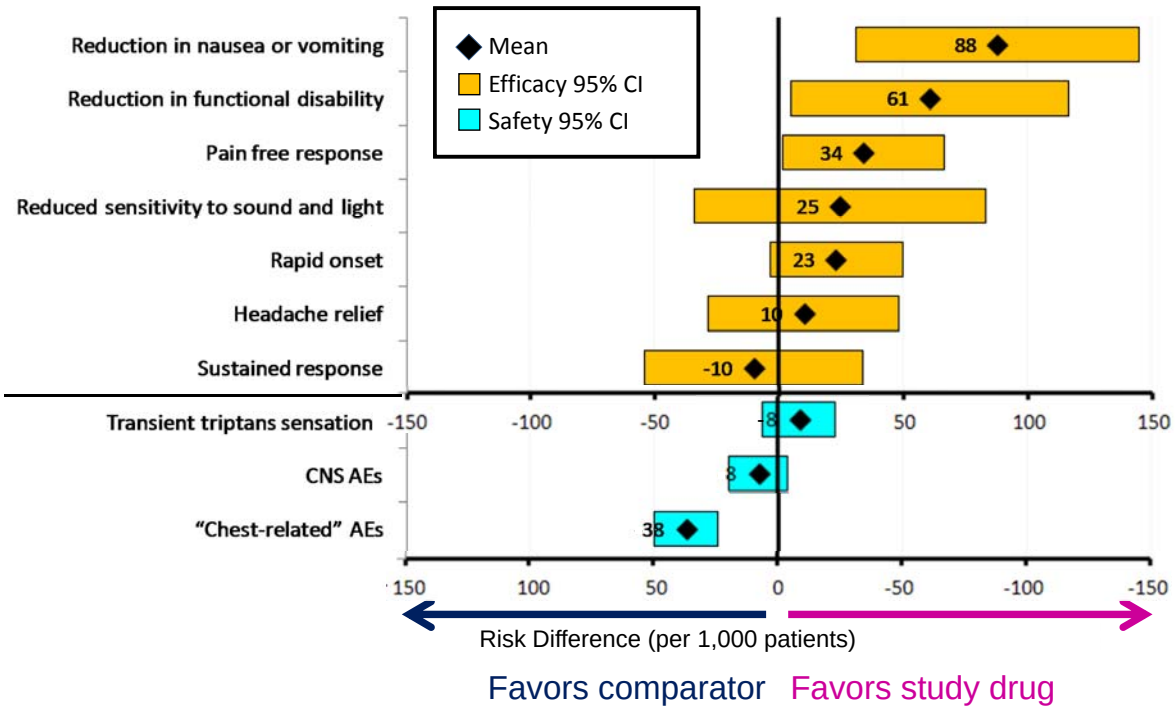
- Top-level representation of information in the framework
- The most critical view that decision makers will have on the data
- Use of graphic or tabular displays as needed to support rapid interpretation of information on multiple outcomes

		Outcome	Study Drug Risk (/1,000 pts)	Comparator Risk (/1,000 pts)	Odds Ratio (95% CI)	Odds Ratio (Log Scale)
Benefits	↓ Pain	Rapid onset	271	248	1.13 (1.00,1.27)	
		Headache relief	643	633	1.04 (0.94,1.15)	
		Pain free response	383	349	1.16 (1.03,1.30)	
		Sustained response	285	295	0.95 (0.80,1.14)	
	↓ Sensitivity	Reduced sensitivity to sound and light	530	505	1.10 (0.94,1.30)	
	↓ Other	Reduction in functional disability	540	480	1.28 (1.09,1.49)	
		Reduction in nausea or vomiting	604	517	1.43 (1.22,1.67)	
Risks	↑ Individual Risks	Transient triptans sensations	43	52	0.83 (0.61,1.14)	
		CNS AEs	53	45	1.18 (0.92,1.51)	
		"Chest-related" AEs	58	21	2.93 (2.04,4.20)	



Risk Difference Forest Plot

Increasingly common for dichotomous endpoints in benefit-risk



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BRAT in the Real World

Key Role of Soft Pilots

- 'bench work' on framework maxed out
- need real world demonstration of acceptable operating characteristics
- Unbeatable test-bed for context-specific (read BR bucket) fine tuning
- immediate benefits 'out of the gate'

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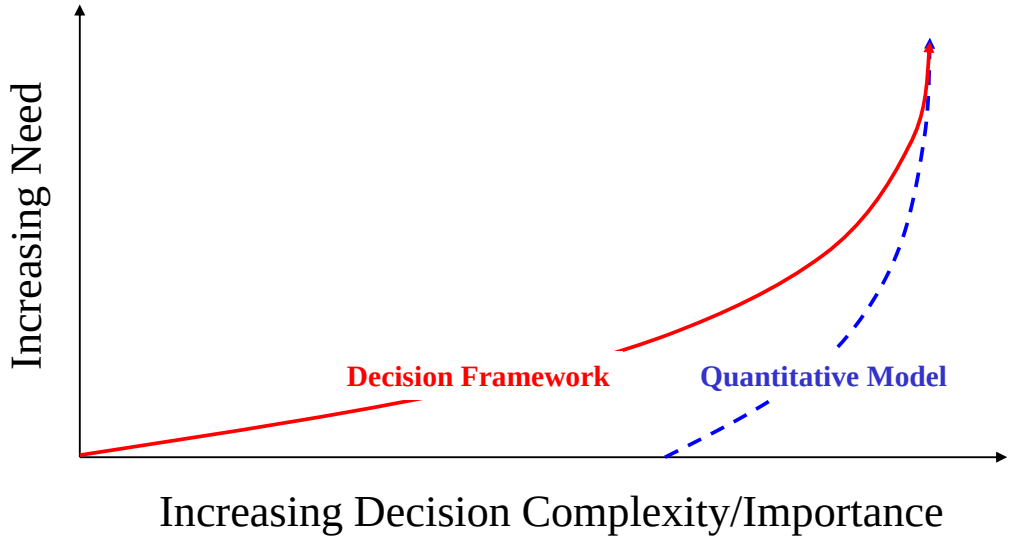
Key role of weights!

Fully Quantitative Models

Need for Structure in Decision-Making

Framework vs. Quantitative Model



Epiphany!!

Low Hanging Fruit

Modeling (i.e., like the BRAT framework) forced stakeholders to frame the issues and reach a common understanding about them.

“Don’t wait for spring *do it now!*”

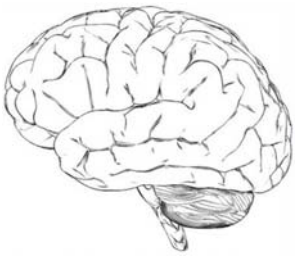
A Sampling of Quantitative Methods

- Multi Criteria Decision Analysis (MCDA)
- Number Needed to Treat (NNT)
- Number Needed to be Exposed (NNE)
- Unqualified Success (NNTUS) & Unmitigated Failure (NNTUF)
- Utility - and Timing-Adjusted Number Needed to Treat (NNTU&T)
- Threshold Number Needed to Treat (NNTT)
- Relative Value - Adjusted Number Needed to Treat (RV-NNT)
- Relative Value - Minimum Clinical Efficacy (RV-MCE)
- Benefit-Risk Ratio
- r1 & r2
- Risk- and Preference-Adjusted Surplus Efficacy
- Incremental Net Benefit
- “Risk-Benefit Contour”
- Q-TWIST
- Other

Fully Quantitative BR Modeling
A Modest Proposal *

- establish prerequisites for use
- models must deal adequately with:
  - bias
  - uncertainty
  - gaps in knowledge
- all models make assumptions
  - assumptions should be tested
  - assumptions should be tested
  - judgments should be made regarding whether assumptions are met to a degree that is *sufficient to warrant use*
  - tested for internal and external validity

Enquiring minds want to know



operating characteristics

Key Point

Frameworks and models are merely decisions aids and sound clinical judgment will remain the cornerstone of structured BR for the foreseeable future

"people decide, not models!" *

* L. Phillips. Improving the process of balancing benefits and risks in approving drugs. April 21, 2010

Implications for Vaccines

Vaccines

- not a focus of BRAT, Next Steps Working Group or Academic groups
- RM and structured BRM lagging
- pandemic changed the playing field
- marked increase in RM activity
- structured BRM beginning to appear

H1N1 Pandemic *

Necessity is the mother of invention

- EMA Benefit-Risk Methodology Project
- Application of “fourfold table” methodology *
- H1N1 case study
- process generated alignment of participants
- revealed characteristics of the decision problem that were not obvious
- model made explicit reasoning behind decision
- model and process helped participants to form their own preferences

* L. Phillips. Improving the process of balancing benefits and risks in approving drugs. April 21, 2010

H1N1 Pandemic *

Structured BR – Lessons Learned

- modeling can deepen insights in problematical situations
- Working with groups of key players allows an exchange of views
- modeling enabled the group to challenge assumptions and develop new perspectives
- The process generated shared understanding
- The results are auditable, transparent and communicable

* L. Phillips. Improving the process of balancing benefits and risks in approving drugs. April 21, 2010

"… as simple as possible and no simpler" *

* Albert Einstein