


**Risk Benefit Management:
Regulatory Management and
Assessments for Drug Development**

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**Risk Benefit Monitoring Worldwide
Regulatory Guidance Resources?**

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Introduction

- Risk and benefit assessment and monitoring are significant contributors to promoting safety and quality in the delivery of health care.
- Responsibility for providing "risk-benefit" information on new and marketed drugs resides with sponsors of drug development i.e. pharmaceutical companies, universities, governmental organizations.
- However, guidance resources and policy information from a regulatory perspective on risk and benefit monitoring processes of drugs are limited to few selected countries (Maistrello et al., Pharmacoepidemiology and Drug Safety, 1998).

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Objective

To describe and compare requirements for drug risk and benefit monitoring processes, worldwide and by region, through reviewing current websites of regulatory agencies

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Methods

Identified Countries and Health Care Authority and Regulatory agency websites* from –

1. Website of Food and Drug Administration <http://www.fda.gov/oia/agencies.htm>
2.  **ISPOR GLOBAL HEALTH CARE SYSTEMS ROAD MAP**
<http://www.ispor.org/HTARoadMaps/Default.asp>




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Methods (Contd.)

- Created a Table template for data collection of critical elements as follows:
 - Country
 - Region (Africa, Americas, Asia, Europe, Middle East)
 - Type (Developed or Developing)
 - Income category (High; Middle - upper, lower; Low)
 - Name of Agency, Website, Language of website
 - Evaluating Center Name
 - Clinical trial data (phase 1 to 3)
 - Post marketing data (phase 4)
 - Availability of form for reporting adverse events on marketed products
 - Determination of risk (who does?)
 - Requirement of medication guide for greater than average risk products

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Preliminary Results

Information searched for countries (n=108*), by region:


- 17 = Africa
- 26 = Americas
- 19 = Asia
- 37 = Europe
- 09 = Middle East

Excluded for lack of access to information (50/108)

- 16 = no website found
- 34 = Language of website not English

*Consider updating with countries from the United Nations website

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Preliminary Results (Contd.)

Table: Resources from Evaluable Country websites (n=58)

Regulatory Agency Name/ Website	Evaluating Center Name	Pre-clinical	Clinical Phases				ADR reporting Form	Who determines greater-than-average risk?	Medication guide for greater than-average risk products
			1	2	3	4			
Malta, Europe Ministry for Social policy www.sahha.gov.mt	Medicine Authority	Y	Y	Y	Y	Y	NA	NA	NA
USA, FDA http://www.fda.gov	CDER	Y	Y	Y	Y	Y	MedWatch	Agency	Required
UK, http://www.mhra.gov.uk/index.htm	MHRA	Y	Y	Y	Y	Y	Yellow Card	Agency	NA

*Center for Drug Evaluations and Research
 **Medicines and health care products regulatory agency

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Preliminary Results (Contd.)

Key Similarities and Differences

- Regulatory agencies in US and Europe provide MORE comprehensive data than Asia or Africa on websites
- Developing countries were missing key information
- Developing countries were more likely to have no detailed data available


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Conclusions

- Preliminary analyses show inconsistencies in data across countries and regions
- "Benefit" information guidance for drugs is minimal and "risk" information guidance is even less
- Countries need to provide more guidelines on the websites of their regulatory agencies that will be helpful to sponsors of drug development and other decision-makers in understanding risk-benefit monitoring across countries and regions.

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Conclusions (Contd.)

Next steps

- Complete data collection
- Draft a manuscript for Value in health/Pharmacoepidemiology and Drug Safety Journal/ISPOR Connections
- Circulate among team members for inputs/edits
- Submit revised manuscript by end October, 2009


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Special Interest Groups

THANK YOU....

Questions

1. Have you encountered these problems as sponsors or researchers of drug development?
2. How do you address these problems?
3. What ideas and experiences can you think of or are aware of for improving these systems?



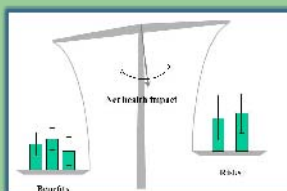
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Working Paper: A Review of Risk-Benefit Assessments for Drug Development



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Dennis W. Raisch, RPh, PhD
Many Colleagues from ISPOR Risk Benefit SIG


[Coming Event] ISPOR Workshop: W29
 Wednesday, May 20, 2009
 2:00 PM - 3:00 PM

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Purposes

- To review the current methodologies for benefit-risk assessments employed by industry and regulators
- To compare quantitative approaches of benefit-risk assessments

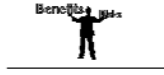
FDA evaluates scientific data for the population



Provider makes benefit-risk tradeoffs for a patient



Patient evaluates tradeoffs in terms of personal utility



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Literature Review & Findings: “Finding some needles from oceans”

Over 12,000 articles
Found by key words

↓

2000 – 5000 articles
Limited to English, Human, Drug Safety, & Academia

↓

300 - 400
Further exclusions: ADR data mining, signal detection, effectiveness, case report, no-abstract, etc.

↓

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Final number of useful manuscripts that focus on quantitative risk-benefit assessments

Key words: Risk, benefit, risk-benefit assessment, drug safety surveillance, adverse drug reactions, post-marketing surveillance, pharmacovigilance

Search engines: Web-based Medline & Cochrane plus Intranet search for country specific drug regulatory.

Inclusion criteria: English, drug intervention, quantitative risk and/or benefit assessments.


Exclusion criteria: trade information, animal studies, case reports, no abstract.

Footnotes: Use key articles to find relevant references. Use expertise to find relevant articles.

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Eleven Quantitative RBA Techniques

Seq.No.	Quantitative Approaches of Risk-Benefit Assessments
1	Quantitative Framework for Risk and Benefit Assessment (QFRBA)
2	Benefit-Less Risk Analysis (BLRA)
3	Quality-adjusted Time Without Symptoms and Toxicity (Q-TWIST)
4	Number Needed To Treat (NNT) versus Number Needed to Harm (NNH)
5	Relative Value Adjusted Number Needed To Treat (RV-NNT)
6	Minimum Clinical Efficacy (MCE)
7	Incremental Net Health Benefit (INHB)
8	Risk-Benefit Plane (BRP) and Risk-Benefit Acceptability Threshold (RBAT)
9	Probabilistic Simulation Methods (PSM) and Monte Carlo Simulation (MCS)
10	Multi-Criteria Decision Analysis (MCDA)
11	Risk-Benefit Contour (RBC)



#1: Quantitative Framework for Risk Benefit Assessments - QFRBA

- Risk of ADR /ADE
- Relative Risk (RR)
- Attributable Risk (AR)
- Relative Risk Reduction (RRR)
- Absolute Risk Reduction (ARR)
- Benefit Parameters and Criteria




#2: Benefit-Less Risk Analysis (BLRA)

- Discount benefit (E_i) by risk ($F \cdot R_i$) to obtain benefit-less risk measure (E_i^*) for individual i

$$E_i^* = E_i - F \cdot R_i$$


Sources: Chuang-Stein, Contr Clin Trials, 1994; Tallarida et al, Clin Pharmacol Ther, 1997.



#3: Quality-Adjusted Time Without Symptoms and Toxicity (Q-TWiST)

- Benefit: drug attributed gain of QALY
- Risk: drug attributed loss of QALY.
- Net benefit:
(Benefit – Risk) or Benefit/Risk


Source: Gelber, et al. J Natl Cancer Inst. 1996.



#4: Number Needed to Treat (NNT) and Number Needed to Harm (NNH)

- Number needed to treat (NNT):
 - number of patients who need to be treated to prevent the occurrence of one additional event of disease of interest
- Number needed to harm (NNH):
 - number of patients who receive treatment, resulting in one adverse drug (treatment) reaction
- Treatment is warranted if $NNT < NNH$

Sources: Cook, et al, BMJ, 1995; Holden, et al, PEDS, 2003a; Holden, et al, PEDS, 2003b.



#5: Relative Value adjusted-NNT (RV-NNT) & Risk-Benefit Ratio

- Incorporates patient's relative utility value (RV) for disease outcomes and adverse events incorporated into NNT/NNH, respectively
- Modified RV-NNT and RV-NNH can be calculated.
- Risk-Benefit Ratio $\rightarrow \frac{NNT}{NNH} < 1$


Sources: Holden, et al, PEDS, 2003a; Holden, et al, PEDS, 2003b.



#6: Minimum Clinical Efficacy (MCE)

- MCE required in comparison with a standard treatment and new treatment while considering natural characteristics of disease in population.
- Minimal therapeutic benefit:
 - New treatment is warranted over standard if: Risk < Benefit

Sources: Holden, et al, PEDS, 2003a; Holden, et al, PEDS, 2003b.


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#7. Incremental Net Health Benefit (INHB)

- The incremental net health benefit (INHB) between a new drug and conventional drug therapy can be calculated as the difference between effectiveness and risk changes


$$INHB = (E_2 - E_1) - (R_2 - R_1)$$

Effectiveness (E) and Risk (R) measured in QALYs

- A “favorable” risk-benefit balance becomes $(E_2 - E_1) > (R_2 - R_1)$, where the expected QALYs gained as a result of efficacy exceed the expected losses to safety problems

Parameters for Assessment	Key Features
<ul style="list-style-type: none"> Risk in terms of QALY Benefit in terms of QALY 	<ul style="list-style-type: none"> Population health impact model Can be used for comparing treatment and control groups Variance in the estimates of both risks and benefits can be calculated

Source: Garrison et al. *Health Affairs* 2007;26(3):684-695; Abstract: *A Review of Risk-Benefit Assessments for Drug Safety*, 2009


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#8. Risk-benefit Plan (RBP) and Risk-benefit Acceptability Threshold (RBAT)

- The benefit risk ratio can be interpreted as the increase in the number of expected patients who will benefit for each additional adverse event that is incurred from using the experimental treatment rather than the control


$$R = (p_e - p_c) / (q_e - q_c)$$

Probabilities of benefit in experimental treatment (p_e) and control arms (p_c) / Probabilities of risk in the experimental treatment (q_e) and control arms (q_c)

- An acceptable risk-benefit threshold (RBAT) can be viewed in the benefit-risk plane (RBP) as the slope of the line that passes through the origin and the point defined by the observed difference in risk and observed difference in benefit

Parameters for Assessment	Key Features
<ul style="list-style-type: none"> Risk measurement such as incidence or frequency of ADEs Benefit measurement such as incidence of benefit or the product efficacy and responder rates 	<ul style="list-style-type: none"> Well-defined hypothetical model Often used for explaining the phenomenon of drug safety surveillance

Source: Shaffer et al. *BMC Med Res Methodology* 2006, 6:46; Abstract: *A Review of Risk-Benefit Assessments for Drug Safety*, 2009



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#9. Probabilistic Simulation Methods (PSM)

- Modern probabilistic simulation methods permit the estimation of the joint density of risks and benefits with their associated uncertainty and facilitate estimation of the probability that a therapy is net-beneficial
- Two methods for quantifying joint density of uncertainty:
 - Original data available: nonparametric bootstrap sample of data can be selected repeatedly
 - Original data not available: simulation using information on the distributions fit to the data
 - Monte Carlo Simulation (MCS) can be used to compare drugs for both efficacy and safety

Parameters for Assessment	Key Features
<ul style="list-style-type: none"> Probabilities for the risks and benefits of intervention Probabilities for the risks and benefits of control Incremental risk-benefit ratio (IRBR) 	<ul style="list-style-type: none"> Joint density of benefit and risk is presented in the form of risk-benefit acceptability curve Simulation methods used for uncertainty around incremental risk-benefit differences

Source: Abstract: *A Review of Risk-Benefit Assessments for Drug Safety*, 2009



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10. Multi-Criteria Decision Analysis (MCDA)

- Multi-Criteria Decision Analysis (MCDA) is a decision tool aimed at supporting decision makers who are faced with making numerous risk and benefit decisions
- A MCDA-based model allows taking multiple benefit and risk criteria into account, making a judgment on the evidence and the potential uncertainty because of the incompleteness of the evidence, and making trade-offs of the benefits against the risks

Parameters for Assessment	Key Features
<ul style="list-style-type: none"> Risk measured by incidence of ADEs, discontinuation rate due to ADEs, drug interactions, off-label use leading to safety hazards, safety issues observed in preclinical Benefit measurements involve clinical relevant end-points from clinical trials and other benefit criteria 	<ul style="list-style-type: none"> Decision-making tool used to evaluate a drug's risks and benefits A decision tree is required to lay out hierarchical clinical outcomes

Source: Mussen F, et al. *Pharmacoepidemiol Drug Saf* 2007;16:S2-S15; Abstract: *A Review of Risk-Benefit Assessments for Drug Safety*, 2009



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11. Risk-benefit Contour (RBC)

- A Risk-Benefit Contour (RBC) provides a two-dimensional graph involving both degrees of probability for potential benefit of treatment and potential risk due to toxicity and ADEs

Parameters for Assessment	Key Features
<ul style="list-style-type: none"> Drug benefit measured on X-axis such as percentage increase in 3-year survival Risk measured on Y-axis as the probability of severe or worse ADE or toxicity 	<ul style="list-style-type: none"> Both benefit and risk measurements plotted on a two-dimensional graph A set of risk-benefit contours can be calculated for each individual patient, presented as non-linear curves

Source: Shakespeare et al. *The Lancet* 2001;357:1349-53; Abstract: *A Review of Risk-Benefit Assessments for Drug Safety*, 2009


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Conclusion

- The methods reviewed are mathematically sound, involve relatively straight-forward computations and can add to the scientific validity of current RB assessment
- Measuring risk-benefit is fraught with methodological challenges:
 - Heterogeneity of metrics
 - Multiplicity of outcomes
 - Uncertainty
 - Paucity of data
- Multiple RBA techniques may be deployed to triangulate the risk-benefit profile of a product
- Quantitative RBA methods are a supplement to, but do not replace, existing medical decision paradigms



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Wednesday, May 20, 2009
Crystal Ballroom A,B,C
2:00 PM - 3:00 PM



Thank you for attending.

For more information about the ISPOR
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please visit our webpage at
www.ispor.org/sigs/HCDriskMgt.asp