UNIVERSITY of WASHINGTON

Overview of Approaches to Regulatory Health Benefit-Risk Assessment

Presentation to:

INITIATIVE ON METHODS, MEASUREMENT, AND PAIN ASSESSMENT IN CLINICAL TRIALS

IMMPACT-XIV

ARLINGTON, VIRGINIA

June 17, 2011

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Acknowledgements

- Research Collaborators:
  - James T. Cross (Genentech/recent UW PhD)
  - Adrian Towse (Office of Health Economics, UK)

- Public-Private Benefit-Risk Assessment Working Group (PP-BRAWG; also called Next Steps Working Group)
  - Larry Lynd (UBC), Reed Johnson (RTI), and Larry Phillips (LSE).

Agenda—Key Questions

Alternative Methods

1. Why are regulators making efforts to develop their methods of benefit-risk assessment?
2. What methods from economics and decision analysis are potentially useful to apply to benefit-risk assessment?
3. What are the pros and cons of each method?

Implications for Regulation of Analgesics?

1. What might this mean for the future processes of regulatory decision-making?
2. Which methods work best for analgesia?
3. Do the regulatory BRA methods have any implications or lessons for BRA communication with clinicians and patients?

Timeline of Key Regulatory-Related Benefit-Risk Developments, 1997-2011

Year	Event
1997	Five drug withdrawals in the U.S.
1998	WHO-UNESCO report asserts that existing methods for drug BR assessment cannot adequately weigh benefits against risks.
2002	PDUFA III (June 12, 2002) sets "performance goal" for the FDA on a guidance on Risk Management
2003	•(March) FDA issued 3 concept papers on risk management; •(April) FDA Conference to discuss papers; "benefits" an issue.
2004	•(May) FDA issues three draft guidances on risk management. •(Sept.) Memorandum from FDA Associate Director estimated that use of rofecoxib (Vioxx) resulted in more than 27,000 excess AMIs/sudden deaths over 1999-2003. •(Sept.) Merck announces worldwide withdrawal of rofecoxib. •(Dec.) Senate hearings
2005	•FDA asks Institute of Medicine to conduct study •(March) Final risk management guidances issued

Timeline of Key Regulatory-Related Benefit-Risk Developments, 1997-2011 (cont'd)

Year	Event
2006	Congressionally-mandated IOM study released: improve assessment and communication of benefits and risks.
2007	•(Jan) FDA announces 41 initiatives on drug safety; One FDA initiative: "Developing and incorporating new quantitative tools in the assessment of risk and benefit… •(Jan.) EMEA draft Report of CHMP Working Group on Benefit-Assessment Models and Methods •(June) Avandia (rosiglitazone), diabetes drug controversy •(Sept.) FDA Amendments Act: Benefit-risk communication. •Conferences in UK (OHE-Oct.) and US (FDA- Nov.) on regulatory BR assessment. •(Nov.) Next Steps Working Group formed (FDA-PhRMA-BIO)
2008	•(March) EMEA Reflection Paper on Benefit-Risk Assessments •EU, US agencies solicit research proposals on BR analysis and decision support tools.
2009	•Follow-up DIA conference on regulatory BR assessment, organized by Next Steps Working Group

Timeline of Key Regulatory-Related Benefit-Risk Developments, 1997-2011 (cont'd)

Year	Event
2010	•(February) Senate Finance Committee review of FDA's handling of Avandia •(March) FDA Commissioner Dr. Hamburg's response to Senate Finance •(April) FDA sponsored New York Academy of Science meeting •(August) EMA Benefit-Risk Methodology: Work package 2 report: Applicability of current tools and processes for regulatory benefit-risk assessment •(Dec.) EMA Roadmap to 2015
2011	•A Risk-Characterization Framework for Decision-Making at FDA

IOM Drug Safety Study (2006) and FDA Response (2007)

- IOM Recommendation 4.5:
  - Center for Drug Evaluation and Research should "develop and continually improve a systematic approach to risk-benefit analysis for use throughout the FDA in the pre-approval and post-approval settings."

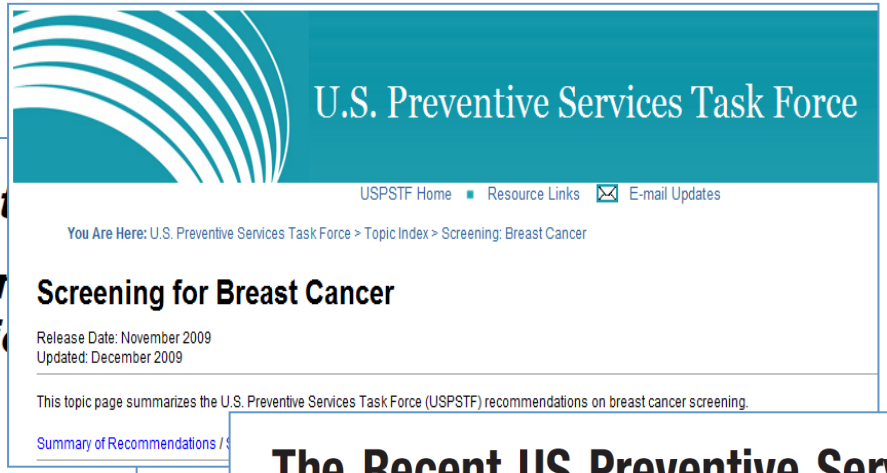
- In January 2007, the FDA announced 41 new initiatives on drug safety, including:
  - "[d]eveloping and incorporating new quantitative tools in the assessment of risk and benefit. . .."

Regulators and Guideline Developers Are Under Increasing Pressures to Be Systematic and Transparent

The Future of Drug Safet

Promoting and Protectin the Health of the Publi

FDA's Response to the Institute of Medicine's 2006 Report



The Recent US Preventive Services Task Force Guidelines Are Not Supported by the Scientific Evidence and Should Be Rescinded

Daniel B. Kopans, MD[a,b]

J Am Coll Radiol 2010;7:260-264.

Some Terminology—Benefits, Risks, Clinical Utility, and Comparative Effectiveness

- There is considerable ambiguity about these concepts and terms.
- We mean:
  - **Benefits**—intended positive clinical and health outcomes associated with a specific medical service, procedure, device, or intervention
  - **Risks**—unintended negative clinical and health outcomes (also called "harms") associated with a specific medical service, procedure, device, or intervention
  - **Clinical utility**—the balance of benefits and risks
  - **Comparative effectiveness**--clinical utility in the real-world—considers both benefit and harms; assessment changes over the product life cycle

Major Benefit-Risk Assessment Methodologies under Consideration by Regulators

1. Semi-Quantitative Information/Data Summary Matrix: PhRMA BRAT (BRF)
2. Stated Choice Survey (also known as stated preference or conjoint (SCS)
3. Multi-criteria Decision Analysis (MCDA)
4. Health Outcomes Modeling using QALYs (also called Incremental Net Health Benefits—INHB) (BR-HOM)

These methodologies are not mutually exclusive and can, in fact, be complementary.

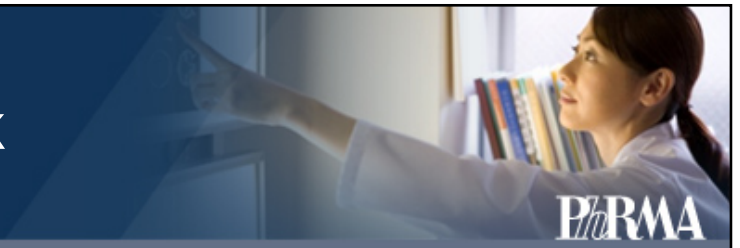
PhRMA

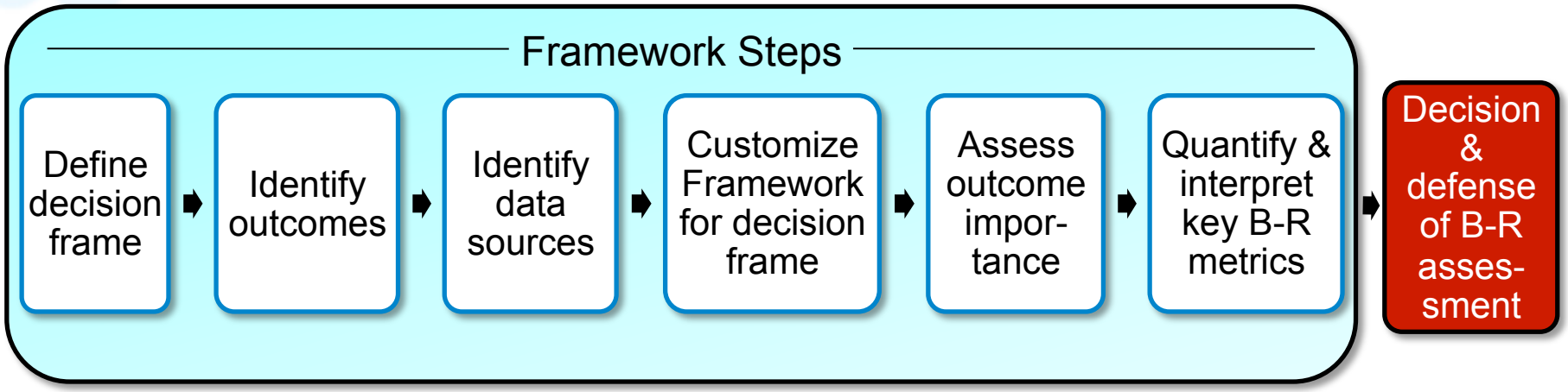
New Medicines. New Hope.

Benefit-Risk Action Team (BRAT):
Achievements & Next Steps

Clinical & Preclinical Development Committee Meeting
April 15, 2010

Steps in the BRAT Framework

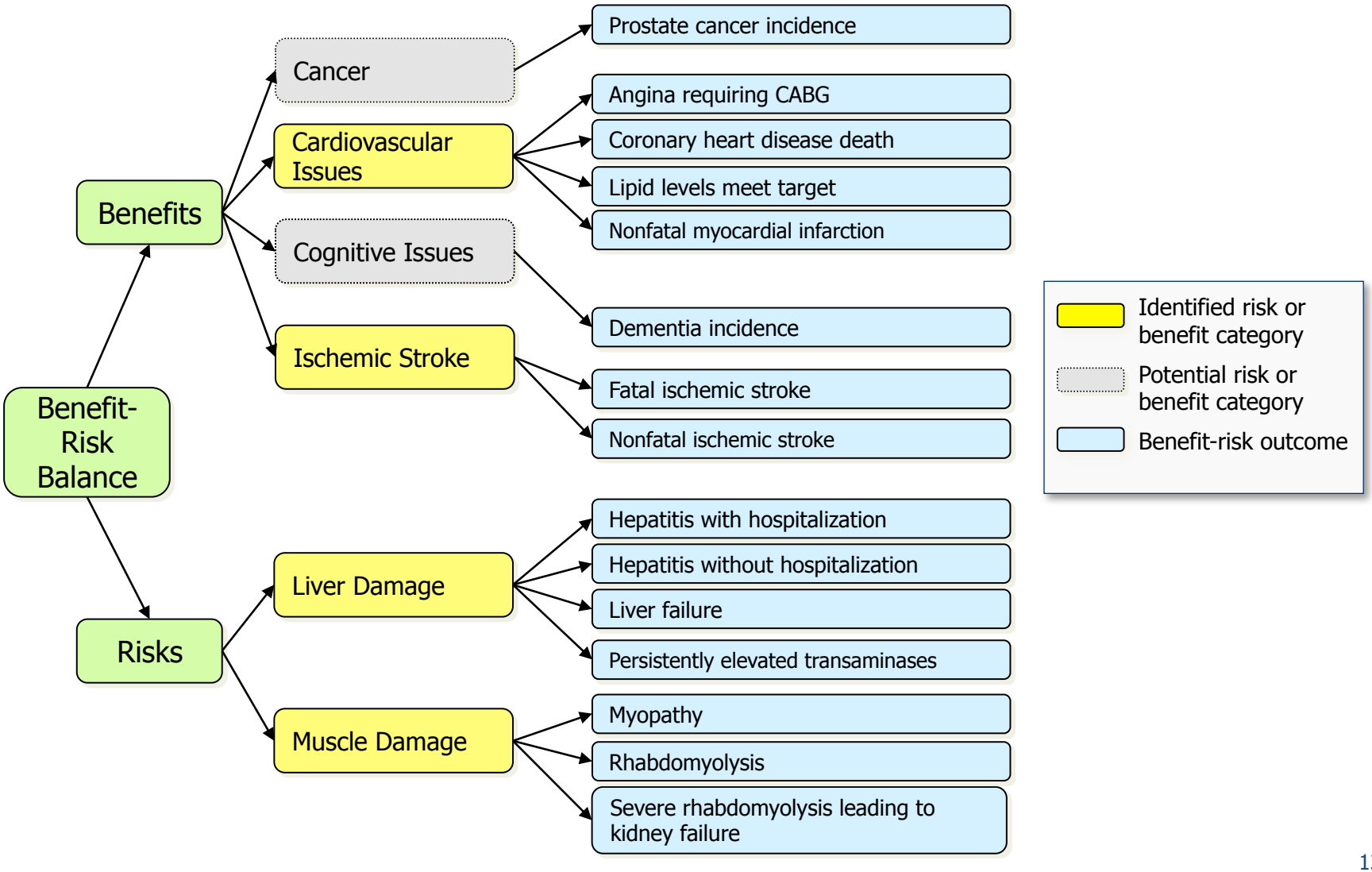




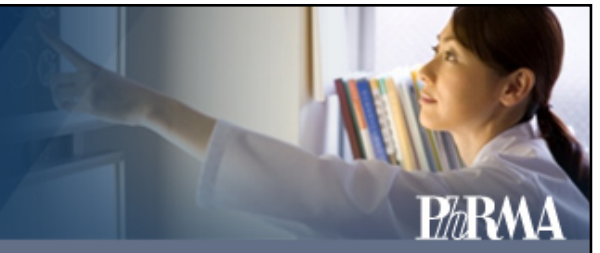
Example application: Late development

Value Tree for PhRMA BRAT Statins Example

Full tree with identified and potential benefits and risks

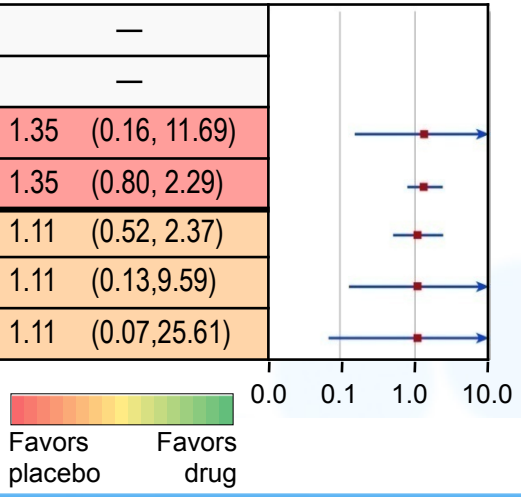


Key Benefit-Risk Summary Table



Use of graphic or tabular displays as needed to support rapid interpretation of information on multiple outcomes

		Outcome	Incidence: study drug (%)	Incidence: placebo (%)	Adjusted RR (95% CI)	Forest Plot of Adjusted RR (Log Scale)
Benefits	Cardio-vascular Issues	Angina requiring CABG	0.11	0.19	0.59 (0.32, 1.10)	
		Coronary heart disease death	1.52	1.65	1.00 (0.64, 1.56)	
		Lipid levels meet target*	67.00	29.00	2.12 (1.77, 2.55)	
		Nonfatal myocardial infarction	0.66	1.30	0.51 (0.05, 5.56)	
	Ischemic Stroke	Fatal ischemic stroke	0.91	1.73	0.57 (0.35, 0.95)	
		Nonfatal ischemic stroke	2.34	2.88	0.84 (0.71, 0.98)	
Risks	Liver Damage	Hepatitis with hospitalization	—	—	—	
		Hepatitis without hospitalization	—	—	—	
		Liver failure*	0.013	0.0095	1.35 (0.16, 11.69)	
		Persistently elevated transaminases	0.26	0.19	1.35 (0.80, 2.29)	
	Muscle Damage	Myopathy	0.11	0.10	1.11 (0.52, 2.37)	
		Rhabdomyolysis*	0.011	0.01	1.11 (0.13,9.59)	
		Severe rhabdomyolysis leading to kidney failure*	0.0006	0.0005	1.11 (0.07,25.61)	



* Mock data for visualization purpose only

Key Benefit-Risk Summary Table
Statins in Primary Prevention

- Analyses from perspectives of multiple stakeholders

		Outcome	Adjusted Rate Difference per 10,000 person-years (95% CI)	Patient* preference weights	Physician* preference weights	Regulator* preference weights
Benefits	Cardio-vascular Issues	Angina requiring CABG	-2.6 (-4.3, 0.6)	0.6	0.8	0.5
		Coronary heart disease death	0.0 (-12.1, 18.8)	0.8	0.6	0.9
		Lipid levels meet target*	3,248.0 (2,233.0, 4,495.0)	0.3	0.5	0.3
		Nonfatal myocardial infarction	-21.2 (-41.1, 197.4)	0.5	0.3	0.5
	Ischemic Stroke	Fatal ischemic stroke	-15.2 (-23.0, -1.8)	0.8	0.7	0.8
		Nonfatal ischemic stroke	-19.8 (-34.6, -2.4)	0.6	0.4	0.4
Risks	Liver Damage	Hepatitis with hospitalization	—	—	—	—
		Hepatitis without hospitalization	—	—	—	—
		Liver failure*	0.2 (-0.5, 6.3)	1.0	0.9	0.9
		Persistently elevated transaminases	3.6 (-2.0, 13.0)	0.1	0.3	0.1
	Muscle Damage	Myopathy	0.6 (-2.6, 7.3)	0.7	0.6	0.9
		Rhabdomyolysis*	0.1 (-0.5, 4.5)	—	—	—
		Severe rhabdomyolysis leading to kidney failure*	0.0 (0.0, 0.6)	0.9	0.7	0.8

*Mock study data used for visualization purpose only

Advantage to study drug | Advantage to placebo

RTI(h)(s)™ RTI HEALTH SOLUTIONS®

BENEFIT-RISK PREFERENCES FOR REGULATORY DECISION MAKING

F. Reed Johnson, PhD

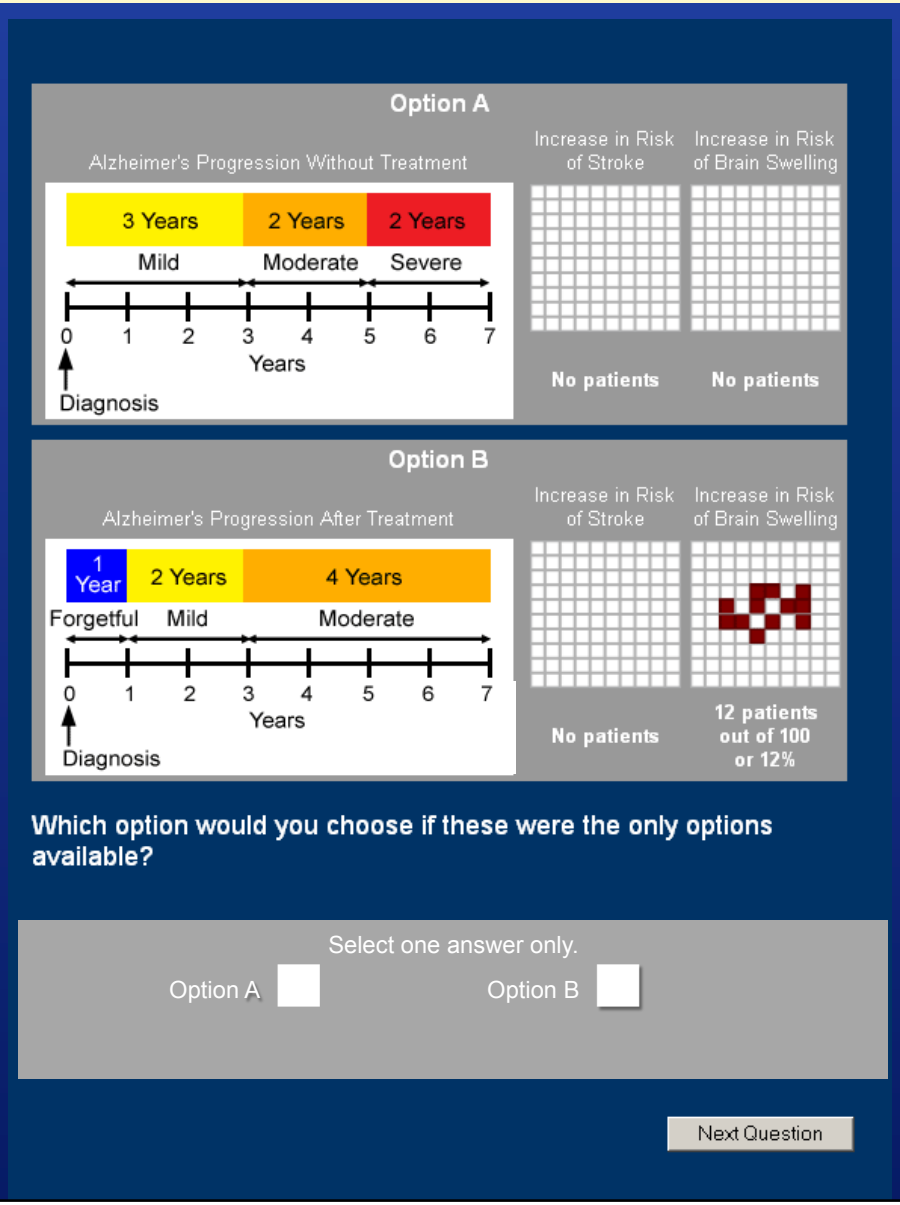
Senior Fellow and Principal Economist
RTI Health Solutions, RTI International

A. Brett Hauber, PhD

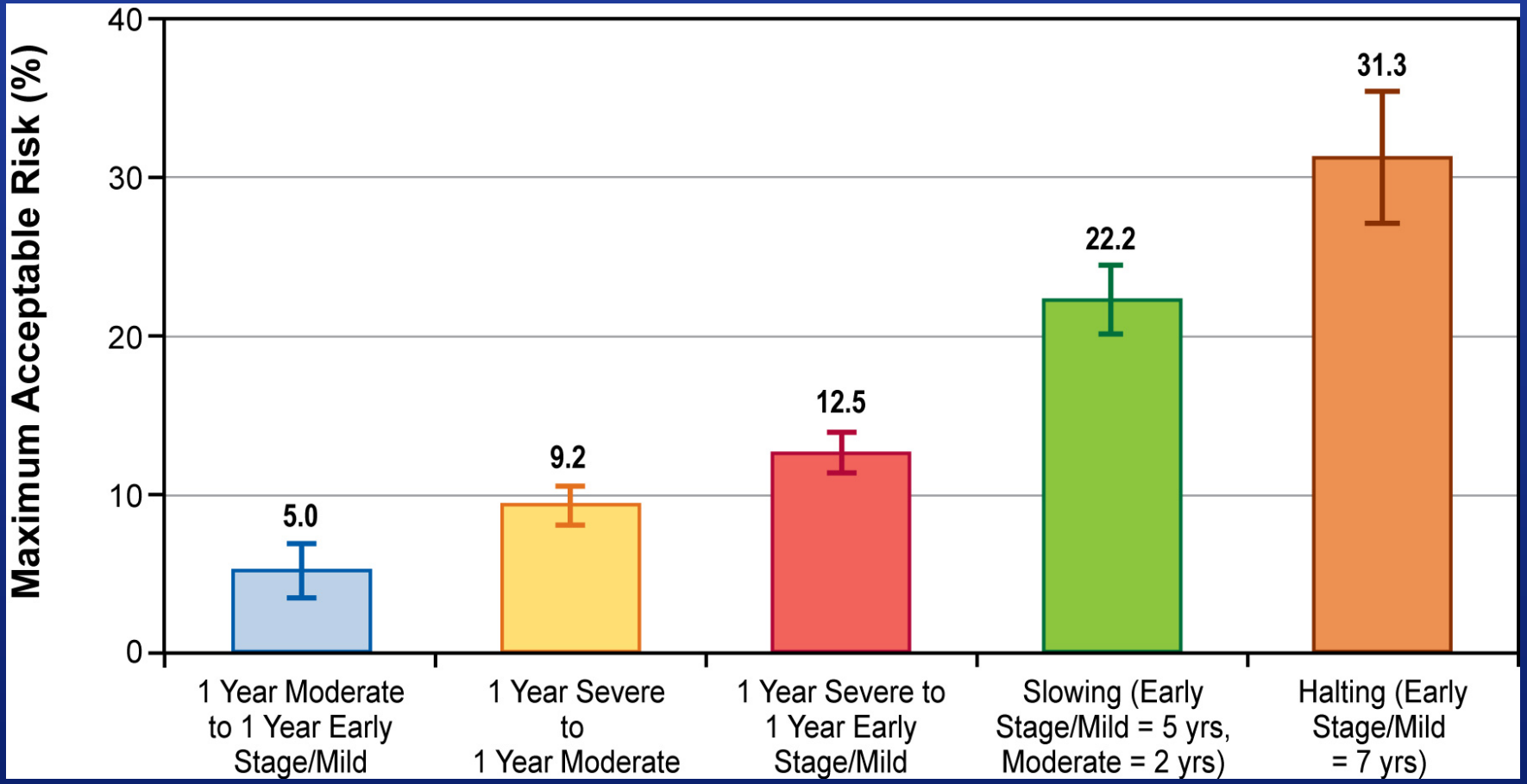
Global Head, Health Preference Assessment
RTI Health Solutions, RTI International

FDA, CDRH Staff College Short Course
Silver Spring, MD, November 16, 2009

Benefit-Risk Tradeoff Question



Risk Tolerance for AD Disease Modification



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

Applying Multi-Criteria Decision Analysis Methods in a Regulatory Body

Dr. Lawrence D. Phillips

Consultant to the European Medicines Agency

Professor, London School of Economics

(but speaking on his own behalf)

How do you put it all together?

Emergent AEs

QTc prolongation

Body weight increase

BPRS **ADRs**

EPS **PANNS score**

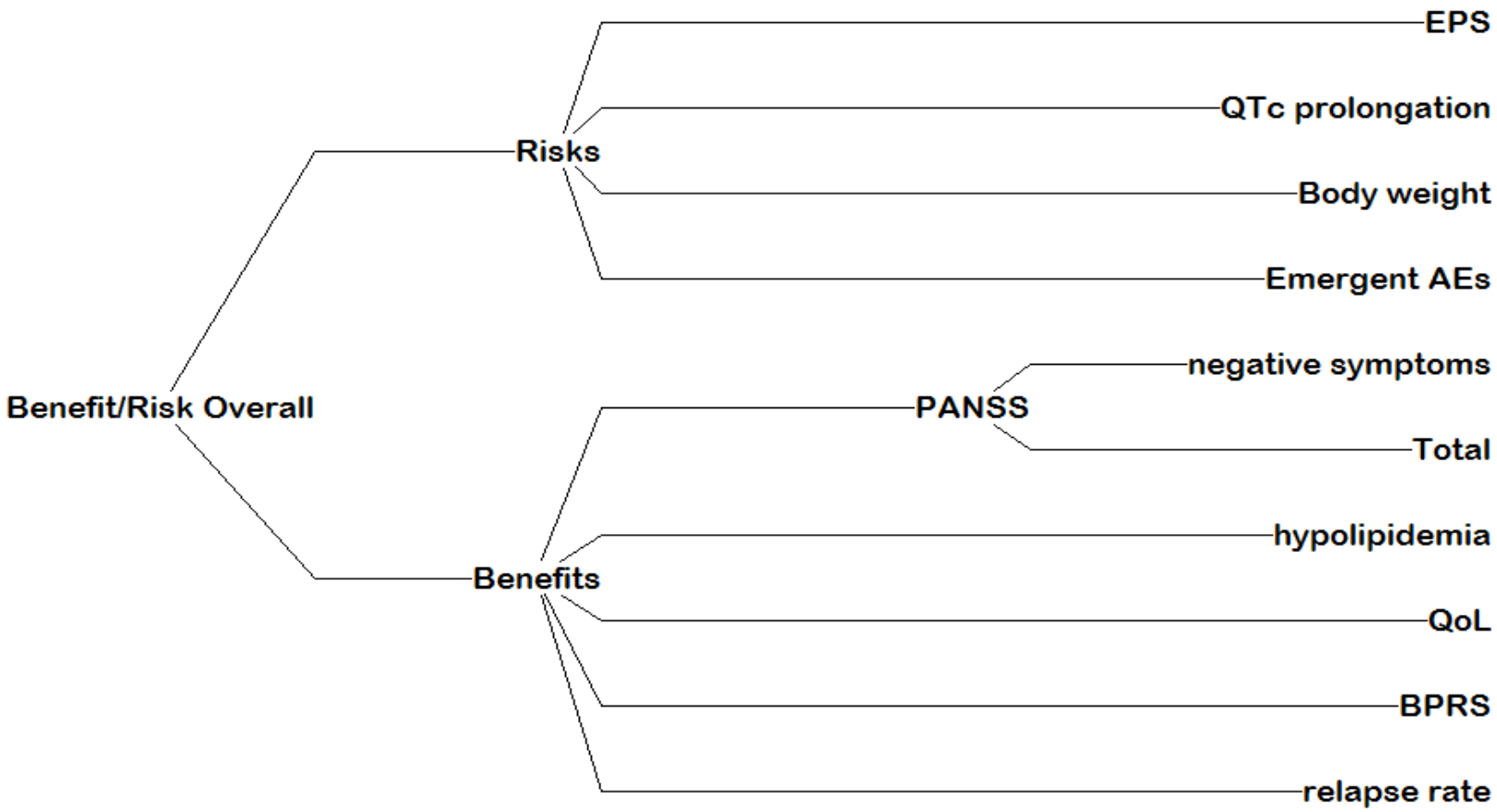
Relapse rate

Quality of Life

Hypolipidemia

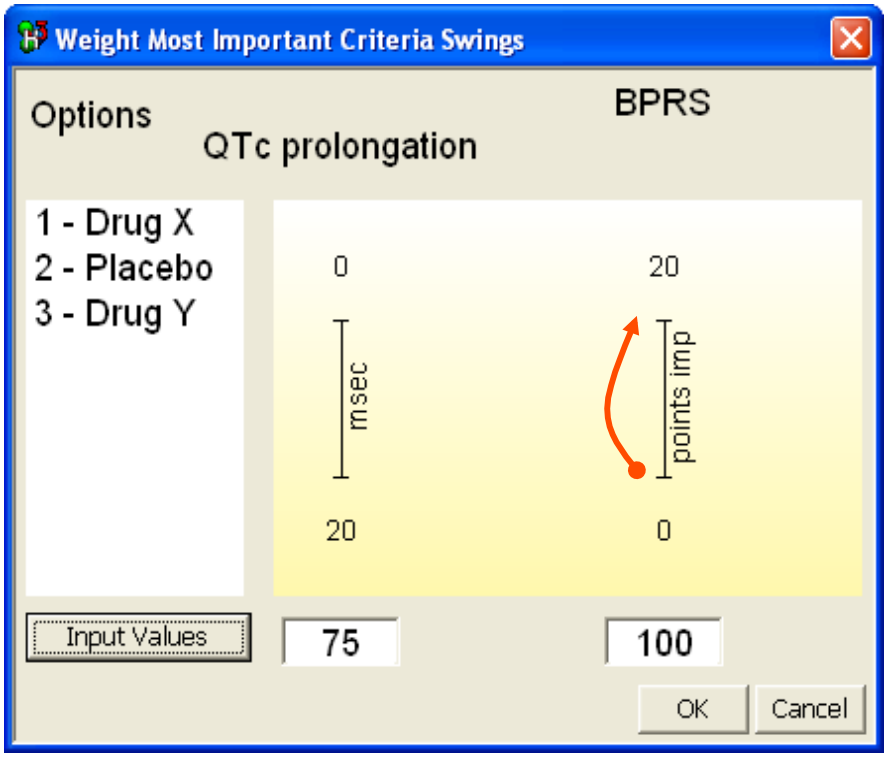
⋮

MCDA model: value tree



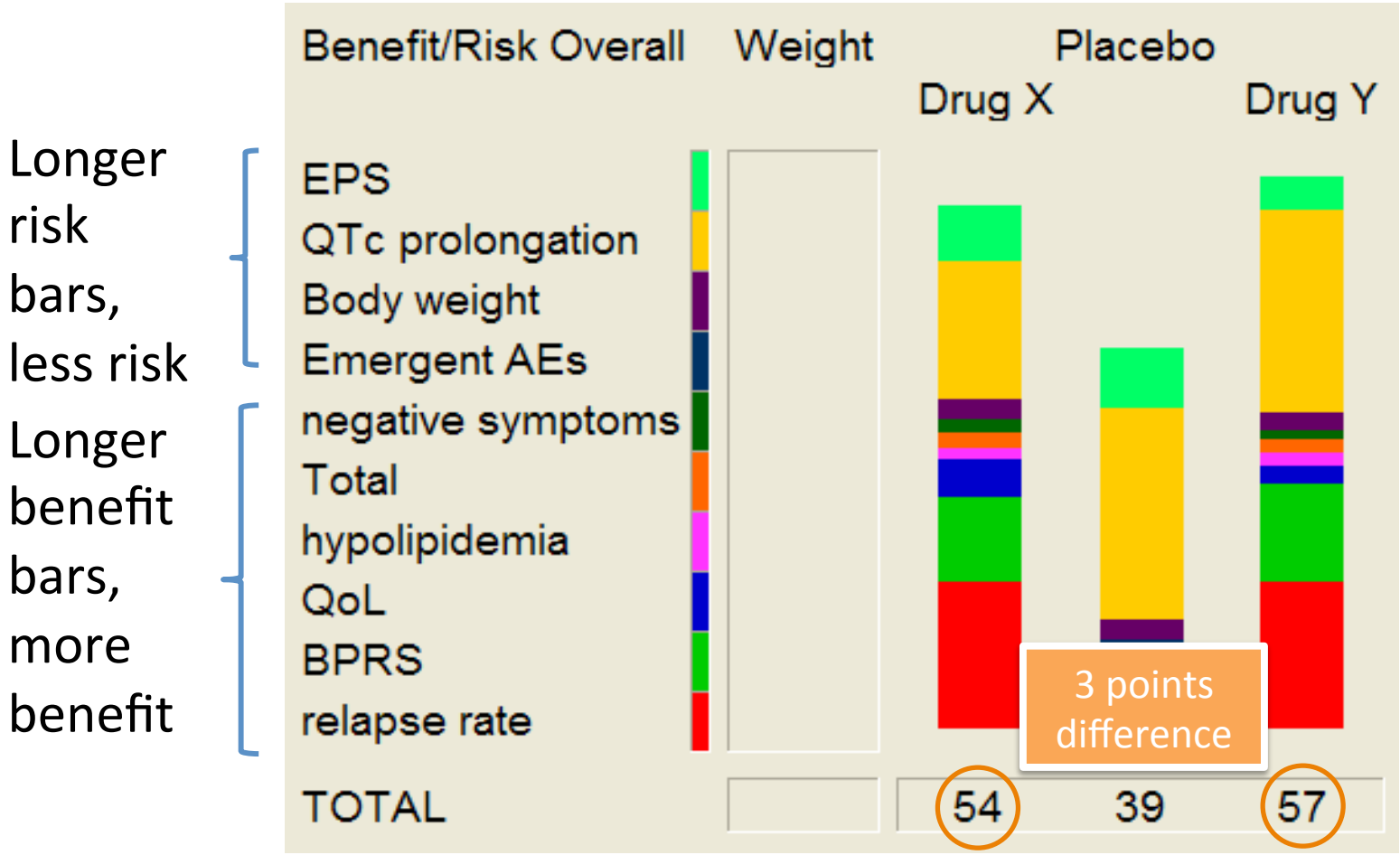
Comparing benefit with risk

Compare the swings in value on the most important benefit and risk scales.



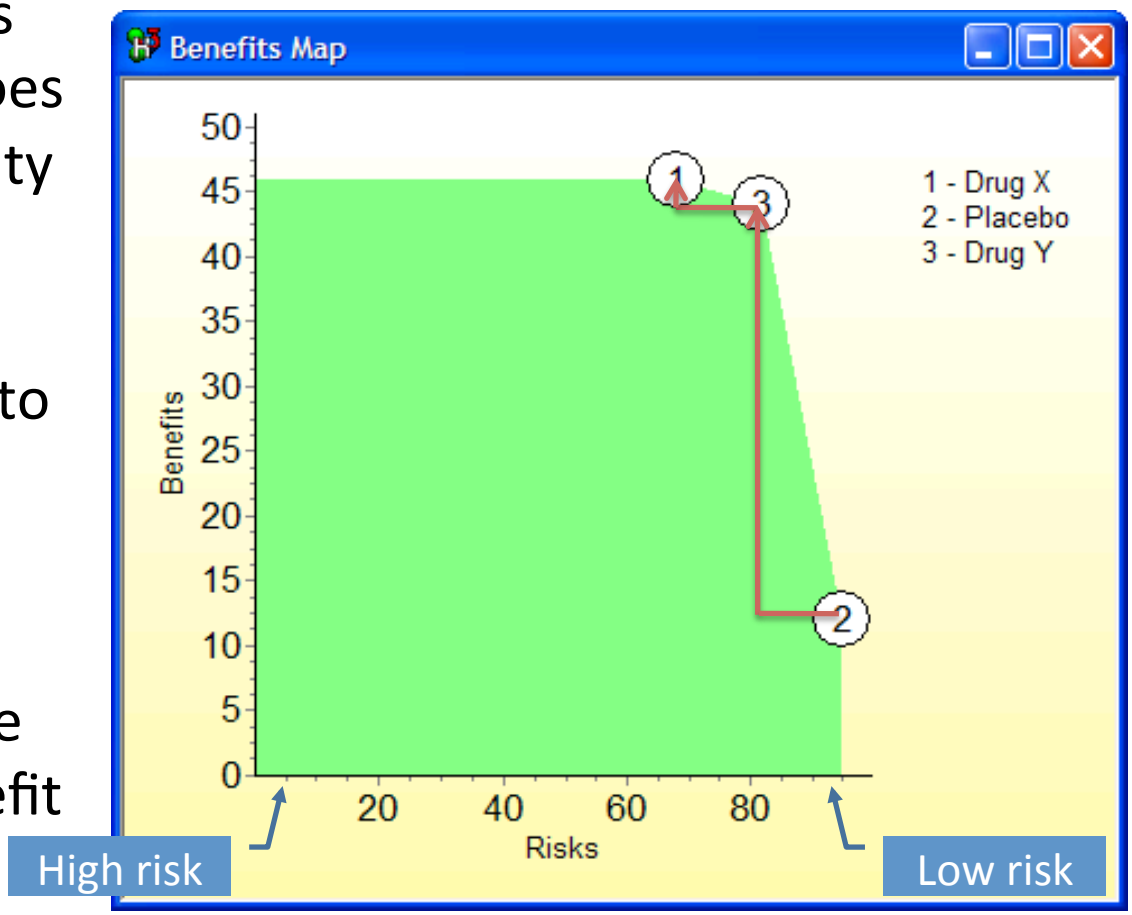
"How big is the difference, and how much do you care about it?"

Examine criteria contributions



Benefits vs. Risk Preference

- Plot benefit versus risk values; this does not assume equality of units.
- Moving from placebo to drug Y to drug X shows:
  - relatively equal increases in risk
  - a relatively large increase in benefit for Y compared to X over Y.



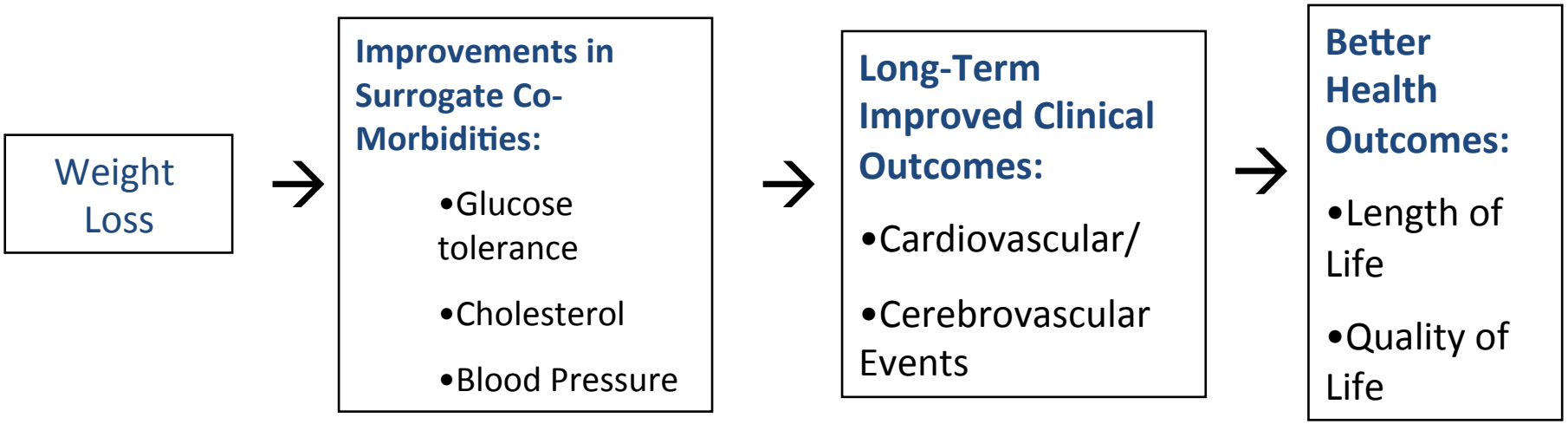
Assessing A Structured, Quantitative Health Outcomes Approach To Drug Risk-Benefit Analysis

Using a health outcomes model to assess drug safety and benefits together could promote consistency and comparability across products and diseases.

by Louis P. Garrison Jr., Adrian Towse, and Brian W. Bresnahan

ABSTRACT: Regulatory authorities make difficult risk-benefit decisions when approving new drugs. Food and Drug Administration (FDA) advisory committees and reviewers must consider a complex body of evidence, including efficacy and safety results of trials, disease epidemiology, potential side effects, and patients' needs. However, this menu of information is not usually presented in a consistent and integrated framework. The members of an FDA review panel vote with some unobserved, implicit weighting of the evidence. This paper argues that outcomes research tools for modeling long-term health outcomes, measuring health preferences, and establishing the value of additional information could provide a more structured, transparent, and quantitative process of assessing risk-benefit balance.
[*Health Affairs* 26, no. 3 (2007): 684–695; 10.1377/hlthaff.26.3.684]

Implicit Bioclinical Health Outcomes Framework: Modeling Can Make this **Explicit** *(i.e., Quantitative and Transparent)*



Obesity Disease Model

Incremental Net Health Benefit (INHB) of New Medicine (2) vs. Control (1)

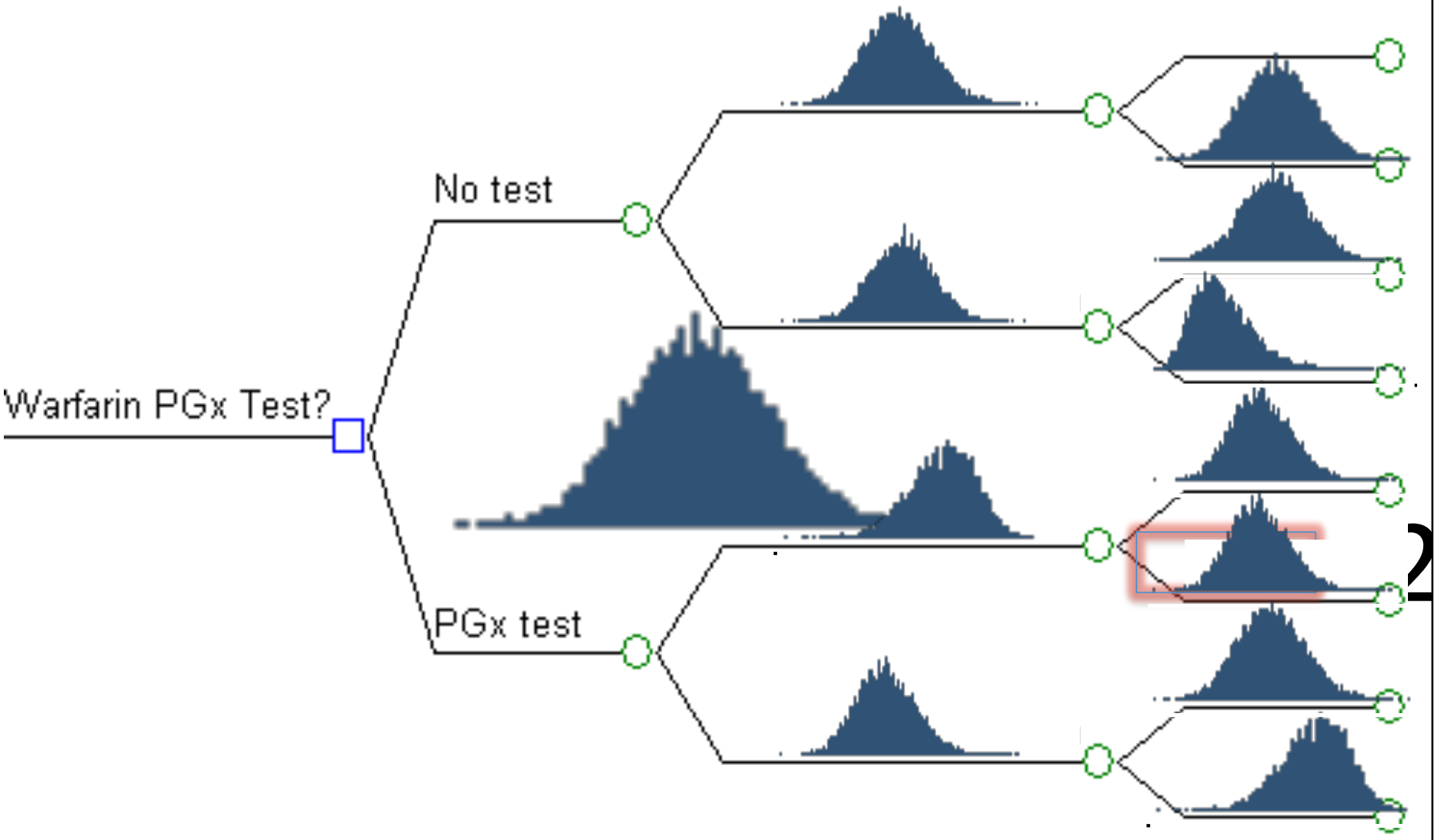
$$INHB = (B_2 - B_1) - (R_2 - R_1)$$

where

- Health benefit (B) is measured in metric *that combines length and quality of life.*
- Risk R (or harms) is measured in a metric *that combines length and quality of life.*

$(B_2 - B_1) > (R_2 - R_1)$ → Favorable benefit-risk balance

The differential needs to be positive given patient risk aversion and greater uncertainty about safety at launch.


No test
Warfarin PGx Test?
PGx test

NO TEST

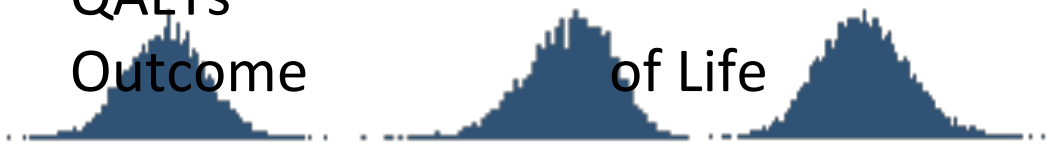
Clinical QALYs Outcome

Years of Life

PGx TEST

Clinical QALYs Outcome

Years of Life



Utility Weights: Tufts CEA Registry

Search the CEA Registry

Basic Search: Select type of information desired (article, ratio, or utility weight).

Enter in the text box one of the following: author last name, journal title (use PubMed abbreviation, e.g., N Engl J Med, or a word from the article title or abstract.

Advanced Search: Allows more complex searches using additional search fields and extended Boolean logic.

Basic Search | Advanced Search

Search Results (Back) Article/Ratios
Your search returned 160 results

Pick Columns to Display(Sort by)

Article ID	Health State	Weigh
2009-01-05154	Baseline; acute shoulder pain	0.494
2009-01-04814	Patient with bone metastasis on pain medicines	0.2
2009-01-04814	Patient with bone metastasis and no pain after single fraction radiation	0.51
2009-01-04814	Patient bone metastasis and no pain after multiple fraction radiation	0.56
2008-01-04644	Coronary artery disease with chest pain	0.7725
2008-01-04644	Coronary artery disease with no chest pain	0.878
2008-01-04459	Chronic pelvic pain	0.55
2008-01-03968	treatment of epigastric pain with proton pump inhibitor	0.744
2008-01-03968	treatment of epigastric pain with h. pylori test and subsequent, appropriate treatment	0.734
2008-01-03861	Patients with chronic low back pain at baseline	0.7
2008-01-03796	Patients with low back pain on graded activity plus problem solving therapy	0.44
2008-01-03796	Patients with low back pain on active combination therapy	0.53
2008-01-03796	Patients with low back pain on active physical treatment	0.49
2008-01-03685	topical NSAID usage for knee pain at 24 months from the preference study	0.607
2008-01-03685	oral NSAID usage for knee pain at 24 months from the prefence study	0.622
2008-01-03685	topical NSAID usage for knee pain at 24 months from RCT	0.684
2008-01-03685	oral NSAID usage for knee pain at 24 months from RCT	0.676

Tufts Medical Center | INSTITUTE FOR CLINICAL RESEARCH AND HEALTH POLICY STUDIES | The Center for the Evaluation of Value and Risk in Health

Pharmaceutical Outcomes Research & Policy Program, University of Washington

Health Outcomes Modeling Can Yield More Than Just a Single INHB Differential

- **Heterogeneity:** Multiple INHB differentials with confidence intervals for different subgroups
  - E.g., subgroups within label and subgroups outside the labeled indication
- **Incidence/Prevalence:** Estimates at a population level: how large are the affected subgroups?
- **Uncertainty**—Sensitivity analyses—probabilistic/structural
- **Value of Information:** Projection of health benefits forgone due to delay→value (and costs) of collecting additional information
- **Risk Management:** Projection of the impact of a risk management plan
- **Life Cycle Management:** Guidance for cost allocation of post-marketing studies

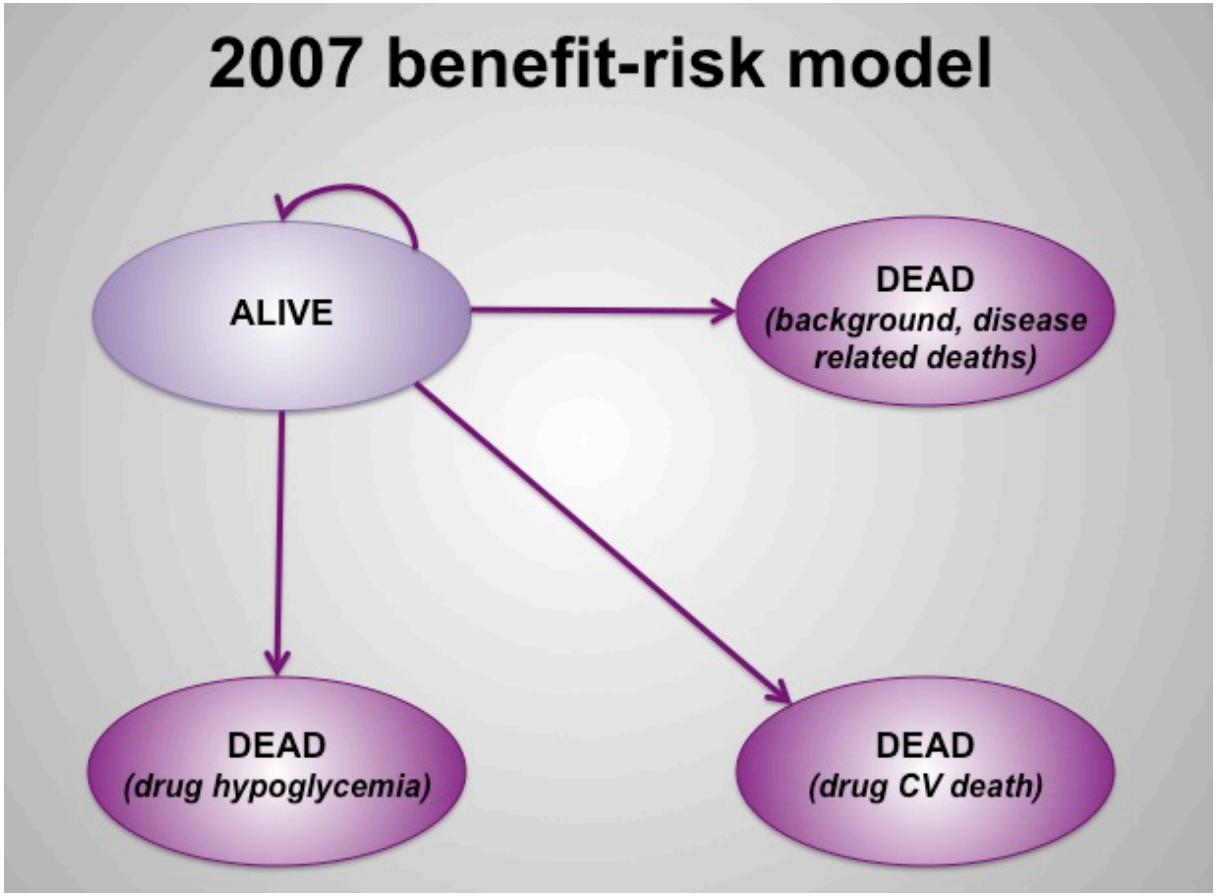
CASE STUDY:
Rosiglitazone (AVANDIA®) for Diabetes

Can Modeling of Health Outcomes Facilitate Regulatory Decision Making?: The Benefit–Risk Tradeoff for Rosiglitazone in 1999 vs. 2007

JT Cross[1,2], DL Veenstra[1], JS Gardner[1] and LP Garrison Jr[1]

Published: Clinical Pharmacology & Therapeutics, 2011

Methods: *Model Structure 2007*



Source: Cross, 2009

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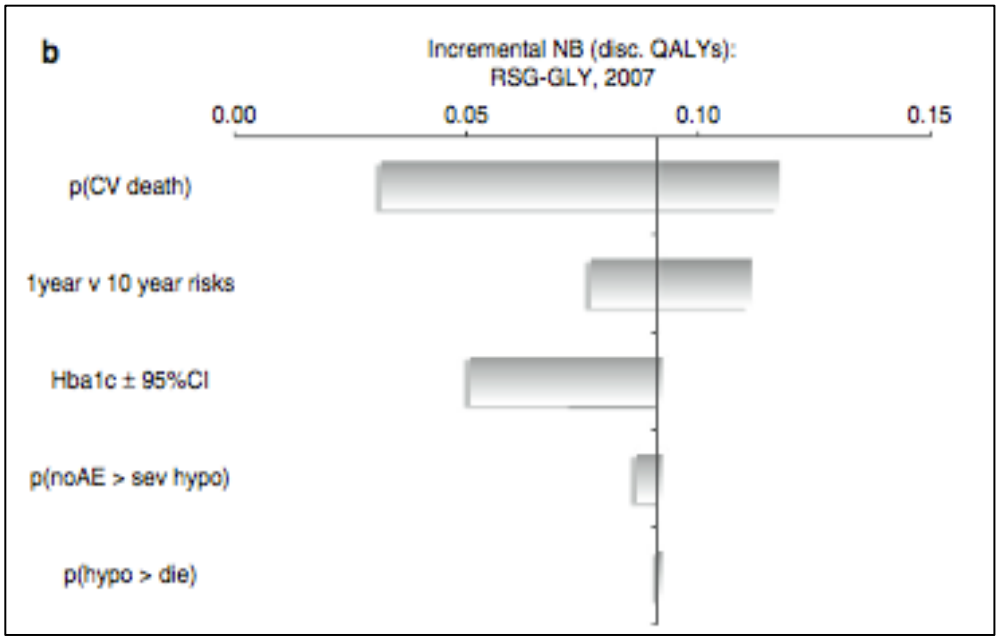
2007 Base Case Results
(Mean QALYs per patient, discounted)

Outcome	Metformin	Glyburide	Rosiglitazone
Benefit	7.903	7.821	7.937
Harm	0.000	0.001	0.026
Net Benefit	7.903	7.820	7.911
Inc. Net Benefit (Rosi vs.)	0.009	0.091	----

Source: Cross et al., 2011

Deterministic Sensitivity Analyses, 2007 Rosiglitazone vs. Metformin



Source: Cross et al., 2011

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Using Incremental Net Benefit for Quantitative Benefit-Risk Analysis – Case Study of Vioxx® : Rofecoxib versus Naproxen for Treatment of Rheumatoid Arthritis

Larry Lynd, PhD

Faculty of Pharmaceutical Sciences
Dept. of Health Care and Epidemiology
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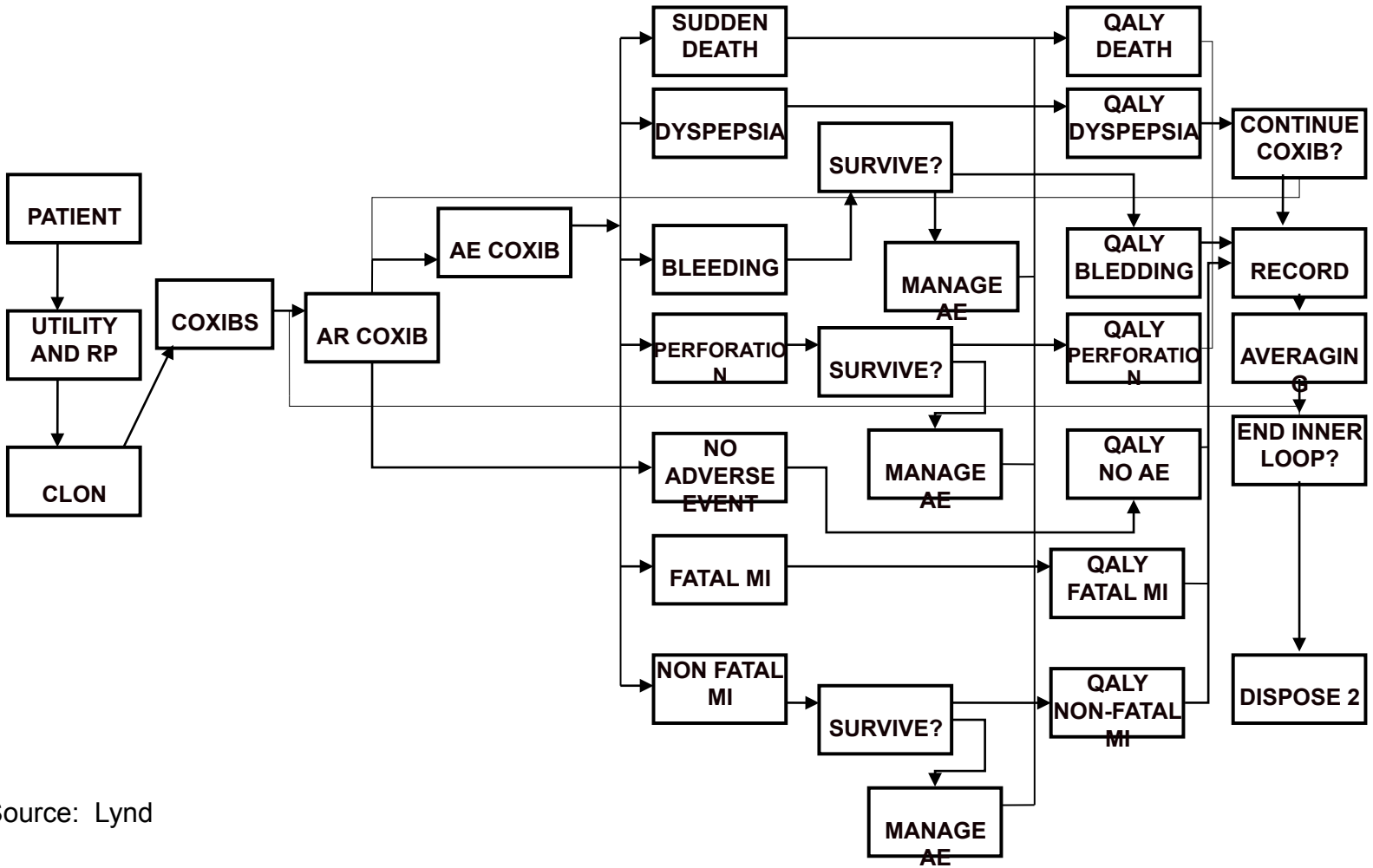
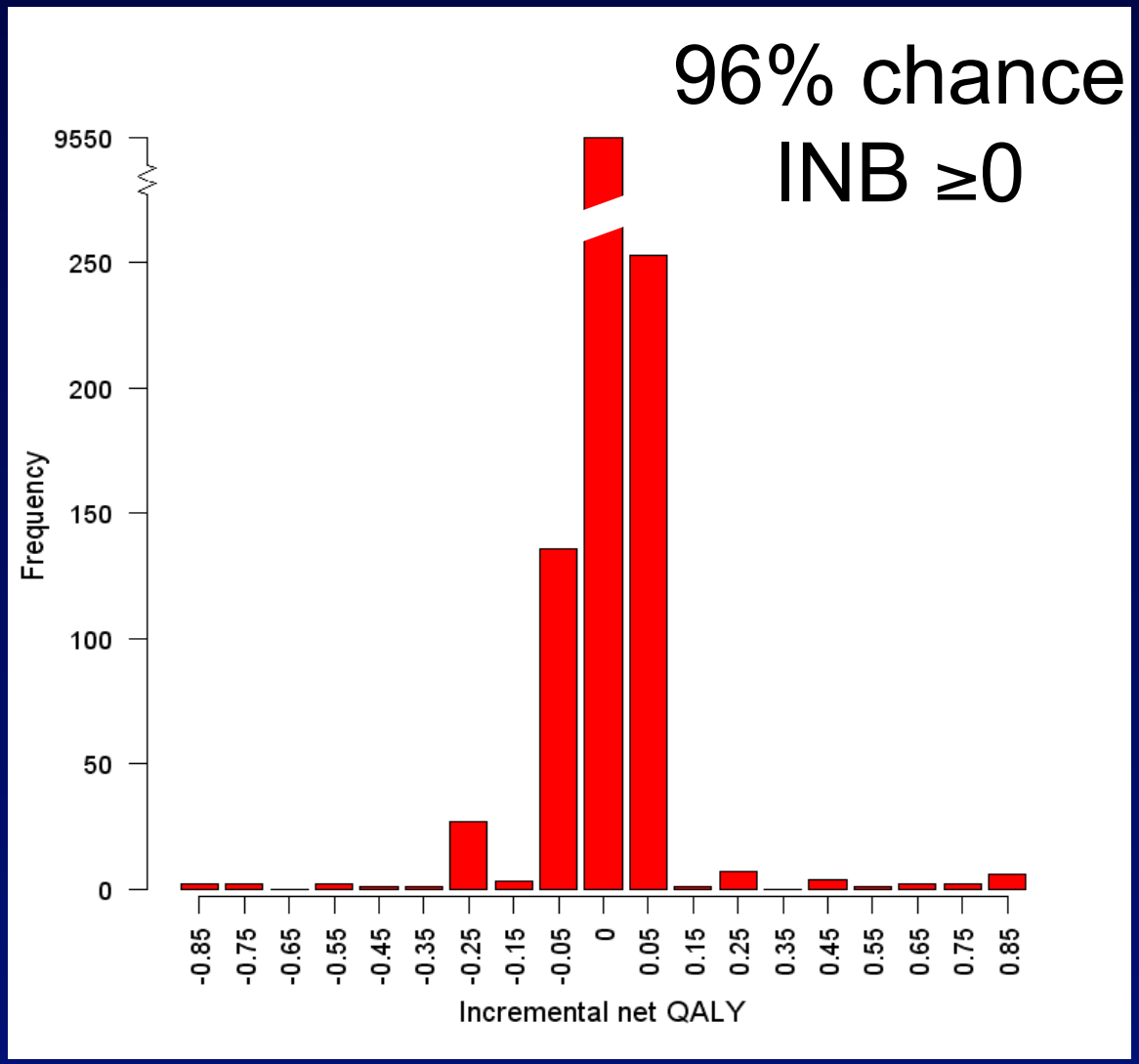

PATIENT
UTILITY AND RP
CLON
COXIBS
AR COXIB
AE COXIB
SUDDEN DEATH
DYSPEPSIA
BLEEDING
PERFORATION
NO ADVERSE EVENT
FATAL MI
NON FATAL MI
SURVIVE?
MANAGE AE
SURVIVE?
MANAGE AE
SURVIVE?
MANAGE AE
QALY DEATH
QALY DYSPEPSIA
QALY BLEDDING
QALY PERFORATION
QALY NO AE
QALY FATAL MI
QALY NON-FATAL MI
CONTINUE COXIB?
RECORD
AVERAGING
END INNER LOOP?
DISPOSE 2

Source: Lynd

Results: assuming equal efficacy



Source: Lynd

What are the pros and cons of each method?

- **Benefit-Risk Framework**
  - Pro: Logical framework based on trial and epidemiologic data
  - Con: Doesn't extrapolate from surrogates; not clear how to aggregate preferences
- **Stated Choice Survey**
  - Pro: Intuitively appealing
  - Con: Hypothetical, innumeracy issues (if very low probabilities and multiple risks).
- **Multi-Criteria Decision-Analysis**
  - Pro: Stakeholder group process
  - Con: Value tree structure dependent on group
- **Benefit-Risk Health Outcomes Modeling**
  - Pro: Can handle long-term extrapolation, provides summary measure (that can vary by subgroup).
  - Con: Reliance on utilities, concerns about extrapolation modeling

What might this mean for the future processes of regulatory decision-making?

- There is clear movement toward a more systematic and quantitative approach at both the FDA and EMA.
- There will be a reluctance to adopt any specific approach.
- Changing regulatory processes can take many years —if not decades.

A Risk-Characterization Framework for Decision-Making at the FDA (NAS, 2011)

Six Key Elements:

1. Exposed population
2. Mortality
3. Morbidity
4. Personal Controllability
5. Ability to detect adverse health effects
6. Ability to mitigate adverse health effects

What are the implications for pain clinicians and reporting of pain clinical trials?

- It is Important to recognize the unique features of pain as a disease condition as it affects benefit-risk assessment.
- Should standard reporting of benefit-risk in pain trials be changed?
- Should additional benefit-risk analyses be conducted to communicate benefit-risk to pain clinicians?
- How should benefit-risk be communicated to patients?

Models Don't Make Decisions, People Do

"All models are wrong, but some are useful."

G.E.P. Box, Statistician, 1979.

The issue is not so much the metric or how it is measured, as it is using models to assist decision-making.

Thank you!

Questions?

Lgarrisn@uw.edu