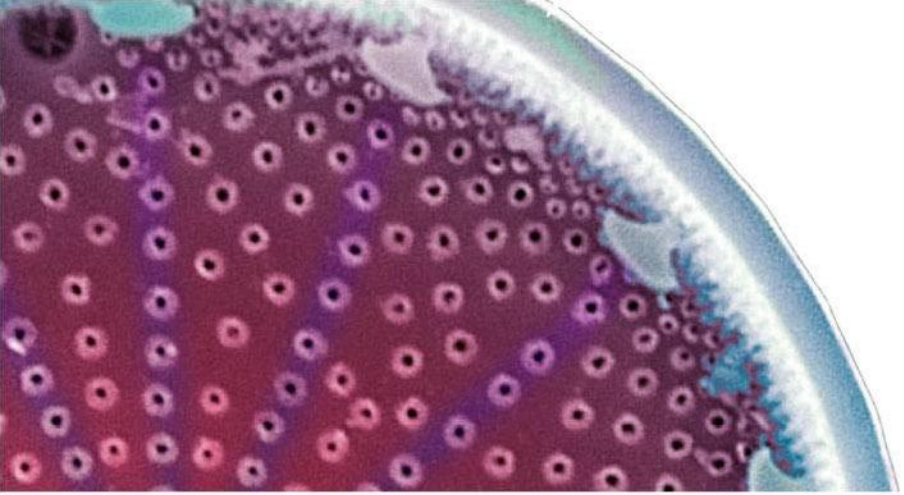

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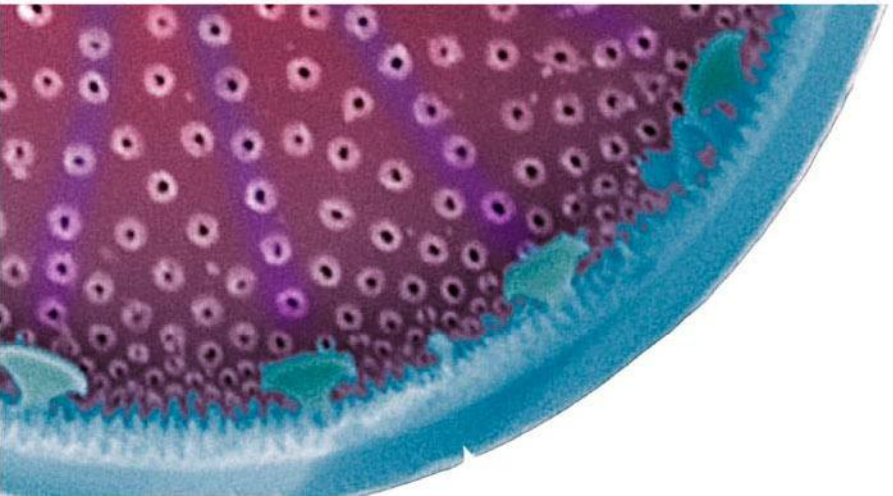
CER and BRA

A Case for Comparative Effectiveness Research and Benefit Risk Analysis Convergence



Dr. John J. Doyle

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CER and BRA

Convergent pathway

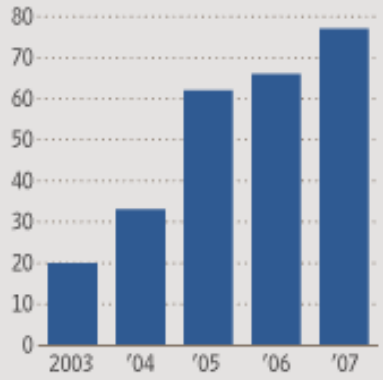
Will CER help us translate a product's safety profile into risk-benefit profile?

The Food and Drug Administration and eHealth Foundation
In cooperation with the Brookings Institute
Sentinel Initiative: Structure, Function and Scope
Washington, D.C.
December 16, 2008

Safety First

The FDA has been insisting that more drugs carry strong warnings, and new drug submissions by the industry have slowed since 2004.

Estimated number of new or revised 'black-box' warnings, the FDA's strongest



Number of new drug applications

Source: University of Kansas Hospital's Drug Information Center (warnings); FDA (applications)

'The Pink Sheet'

PRESCRIPTION PHARMACEUTICALS AND BIOTECHNOLOGY

Printed By Library Firm:(Quintiles Inc) on [November 10, 2008]

FDA Looks To Outcomes Research In Move To Quantify Risk/Benefit Decisions

November 10, 2008

THE WALL STREET JOURNAL.

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SIDE EFFECT

Drug Makers Say FDA Safety Focus Is Slowing New-Medicine Pipeline

By AVERY JOHNSON and RON WINSLOW
June 30, 2008; Page A1

CER and BRA

Risk management

RRA fits under the larger umbrella of risk management, and includes a number of methods that are not meant to replace clinical evaluation, but to enhance such assessments and reduce unnecessary patient exposure to adverse events

- **Risk identification** is the first step in risk management. However, some side effects may not be evident until a drug has been used for many years
- The second element of risk management is **risk assessment**, which includes risk perception. Assessing risk relies on some understanding of numerical values and is influenced by the experience, expectations and behavior of the person facing the risk
- **Risk prioritization and communication's** main goal is to improve collective and individual decision making

CER and BRA

Risk and benefit metrics

Various metrics, methods and approaches need to be considered for a Risk-Benefit Assessment

Metrics

- Proportional Reporting Ratio (PRR)
- Bayesian confidence propagation neural network (BCPNN)
- Multi-item Gamma Poisson Shrinker (M GPS)
- Sequential Probability Ratio Test (SPRT)
- Maximized Sequential Probability Ratio Test (maxSPRT)
- Cumulative Sum Chart (CUSUM)
- Group Sequential Monitoring

Metrics

- Clinical outcomes
- Economic outcomes
- Humanistic outcomes
- QTwist
- QALYs
- Utility
- Visual Analogue Scale
- Standard Gamble
- Time-Trade-Off
- HYEs

Metrics

- NNT / NNH
- Utility / Disutility
- Incremental Risk Benefit Ratio (IRBR)
- Risk Benefit Acceptability Curves (RBAC)
- Expected Incremental Net Benefit (EINB)
- Multi-criteria Decision Analysis (MCDA)

CER and BRA

Methods

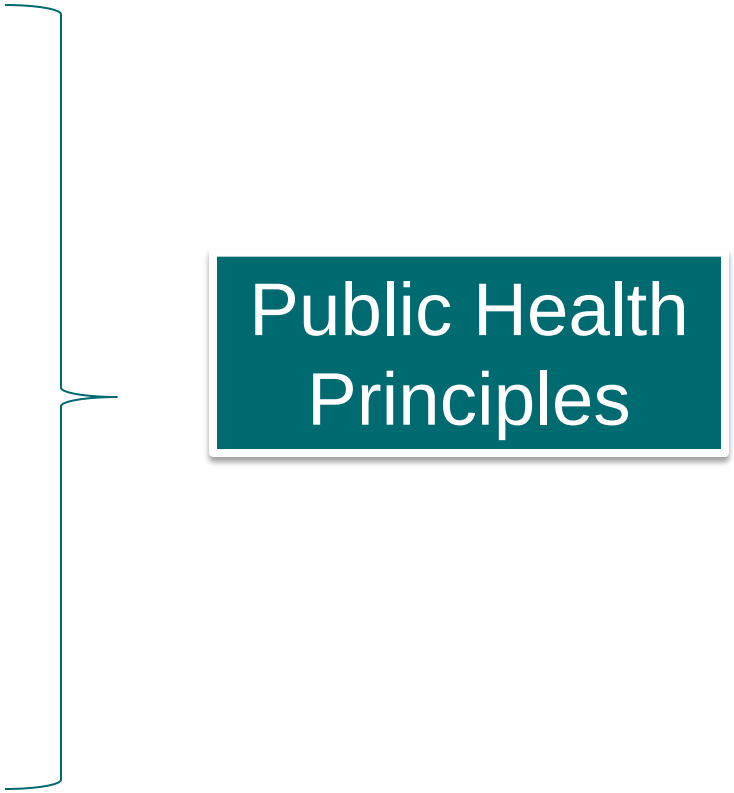
The present regulatory climate demands BRA, yet there are few formalized methods that contain quantitative syntheses of benefit and risk.

Method	Description
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) vs. 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 (RBP) and Risk Benefit Acceptability Threshold (RBAT)
9	Probabilistic Simulation Methods (PSM)
10	Monte Carlo Simulation (MCS)
11	Multi-Criteria Decision Analysis (MCDA)
12	Risk-Benefit Contour (RBC)

Source: Jeff J. Guo et al. A Review of Risk-Benefit Assessments for Drug Development ISPOR 2009 Workshop: W29. 2009

CER and BRA
Common Denominators

- ✓ Patient-centric focus
- ✓ Population-level analysis
- ✓ Real-world research
- ✓ Generalizability optimized
- ✓ Longitudinal follow-up
- ✓ Heterogeneity explored
- ✓ Superiority tested
- ✓ Outcomes oriented



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CER Cases

Real-world Examples of Real-world Research

CER Case Study: CATIE

Clinical antipsychotic trials of intervention effectiveness

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Background

Treatments

- The CATIE Schizophrenia Study is comparing the effectiveness of six medications approved for market use by the U.S. Food and Drug Administration:
  - ziprasidone (Geodon)
  - olanzapine (Zyprexa)
  - quietiapine (Seroquel)
  - risperidone (Risperdal)
  - clozapine (Clozaril)
  - perphenazine (Trilafon)*
- The CATIE Alzheimer's Disease Study is comparing the effectiveness of four FDA-approved medications for these symptoms:
  - olanzapine (Zyprexa®)
  - quetiapine (Seroquel®)
  - risperidone (Risperdal®)
  - citalopram (Celexa®)

Study Description

- The Clinical Antipsychotic Trials of Intervention Effectiveness project (CATIE) is a randomized control trial that evaluated the clinical effectiveness of atypical antipsychotics in the treatment of schizophrenia and Alzheimer's disease

Outcomes & Implications

- The results conclude that the older (first generation) antipsychotic medication perphenazine was less expensive and no less effective than the newer (second generation) medications used in the trial during initial treatment, suggesting that older antipsychotics still have a role in treating schizophrenia

Source: http://www.catie.unc.edu/schizophrenia/about-public.html

CER Case Study: GeCCO

Genotype guided comparison of clopidogrel & prasugrel Outcomes

Background

Disease

- About 25 percent of people worldwide are born with a version of the *CYP2C19* gene that produces a cytochrome P450 2C19 enzyme that is not fully functional
- Patients who are "extensive metabolizers" of clopidogrel were born with a normally functioning version of the *CYP2C19* gene have comparable outcomes to those patients taking prasugrel, a newer, higher cost drug with metabolism less dependent on genetic variations

Treatments

- Prasugrel has shown greater efficacy but higher bleeding risk than clopidogrel in head-to-head clinical trials, but to date none of the studies limited the patient population to those who extensively metabolize clopidogrel, which could substantially impact the results

Study Description

- Genotype Guided Comparison of Clopidogrel & Prasugrel Outcomes (GeCCO) is a head-to-head prospective, observational study comparing clopidogrel (Plavix) and prasugrel (Effient)
- The trial will study more than 14,000 extensive metabolizers of clopidogrel were born with a normally functioning version of the *CYP2C19*

Outcomes & Implications

- The study will compare effectiveness of the two drugs by measuring the rate of cardiovascular deaths, nonfatal heart attacks and nonfatal strokes over a six-month period
- The study could have important patient safety ramifications and significant cost implications for health plans that pay for these drugs. Clopidogrel, the third largest selling drug in the United States with $4.9 billion in 2008 sales, could face generic competition when its patent expires in late 2011, creating additional savings opportunities

Source - Medco Launches Plavix(R), Effient(R) Comparative Effectiveness Study Examining Role Of Genetics, Medco Health Solutions, Inc

CER Case Study: CATT

Comparison of AMD treatment trials

Background

Disease

- AMD is a disease that damages the macula. The macula is the area of the retina responsible for central vision. AMD is a leading cause of blindness among older Americans. Nearly two million Americans are visually impaired by AMD, while more than seven million are at increased risk of vision loss from the disease

Treatments

- Lucentis (ranibizumab) was approved by the U.S. Food and Drug Administration (FDA) in June of 2006 for the treatment of advanced, or wet, AMD. The approval was based on evidence from clinical trials showing that Lucentis slows the rate of progression of vision loss from wet AMD
- Avastin (bevacizumab) was approved by the FDA in 2004 as an intravenous treatment for patients with advanced colorectal cancer and therefore has been available off-label to treat wet AMD. Avastin is thought to remain in the eye longer than Lucentis and therefore possibly allow for less frequent injections

Study Description

- Comparison of AMD Treatments Trial (CATT) is a multicenter clinical trial to compare the relative safety and effectiveness of two drugs currently used to treat advanced age-related macular degeneration (AMD)
- The trial determined the relative safety and effectiveness of treating wet AMD in 1,200 patients. This clinical trial will be conducted at 47 clinical centers across the country

Outcomes & Implications

- It is hoped the results of this study will improve the treatment of wet AMD. Reducing the frequency of treatments without compromising effectiveness would reduce the treatment burden for patients and produce a potential cost savings
- The initial study results conclude that Lucentis and Avastin had equal effects on visual acuity when administered according to the same schedule. This means that providers and payers will now have to rationalize the cost of using Lucentis when a low-cost, effective alternative exists

Source - NEI Press Release, National Institute of Health, National Eye Institute For Immediate Release February 22, 2008

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Appendix

Demonstrating Real World Value

RBA quantitative approaches and techniques

The present regulatory climate demands RBA, yet there are few formalized methods that contain quantitative syntheses of benefit and risk. The methods proposed below represent an initial step towards such an approach

Method	Description
1	Quantitative Framework for Risk and Benefit Assessment (QFRBA)
2	Benefit-Less Risk Analysis (BLRA)
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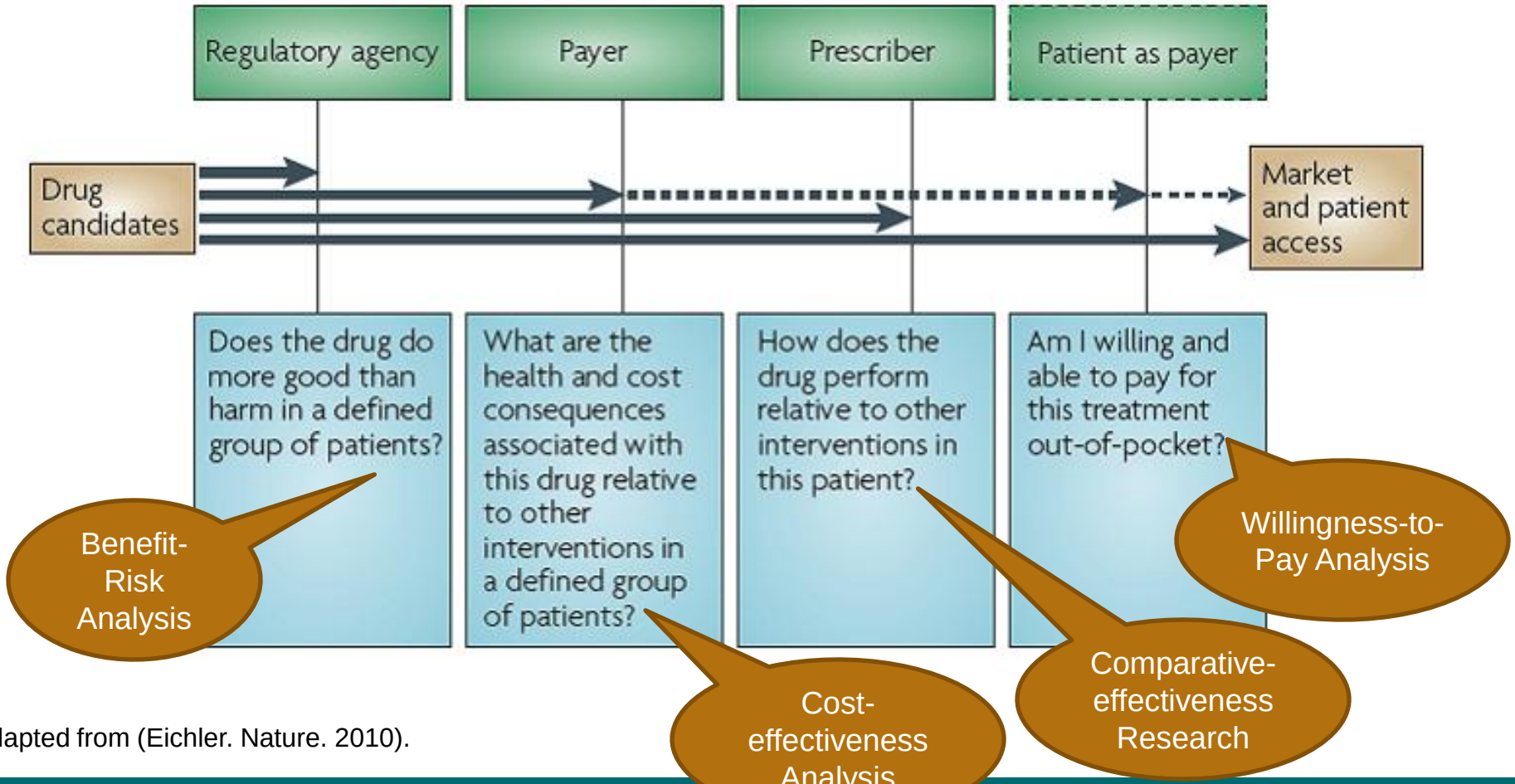
Source: Jeff J. Guo et al. A Review of Risk-Benefit Assessments for Drug Development ISPOR 2009 Workshop: W29. 2009

CER Explained

Role in market access

The road to market access for pharmaceutical products is moderated by several stakeholders with the patient serving as the final decision-maker



Adapted from (Eichler. Nature. 2010).

Demonstrating Real World Value

Global approaches to RBA

Both the US Food and Drug Administration (FDA) and the European Committee on Proprietary Medicinal Products (CPMP) are increasingly requesting RBA of pharmaceutical products

United States

- In the US, the FDA has established a Drug Safety and Risk Management division, which is charged with evaluating the safety, efficacy, and abuse potential of drugs, as well as risk management and risk communication
- The FDA relies on multiple approaches because no single approach is sufficiently comprehensive to permit full evaluation of all important problems- and then recommends analysis of report data and use of large population-based databases

Worldwide

- The CPMP also does not have a standardized method for benefit-risks studies, other than the assessment of risks
- The Council for International Organizations of Medical Sciences (CIOMS) has called for a standardized definition for risks and benefits and a universal quantitative approach to RBA

Source: Holden, W. Benefit Risk Analysis. Drug Safety 2003.

CER and BRA

Introduction

CER may trigger downstream 'check-points' for companies to revisit the risk-benefit and related cost-benefit profiles of their drugs, thus supporting a 360° perspective on value appraisal

Risks

- The term risk refers both to the probability of a harm resulting from an activity and to its magnitude
- Will this be hazard ratio, adverse events, or incidence rates?
- Examples: Bodily harm, suffering, psychological risks

Benefits

- The term benefit refers to any sort of favorable outcome of the research to society or to the individual
- Will this be quantified on a scale of primary endpoint?
- Examples: Improvement of disease, decreasing morbidity and mortality

Source: Cristina E. Torres, Ph.D.