PHARMACEUTICAL BENEFIT-RISK ASSESSMENT

WHAT SHOULD WE DO IN THE ABSENCE OF REGULATORY GUIDANCE?

Introduction

ISPOR International Meeting
Symposium, May 24, 2011

Elizabeth B. Andrews, PhD, MPH, FISPE
VP, Pharmacoeconomics and Risk Management
RTI Health Solutions

Common Goals

- Systematic, predictable decision making about drug products
- Rigorous evaluation of the evidence on drug risks and benefits
- Decisions consistent with public values
- Transparent communication of decisions, earning trust for FDA and industry

Slide source: Baruch Fischhoff, Carnegie Mellon University

Quantitative Benefit-Risk Analysis – Recent Developments

2006  Institute of Medicine, The Future of Drug Safety (current analyses "ad hoc, informal, and qualitative")

2007  Benefit-risk requirements in FDA reauthorization
       First FDA, EMEA, industry, academic conference on B-R methods

2009  Second FDA, EMEA, industry, academic conference on B-R methods
       NY Academy of Sciences/FDA conference

2010  European Medicines Agency Roadmap to 2015

Ongoing: FDA Semi-Quantitative Matrix
          EMA Benefit-Risk Work Packages
          Benefit-Risk Working Group
          PhRMA Framework, Case Studies

European Medicines Agency, Road Map to 2015

- “The current risk management plan for medicines should be converted into a benefit/risk management plan."
- Increased transparency of benefit-risk assessments
- More use of quantitative methods
- Explicit accounting for patients’ values

Woodcock, Describing FDA framework (4/5/2011)

“intuitive-type of benefit-risk framework that a person on the street or a physician could look at and understand. It doesn’t have a lot of equations or math in it. It really walks you through the reasoning of what the disease is and why it needs treatment, what the consequences of the disease are and what the available alternatives are, and how this new intervention fits in. This is really a decision tool to help people get on the same page about why you may disagree about what to do about any given drug safety issue... I think this will be very successful and I’m very happy about this, but we have to give it a few more internal rounds and tweaks. Eventually, I would hope to see this as an executive summary of a medical review so that there would be a concise summary of where this drug fits into the armamentarium — or not.”

Finding a Path Forward for Benefit-Risk Assessment

From here

To here

A reasonable way forward

Concepts
Methods
Perspectives
Communication Tools
**Our Plan**

- Illustrate methods for assessing and communicating benefits and risks using a hypothetical example:
  
  **New Statin**
  
  - Indication: Primary prevention of atherosclerosis
  - Pharmaceutical company seeks regulatory approval (US?
    EU?)
  - Benefits of statins: Well-documented lipid effect shown in clinical trials. Morbidity and mortality benefits shown in long-term studies and meta-analyses.
  - Risks: Some well-documented, some case report only.
  - Considerations: Precedent, benefits not immediately obvious to patients, uncertain effectiveness with real-world compliance, common side effects, other treatments on the market, other methods to reduce, ...

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**Speakers**

- Lou Garrison, PhD
  Professor, University of Washington, School of Pharmacy

- Bennett Levitan, MD, PhD
  Director, Department of Epidemiology, Johnson & Johnson P&G

- F. Reed Johnson, PhD
  RTI Distinguished Fellow and Principal Economist, RTI Health Solutions

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**PhRMA Benefit-Risk Action Team (BRAT) Framework**

*Bennett Levitan, M.D.-Ph.D.*  
*Director, Epidemiology, Johnson & Johnson Pharmaceutical R&D*  
*International Society for Pharmacoeconomics and Outcomes Research 16th Annual Meeting*

*May 24, 2011*

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**PhRMA Benefit Risk Action Team (BRAT) Framework**  
Recognition of need for structured approach to benefit-risk

- **IOM, CHMP statements on benefit/risk assessment**
  - Need to improve methodology, transparency, consistency and communication
  - Recommendation to take a systematic approach
  - Need to develop and incorporate new quantitative tools

- **Birth of BRAT (May 2006)**
  - PhRMA announcement that it would develop a framework for benefit-risk assessment
  - Collaborative team (~10 companies)
  - Designed to enrich (not replace) judgment

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**BRAT: Overview of Goals and Focus**

- **Strategic Goals**
  - To increase the transparency, predictability and consistency with which Benefit-Risk (B-R) assessments are conducted
  - To improve the communication of B-R information to patients and healthcare professionals
  - To strengthen the drug development and regulatory approval process

- **Tactical Focus**
  - Developing a structured, transparent framework for B-R assessment
  - Facilitating its use by pharmaceutical companies
  - Facilitating its integration into regulatory decision-making at both approval and post-approval

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**BRAT Framework: Concepts and Prerequisites (1)**

**What is the “Framework”?**

- A framework is a set of principles, guidelines and tools to guide decision-makers in
  - Selecting
  - Organizing
  - Understanding
  - Summarizing evidence relevant to benefit-risk decisions

- The Framework is not a mathematical model
BRAT Framework: Concepts and Prerequisites (2)

- Applicable in multiple contexts
  - NDA, kEMS/HMPS, emerging efficacy/safety data, post-approval commitments
  - Ability to include non-trial data (surveillance, observational, preclinical)

- Accounts for comparative nature of benefit-risk
  - Trial comparators or standard of care

BRAT Framework: Concepts and Prerequisites (3)

- Framework processes of value by themselves
  - Use flexible guidelines, not rigid rules
  - Encourage transparency throughout

- Accounts for the complexity of real-world data
  - Represents and accounts for uncertainty and missing information
  - Allows for multiple efficacy endpoints and adverse effects (benefit-risk cannot be captured by a single attribute)

- Account for nature/importance of different benefits and risks
  - Facilitates use of subjective weighting as well as objective data
  - Allow for viewpoints of multiple stakeholders (regulator, patient, physician, sponsor)

Steps in the BRAT Framework

Example application: Late development

Before Phase III → By NDA Filing → By review

BRAT’s origins lay in Multi-criteria Decision Analysis (MCDA)

Steps in the BRAT Framework

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Define the decision context</td>
<td>Define drug, dose, formulation, indication, patient population, comparator(s), time horizon for assessment, perspective of the decision-maker (stakeholder)</td>
</tr>
<tr>
<td>2. Identify outcomes</td>
<td>Select all important outcomes and create the initial value tree, define a preliminary set of outcome measures/endpoints for each, document rationale for outcomes included/excluded</td>
</tr>
<tr>
<td>3. Identify and extract source data</td>
<td>Determine and document all data sources (e.g., clinical trials, observational studies), extract all relevant data into the data source table, including detailed references and any annotations to help the subsequent interpretations</td>
</tr>
<tr>
<td>4. Customize the framework</td>
<td>Modify the value tree based on further review of the data and clinical expertise, refine the outcome measures/endpoints, may include tailoring of outcomes not considered relevant to a particular benefit-risk assessment or that vary in relevancy by stakeholder group</td>
</tr>
<tr>
<td>5. Assess outcome importance</td>
<td>Apply or assess any ranking or weighting of outcome importance to decision-makers or other stakeholders</td>
</tr>
<tr>
<td>6. Display and interpret benefit-risk metrics</td>
<td>Summarize source data into tabular and graphical displays to aid interpretation, challenge summary statistics, review source data, identify and fill any information gaps, interpret summary information</td>
</tr>
</tbody>
</table>

Decision Context: Statins for primary prevention of atherosclerotic cardiovascular disease

- Drug:
  - Hypothetical Statin

- Indication:
  - Primary prevention of atherosclerotic cardiovascular disease in mcn: i.e., adults with no clinically evident CHD

- Population (abbreviated):
  - Men above 55 years of age without established CHD
  - LDL 130 – 160 mg/dL
  - One CV risk factor (high BP, low HDL, smoking, family history)
  - No frailty, multisystem disease (renal failure, alcohol abuse, ...)

- Comparator:
  - Placebo

- Perspective:
  - Regulators for a statin already approved for secondary prevention

- Time frame:
  - 1 year of use

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
Value Tree for BRAT Statins Example
Full tree with identified and potential outcomes

Tuning the Value Tree Reflects Interests and Risk Tolerance of Decision-Makers
Tuning the tree helps simplify the assessment, temporarily simplifying the display to focus on the more critical outcomes or those with data

Tuned Value Tree for Statins Example
Top-level representation of information in the framework

Key Benefit-Risk Summary Table:

Risk Difference Forest Plot
Increasingly common for dichotomous endpoints in benefit-risk

Accounting for Differential Impact of Outcomes - Weighted Approaches

- Variety of methods in the literature
  - B/1 weighting (done implicitly)
  - Point allocation
  - Utility weighting
  - Preference weighting (from stated choice conjoint studies)
  - Quality-adjusted life years (QALYS) or DALYs
  - Multi-criteria decision analysis (MCDA)

- No regulatory standards or guidelines
- All methods are in the literature
- BRAT Framework currently does not promulgate a particular method, but provides the prerequisites for applying whichever approach best serves the decision-makers’ needs
## Analyses from perspectives of multiple stakeholders

<table>
<thead>
<tr>
<th>Outcome</th>
<th>AIIR (adjusted) per 10,000 person-years (95% CI)</th>
<th>Patient*</th>
<th>Physician*</th>
<th>Regulator*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>-2.6 (-6.1, 1.0)</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Coronary heart disease death</td>
<td>-2.7 (-3.5, 0.6)</td>
<td>0.6</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>-1.3 (-2.6, 0.1)</td>
<td>0.6</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Fatal ischemic stroke</td>
<td>-16.9 (-23.2, -10.0)</td>
<td>0.6</td>
<td>0.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Non-fatal ischemic stroke</td>
<td>-12.2 (-18.4, -6.0)</td>
<td>0.6</td>
<td>0.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

### Benefits

<table>
<thead>
<tr>
<th>Injury</th>
<th>Adjusted Rate Difference per 10,000 person-years (95% CI)</th>
<th>Time to Onset*</th>
<th>Median follow-up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td>-2.6 (-6.1, 1.0)</td>
<td>&gt; 2 years</td>
<td>3.0</td>
</tr>
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<td>-2.7 (-3.5, 0.6)</td>
<td>&gt; 2 years</td>
<td>4.9</td>
</tr>
<tr>
<td>Lipid levels met target*</td>
<td>0.00 (0.00, 0.00)</td>
<td>&gt; 3 months</td>
<td>1.0</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>-2.1 (-2.6, 0.4)</td>
<td>&gt; 2 years</td>
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### Risks

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### Current Status

- **BRAT Framework in use by several PhRMA companies**
- **Continued technical development by BRAT Core team**
- **Soft Pilot Program**
  - Voluntary Soft Pilot Program (SPP) with PhRMA member companies in 2011
  - Goals are to gain member company experience with the Framework and to use that experience for further development
- **To learn more:**
  - Publications
  - Soft pilot (for PhRMA member companies)
    - Kristin Van Goor (KVanGoor@phrma.org)

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### BRAT Core Team

- **Carmen Bozic**
  - Biogen Idec
- **Paul Coplan**
  - Purdue Pharma
- **John Ferguson**
  - Novartis
- **Rick Hermann**
  - AstraZeneca
- **Stacy M Holdsworth**
  - Eli Lilly
- **Diana Hughes**
  - Pfizer
- **Bennett Levitan**
  - Johnson & Johnson
- **Marilyn Metcalf**
  - GSK
- **Filip Mussen**
  - Johnson & Johnson
- **Rebecca Noel**
  - Eli Lilly
- **Alice Till**
  - PhRMA
- **Doug Watson**
  - Merck

### Key Benefit-Risk Summary Table

**Depiction of temporal and other relevant information as needed during a B-R assessment**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjusted Rate Difference per 13,000 person-years (95% CI)</th>
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### Draft Drill Down For Headache Relief

- **Source details readily available in Framework**
- **Allows decision-makers to instantly answer questions on data source, quality and heterogeneity**

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### Backups

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### Key Benefit-Risk Summary Table

**Non-fatal Ischemic Stroke**

- **Source details readily available in Framework**
- **Allows decision-makers to instantly answer questions on data source, quality and heterogeneity**

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*Mock study data used for visualization purpose only*
Quantifying Regulatory Benefit-Risk Assessment: Health Outcomes Modeling

Presentation to:
PHARMACEUTICAL BENEFIT-RISK ASSESSMENT – WHAT SHOULD WE DO IN THE ABSENCE OF REGULATORY GUIDELINES?
RTI Symposium
ISPOR International Meeting
Baltimore, Maryland
May 24, 2011

Lou Garrison, Ph.D.
Professor, Department of Pharmacy
University of Washington

Acknowledgements

• Research Collaborators:
  — Justin Robertson (UW Graduate Student)—Statin Modeling
  — James T. Cross (Genentech/recent UW PhD)
  — Adrian Towe (Office of Health Economics, UK)

• Next Steps Working Group (aka Public-Private Benefit-Risk Assessment Working Group)
  — Larry Lynd, Reed Johnson, Bennett Levitan, and others.

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.

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. Garberon Jr., Adrian Towe, and Brian W. Brennan

ABSTRACT: Regulatory agencies make key drug approval decisions, and drug approval decisions can have significant consequences for patient health and economic outcomes. The current regulatory framework for drug approval is often criticized for its complexity, and its ability to account for differences in drug benefits and risks is limited. This study examines the impact of regulatory changes on drug approval decisions and outcomes. The authors conducted a systematic review of the literature on drug approval and regulatory processes, and the results were used to inform the development of a regulatory framework for drug approval.

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

INHB = (B₂ − B₁) − (R₂−R₁)

where

— Health benefit (B) is measured in terms of its length and quality of life.

— Risk R (or harms) is measured in terms of its length and quality of life.

(B₂ − B₁) − (R₂−R₁) → Favorable benefit-risk balance

Risk aversion → Benefit premium is required.
Case Study:
Hypothetical Statin for Primary Prevention of Cardiac Events

How can we weight the differential survival and quality-of-life impacts of these events?

Source: Lawton, 2011

Health State Diagram (for Statin Arm)

Key Inputs for the Model
- Survival data derived from Scandinavian Simvastatin Survival Study (Lancet, 1994)
- The excess risks (for statin compared to placebo) assumed for the five risks considered were (per 10,000 person-years) [FROM BRAT FRAMEWORK]
- Time Horizon = 10 years

Key Inputs for the Model (cont’d)
- The utility assumptions for morbidity risks were
  - Persistently elevated transaminases: 15% percent reduction in utility (for 1 year)
  - Myopathy: 10% percent reduction in utility (for 6 months)
  - Rhabdomyolysis: 3.0% percent reduction in utility (for 1 month)
  - Liver Failure: utility weight = 0.25
  - Severe rhabdomyolysis (leading to kidney failure): utility weight = 0.60
- Mortality risk assumptions
  - Liver Failure: 75% mortality rate for 1st year, 100% mortality rate for 2nd year
  - Severe rhabdomyolysis (leading to kidney failure): 20% disease-specific mortality rate for 1st year

Results
- Including risks, the incremental net health benefit (INHB) over 10-year horizon is
  - LYS: 0.265
  - QALYs: 0.212
- Excluding risks, the INHB over a 10-year horizon is:
  - LYS: 0.266
  - QALYs: 0.213
- Risks reduce the INHB by less than 1%.
Impact of Risks on INHB

Advantages of this Approach

- Provides a quantitative calculation of the benefit-risk balance in understandable, commensurable terms
- The inputs can be easily varied so that decision makers can determine the effects of uncertainty (in risk estimates) on the overall benefit-risk balance

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

- Multiple INHB differentials with confidence intervals for different subgroups
  - E.g., subgroups within label and subgroups outside the labeled indication
- Estimates at a population level: how large are the affected subgroups?
- Projection of health benefits forgone due to delay → value (and costs) of collecting additional information
- Projection of the impact of a risk management plan
- Guidance for cost allocation of post-marketing studies

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.

Models Don’t Make Decisions, People Do

“All models are wrong, but some are useful.”

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
Why Benefit-Risk Assessments are Hard

- Measurement challenges
  - Multiple efficacy and safety endpoints
  - Large uncertainty about low-frequency adverse events
  - Variable outcomes among subgroups
  - Potential latency
  - Implications of compliance, reversibility, manageability

- Evaluation challenges (the weighting problem)
  - Outcomes not scaled comparably
  - Outcomes not of equal significance
  - Societal perspective may differ from patient perspective

Approaches to Comparing Benefits and Risks

<table>
<thead>
<tr>
<th>Type of Weights</th>
<th>Applications</th>
</tr>
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<tbody>
<tr>
<td>Implicit decision-maker weights</td>
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</tr>
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<td>Explicit decision-maker weights</td>
<td>Multicriteria Decision Analysis (MCDA)</td>
</tr>
<tr>
<td>Equal weights</td>
<td>NNT/NNH</td>
</tr>
<tr>
<td>QALYs</td>
<td>• Net benefits</td>
</tr>
<tr>
<td></td>
<td>• Q-TWIST</td>
</tr>
<tr>
<td></td>
<td>• Weighted NNT/NNH</td>
</tr>
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<td>• Decision modeling</td>
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<tr>
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<td>• Maximum acceptable risk</td>
</tr>
<tr>
<td></td>
<td>• Net benefits</td>
</tr>
<tr>
<td></td>
<td>• Minimum acceptable efficacy</td>
</tr>
<tr>
<td></td>
<td>• Maximum acceptable NNT</td>
</tr>
<tr>
<td></td>
<td>• Minimum acceptable NNH</td>
</tr>
<tr>
<td></td>
<td>• Q-TWIST</td>
</tr>
</tbody>
</table>

Ex Ante Versus Ex Post Evaluations

- **Ex post**
  - Assigns health-state utility weights to realized outcomes
  - Assumes no risk aversion

- **Ex ante**
  - Weights attached to outcome probabilities
  - Explicitly accounts for risk aversion
  - Consistent with regulatory perspective

Quantitative Benefit-Risk Analysis: Incremental Net Benefits and Maximum Acceptable Risk

\[
\text{Incremental Net Benefits} = \frac{w_B}{p_B} - \frac{w_{AE}}{w_{AE}^*} \cdot \frac{\Delta N_{AE}}{\Delta N_B}
\]

\[
\text{Preference Weights: } W_B, W_{AE}
\]

\[
\text{Maximum Acceptable Risk} = \frac{w_B}{p_B} - \frac{w_{AE}}{w_{AE}^*} \cdot \text{MAR} = 0
\]
Statin Case Study: Validity

Time to Think (TTT) Experiment

- Potential problem of hypothetical bias in conjoint (discrete-choice experiment or stated-choice) studies
- Allowing subjects time to think about tradeoffs provides more realistic decision context
- In WTP studies for environmental improvements, WTP smaller in TTT arm
- Expected MAR to be smaller in TTT arm

Benefits and Side-Effect Risks

<table>
<thead>
<tr>
<th>Type of Attribute</th>
<th>Attribute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular benefits</td>
<td>Lower chance of angina that requires minor surgery</td>
</tr>
<tr>
<td></td>
<td>Lower chance of nonfatal heart attack or stroke</td>
</tr>
<tr>
<td></td>
<td>Lower chance of death from heart attack or stroke</td>
</tr>
<tr>
<td>Liver toxicity</td>
<td>Chance of bad liver test results with no damage</td>
</tr>
<tr>
<td></td>
<td>Chance of short-term hepatitis without hospitalization</td>
</tr>
<tr>
<td></td>
<td>Chance of hepatitis with hospitalization</td>
</tr>
<tr>
<td></td>
<td>Death from liver failure</td>
</tr>
<tr>
<td>Kidney toxicity</td>
<td>Chance of mild weakness (myopathy)</td>
</tr>
<tr>
<td></td>
<td>Chance of severe muscle weakness (rhabdomyolysis)</td>
</tr>
<tr>
<td></td>
<td>Muscle weakness that leads to kidney failure requiring transplant</td>
</tr>
</tbody>
</table>

Example Choice Task

<table>
<thead>
<tr>
<th>Medicine A</th>
<th>Medicine B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td></td>
</tr>
<tr>
<td>Nonfatal heart attack</td>
<td>Choice of 10 out of 50 cases</td>
</tr>
<tr>
<td>Liver damage (no effect)</td>
<td>Choice of 10 out of 50 cases</td>
</tr>
<tr>
<td>Lung damage (no effect)</td>
<td>Choice of 10 out of 50 cases</td>
</tr>
<tr>
<td>Kidney damage (no effect)</td>
<td>Choice of 10 out of 50 cases</td>
</tr>
<tr>
<td>Mild muscle weakness</td>
<td>Choice of 10 out of 50 cases</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>Choice of 10 out of 50 cases</td>
</tr>
</tbody>
</table>

TTT Study

- 706 subjects
- N=327 NTNTT – survey completed in one session
- N=379 TTT – survey completed in two sessions
  - First session – describe attributes, example choice task, review choice questions
  - 24-72 hours between sessions
    - TTT respondents could access the survey between sessions
  - Second session – answer choice questions

MARs to Lower Fatal MI Risk from 1% to 0%

No significant differences between arms...

…but TTT MAR greater in 5 out of 6 cases
Taste more homogeneous in TTT sample in 5 out of 6 cases

Statin Case Study: Benefit-Risk Preferences

Preference-Weight Estimates

Net Clinical Benefits
Event Simulation with Patient-Preference Weights

- Accounts for uncertainty in both outcomes and preference weights
- Probability of positive NCB > 99%