Quantitative benefit-risk assessment: An analytical framework for a shared understanding of the effects of medicines

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29 March 2010
Challenges in understanding the effects of medicines
Benefit-risk analysis process

Available data → Analytical Framework* → Shared understanding

Stakeholder preferences

*tailored to the complexity of the decision
Diversity of data availability

Potential imbalance in data availability between alternative treatments

- Product labels
- Observational studies
- Medical Literature
- Spontaneous reports

- Clinical trials
- Case series
- Expert opinion

- Animal/Computer models
- Hypotheses

Bob Powell, ISPOR 2008
Components of an analysis framework

- Define decision
- Identify health outcomes
- Synthesize data
- Model decision and conduct analysis
- Interpret and evaluate results
A set of principles, processes and tools to guide decision-makers in
- Selecting
- Organizing
- Understanding
- Summarizing
Evidence relevant to benefit-risk decisions

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Define decision

• Multiple stakeholders face decisions throughout the medical product lifecycle:

  Industry: **Do we continue investing?**
  Regulatory: **Do we approve?**
  Payer: **Do we reimburse?**
  Provider: **Is this best for my patients?**
  Patient: **Is this the best drug for me?**

• Analysis needs to be flexible to accommodate diverse perspectives to inform stakeholder decision-making processes
Illustrative example: Identify health outcomes

- No Disease
- Disease
- No Disease & AE
- Disease & AE
- Death
Illustrative example:
Transitions between health states

- No Disease
- Disease
- Death
- No Disease & AE
- Disease & AE
Illustrative example:
Transitions between health states
Illustrative example: Building a full model.

- No Disease
- No Disease & AE
- Disease
- Disease & AE
- Death
Illustrative example: Modeling meets data challenges

What if there are no data available to characterize adverse event resolution?
Comparing alternative treatments

Treatment A:
70% benefit, 25% risk

- P(B&R) = 0.60
- P(B&~R) = 0.10
- P(~B&R) = 0.15
- P(D) = 0.01
- P(~B&~R) = 1 - Σp = 0.14

Death

No Disease

No Disease & AE

Disease

Disease & AE

Treatment B:
60% benefit, 15% risk

- P(B&R) = 0.55
- P(B&~R) = 0.05
- P(~B&R) = 0.10
- P(D) = 0.01
- P(~B&~R) = 1 - Σp = 0.29

Death

No Disease

No Disease & AE

Disease

Disease & AE
Potential tradeoffs in a benefit-risk analysis

- **Competing risks**
  - Ex: rofecoxib vs. NSAID: GI bleed vs. acute myocardial infarction

- **Competing benefits**
  - Ex: RA: inflammation pain relief vs. QoL measures

- **Higher benefit and higher risk**
  - Ex: natalizumab: MS treatment vs. PML

- **Outcomes occurring at different times**
  - Ex: chemotherapy: immediate nausea, alopecia vs. long-term survival

- **Varying uncertainty**
  - Ex: Typical vs. atypical antipsychotics

Any or all of these tradeoffs can play out in a given decision:
Multiple competing benefits with multiple competing risks over time
### Translating concept into practice

<table>
<thead>
<tr>
<th>Ideal scenario</th>
<th>Real scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each drug has one dose</td>
<td>Multiple dose regimens</td>
</tr>
<tr>
<td>Patient data for both drugs</td>
<td>Aggregate summaries from literature</td>
</tr>
<tr>
<td>Clear choice of B&amp;Hs</td>
<td>Single AEs or ‘Any Grade 4’?</td>
</tr>
<tr>
<td>All B&amp;H reported as rates</td>
<td>Mix of rates, ratios, means</td>
</tr>
<tr>
<td>Event times are equally spaced</td>
<td>Event are sporadic or nonlinear</td>
</tr>
<tr>
<td>Undisputed trade-offs</td>
<td>No preference data</td>
</tr>
<tr>
<td>Events occur independently</td>
<td>Don’t know if events are correlated</td>
</tr>
<tr>
<td>Patients have same baseline risks.</td>
<td>Different patient subgroups</td>
</tr>
</tbody>
</table>
Real example: Adjuvant therapy

Assumptions:
• Treatment is 1yr, so AE rates only occur within 1 yr, then same as control.
• AE onset are tunnel states (t=0)
• AEs: Hy’s Law, LVEF decreased, CHF
• Recurrence rate independent of AEs
• Hypothetical cohort of 10,000 patients for 4 years, with 1 month transition periods
Real example: Preventative Therapy

- No Dx no AE
- No Dx Hypertension
- No Dx Fatig/Diarr
- No Dx Naus/vomit
- No Dx Ab pain
- No Dx Dyspn
- No Dx H-F Syn
- No Dx Bleed
- Dx Bleed
- Dx Dyspn
- Dx H-F Syn
- Dx Naus/vomit
- Dx Ab pain
- Dx Fatig/Diarr
- Dx Hypertension
- Death

All patients started with No Dx no AE and progressed through various conditions until reaching Death.
Identify Health States

Set Objective Selection Criteria:

• Clinical benefits
• Functional / QoL harms or benefits
• AEs occurring in >\(x\)% of patients
• AEs graded \(x\) or higher
• AEs related to treatment discontinuation
• AEs with known drug class effects
• AEs that are nonreversible
• Rare AEs that received regulatory warnings

Determine which health states should be combined into a single state or split into two states.

Decide best length of time for 1 event per interval.
### Synthesizing Data
ex. preventative therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>Drug</th>
<th>Comparator</th>
<th>Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefits</strong></td>
<td>Value</td>
<td>Source</td>
<td>Value</td>
<td>Source</td>
</tr>
<tr>
<td>% Disease-free - Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Months 0-3</td>
<td>1.00</td>
<td>RCT-301</td>
<td>1.00</td>
<td>RCT-301</td>
</tr>
<tr>
<td>Months 3-6</td>
<td>0.90</td>
<td>RCT-301</td>
<td>1.00</td>
<td>RCT-301</td>
</tr>
<tr>
<td>Months 6-9</td>
<td>0.80</td>
<td>RCT-301</td>
<td>0.95</td>
<td>RCT-301</td>
</tr>
<tr>
<td>Month 9-12</td>
<td>0.70</td>
<td>RCT-301</td>
<td>0.90</td>
<td>RCT-301</td>
</tr>
<tr>
<td>% Alive-Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Months 0-3</td>
<td>1.00</td>
<td>ISE</td>
<td>1.00</td>
<td>ISE</td>
</tr>
<tr>
<td>Months 3-6</td>
<td>0.86</td>
<td>ISE</td>
<td>0.95</td>
<td>ISE</td>
</tr>
<tr>
<td>Months 6-9</td>
<td>0.76</td>
<td>ISE</td>
<td>0.90</td>
<td>ISE</td>
</tr>
<tr>
<td>Month 9-12</td>
<td>0.67</td>
<td>ISE</td>
<td>0.86</td>
<td>ISE</td>
</tr>
<tr>
<td><strong>Risks</strong></td>
<td>Value</td>
<td>Source</td>
<td>Value</td>
<td>Source</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.10</td>
<td>ISS</td>
<td>0.15</td>
<td>ISS</td>
</tr>
<tr>
<td>Hepatic</td>
<td>0.00</td>
<td>ISS</td>
<td>0.02</td>
<td>ISS</td>
</tr>
<tr>
<td>Cardiac</td>
<td>0.00</td>
<td>ISS</td>
<td>0.00</td>
<td>ISS</td>
</tr>
</tbody>
</table>
Synthesizing Data  continued

**Data Limitation**
- Data come from \( \geq 1 \) study
- Safety data for combined doses
- Safety data reported as cumulative incidence
- An AE is not reported for comparator

**Assumption?**
- Study populations are comparable
- Safety events are not dose-related
- Events occur at a constant rate
- Probability is either 0 or below x%
Integrate Data into Analysis

There are many methods for integrating the data. A few examples include:

- Decision Trees
- Markov Models
- Discrete-event simulation
- etc.

Your choice may depend on decisions around:

- Data (individual patient data vs. summary statistics)
- Uncertainty (patient, outcome & parameter variability)
- Output Metrics (Person-time, INB, QALYs, etc.)
Visualization of Output:
No. of patients in each health state by month

**Person status at 3 months**

- Disease-free
- DF+Nausea
- DF+Hepatic
- DF+Cardiac
- Diseased
- Death

**Person status at 6 months**

- Disease-free
- DF+Nausea
- DF+Hepatic
- DF+Cardiac
- Diseased
- Death

**Person status at 9 months**

- Disease-free
- DF+Nausea
- DF+Hepatic
- DF+Cardiac
- Diseased
- Death

**Person status at 12 months**

- Disease-free
- DF+Nausea
- DF+Hepatic
- DF+Cardiac
- Diseased
- Death
Visualization of Output:
Person-time in each health state by month 12

Proportion of person-time over 12 months

- Disease-free
- DF+Nausea
- DF+Hepatic
- DF+Cardiac
- Diseased
- Death

Placebo
Drug
Comparator
**BRAT Framework Key Benefit-Risk Summary Table**

- Top level representation of information in the framework
- The most critical view that decision makers will have on the data

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

*Mock data for visualization purpose only

Evaluate results

Check the robustness of the results
• Are the assumptions still reasonable?
• Do sensitivity analyses show which factors drive the results?
• Do utilities or preference weights shift the emphasis?

Does the analysis need more data or fewer assumptions?

Is the information provided sufficient for clear & transparent decision-making?
Concluding thoughts

• The goal is to gain a “shared understanding” of benefit:risk trade-offs between alternative treatments

• Explicitly stated data & modeling assumptions add transparency to direct and indirect comparisons

• The primary limitation is often available data rather than methodology

• Stakeholders can explore a range of benefit:risk trade-offs, from a patient to societal perspectives

• Statisticians have a significant opportunity to lead this quantitative process to meaningfully inform the appropriate use of medical products
Benefit-risk analysis: enabling the view of the bigger picture
Questions?

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The End