Benefit and Risk Assessment of Medical Product - what can we learn from healthcare databases?

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Pre-conference educational sessions

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The meaning of ‘benefit’ and ‘risk’

• Consider a new drug that can lower the incidence of heart attacks in otherwise healthy people.

• “There is a risk this drug won’t lower your risk and there are risks from taking the drug.”

• risk: the possibility the drug won’t work for an individual
• risk: the chance of a heart attack
• risks: possible side effects
Avoidance of drug-induced harm

Benefit to public health

Maximum risk tolerance
- High likelihood of type I errors

Maximum risk aversion
- High likelihood of type II errors
- Increasing opportunity cost
B/R are perceived and weighted differently

Positive regulatory decision (at population level)

Negative treatment decision (at individual level)

Positive treatment decision (at individual level)

Regulatory and methodological standards to improve benefit-risk evaluation of medicines EMA/141854/2014
Example: Probabilities vs ‘Values’

Benefit-Risk Probabilities

**Shoulder Repair Device**

- **Benefit**: 80% probability of improved baseball game
- **Risks**:
  - 100% probability of VAS pain=8 during three months of recovery
  - 20% chance of impaired baseball game

Benefit-Risk ‘Values’

**Shoulder repair patients**

- ✔ Injured MLB pitcher?  
  “Sound great!”
- ✔ Healthy but poor MLB pitcher?  
  “OK, I’ll try it”
- ✔ Healthy and successful MLB pitcher?  
  “No way!”
Current state of Benefit and Risk assessment (BRA) in EU

- Work package
- 1. Description of current practice (2009)
  - Ensure all the elements of the benefit-risk balance have been considered.
    - Transparency
    - Communicability
- 3. Field tests of tools and methods (2011)
- 5. Training module for assessors (2014, ongoing)
Current state of Benefit and Risk assessment (BRA) in US

- Initiated a systematic approach for drug benefit-risk assessment (2009-2011)
  - Reauthorization of PDUFA V in 2010 – development of a 5-year plan
- Pilot project (2012)
- Further development of the framework (2013)
  - clinical review template, adaptation to key consideration, characterization of uncertainties
Overview of BRA- methodologies

• Diverse
  – Frameworks
  – Metric indices
  – Estimation techniques
  – Utility survey technique

• No 'One-size-fits-all method'
  – Different limitations and strength

Pharmacoepidemiol Drug Saf. 2014;23:667-78
Methodologies of benefit-risk assessment

• Frameworks
  – Qualitative steps in benefit-risk assessment
  – Quantify benefit-risk balance

• Metric indices
  – Threshold indices, health indices, trade-off indices

• Estimation techniques
  – Support benefit-risk modelling and evidence analysis

• Utility survey technique
  – Elicit robust value preferences from relevant stakeholders

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Descriptive frameworks structure

- **BRAF** (further testing)
  - Standardize and communicate *(industry & regulatory)*
  - Assessable for those not familiar with statistical models
- **PrOACT-URL** (further testing)
  - Problem, objective, alternatives, consequences, trade-off, uncertainty, risk and linked decision.
  - Necessary elements in decision problems
- **MCDA** (further examination)
  - Highly structured (based on PrOACT-URL)
  - Integrates multiple benefit and risk criteria and compare multiple opinion
- **SMAA** (further examination)
  - Worked with unknown, uncertain or skew data, including missing value preference.

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## Application of BRAT framework

### The Triptan example


<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 outcomes, perspective of the decision makers (regulator, sponsor, patient, or physician)</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/end points 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)</td>
</tr>
<tr>
<td></td>
<td>Extract all relevant data for the data source table, including detailed references and any annotations, to help the subsequent interpretations create summary measures</td>
</tr>
<tr>
<td>4. Customize the framework</td>
<td>Modify the value tree on the basis of further review of the data and clinical expertise. Refine the outcome measures/end points. May include tuning of outcomes not considered relevant to a particular benefit–risk assessment or that vary in relevance 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>
</tbody>
</table>
| 6. Display and interpret key benefit–risk metrics | Summarize source data in tabular and graphical displays to aid review and interpretation  
Challenge summary metrics, review source data, and identify and fill any information gaps  
Interpret summary information                                                   |
Application of BRAT framework

- Full value tree

- Benefits
  - ↓ Pain
    - Rapid onset
    - Headache relief
    - Pain-free response
    - Sustained response
    - Consistent intrapatient response
  - ↓ Sensitivity
    - Reduced sensitivity to sound and light
    - Reduced sensitivity to touch
  - ↓ Other
    - Reduction in functional disability
    - Reduction in nausea or vomiting
    - Headache relief if used during prodrome/aura

- Benefit-risk balance

- Risks
  - ↑ Individual risks
    - Transient triptan sensations
    - Central nervous system adverse events
    - “Chest-related” adverse events
    - Intensification of migraine symptoms
    - Myocardial infarction
    - Serotonin syndrome
    - Medication overuse headache
Application of BRAT framework

- Tuned value tree

```
Benefits
   ↓ Sensitivity
      ↓ Pain
         Rapid onset
         Headache relief
         Pain-free response
         Sustained response

   ↓ Other
         Reduced sensitivity to sound and light
         Reduction in functional disability
         Reduction in nausea or vomiting

Benefit-risk balance

Risks
   ↑ Individual risks
         Transient triptan sensations
         Central nervous system adverse events
         “Chest-related” adverse events
```
Points to Consider When Selecting Outcomes and Their Measures

• Time periods and populations
• Unit of analysis
• Double-counting
• Using Composite Outcomes or Measures
  – may be more meaningful
  – may hamper identification of important trade-offs
  – have very different effects on patients
  – the direction of the effect of treatment is expected to be different for individual outcomes
Assess the outcome importance

- Weights, whether categorical/informal or elicited via formal methods, are used to help decision makers focus on the more critical outcomes.
  - Categories of Importance
  - Ranking the Outcomes
  - Ad hoc Weights
  - Direct Assessment/Point Allocation
  - Multi-criteria Decision Analysis
  - Preference Weighting
## Key benefit–risk summary table

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study drug risk (/1,000 pts)</th>
<th>Comparator risk (/1,000 pts)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefits</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid onset</td>
<td>271</td>
<td>248</td>
<td>1.13 (1.00,1.27)</td>
</tr>
<tr>
<td>Headache relief</td>
<td>643</td>
<td>633</td>
<td>1.04 (0.94,1.15)</td>
</tr>
<tr>
<td>Pain-free response</td>
<td>383</td>
<td>349</td>
<td>1.16 (1.03,1.30)</td>
</tr>
<tr>
<td>Sustained response</td>
<td>285</td>
<td>295</td>
<td>0.95 (0.80,1.14)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduced sensitivity to sound and light</td>
<td>530</td>
<td>505</td>
<td>1.10 (0.94,1.30)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction in functional disability</td>
<td>540</td>
<td>480</td>
<td>1.28 (1.09,1.49)</td>
</tr>
<tr>
<td>Reduction in nausea or vomiting</td>
<td>604</td>
<td>517</td>
<td>1.43 (1.22,1.67)</td>
</tr>
<tr>
<td><strong>Risks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individual risks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient triptans sensations</td>
<td>43</td>
<td>52</td>
<td>0.83 (0.61,1.14)</td>
</tr>
<tr>
<td>CNS AEs</td>
<td>53</td>
<td>45</td>
<td>1.18 (0.92,1.51)</td>
</tr>
<tr>
<td>“Chest-related” AEs</td>
<td>58</td>
<td>21</td>
<td>2.93 (2.04,4.20)</td>
</tr>
</tbody>
</table>

- Favors study drug
- Favors comparator

Odds ratio (Log scale)
<table>
<thead>
<tr>
<th>Benefits</th>
<th>Pain Reduction</th>
<th>Other</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid onset</td>
<td>27.1</td>
<td>24.8</td>
<td>4.4</td>
<td>1.13 (1.00, 1.27)</td>
<td></td>
</tr>
<tr>
<td>Headache relief</td>
<td>64.3</td>
<td>63.3</td>
<td>4.0</td>
<td>1.04 (0.94, 1.15)</td>
<td></td>
</tr>
<tr>
<td>Pain-free response</td>
<td>38.3</td>
<td>34.9</td>
<td>4.2</td>
<td>1.16 (1.02, 1.30)</td>
<td></td>
</tr>
<tr>
<td>Sustained response</td>
<td>28.5</td>
<td>29.5</td>
<td>4.0</td>
<td>0.95 (0.80, 1.14)</td>
<td></td>
</tr>
<tr>
<td>Reduced sensitivity to sound or light</td>
<td>53.0</td>
<td>50.5</td>
<td>4.3</td>
<td>1.10 (0.94, 1.30)</td>
<td></td>
</tr>
<tr>
<td>Reduction in nausea or vomiting</td>
<td>60.4</td>
<td>51.7</td>
<td>4.5</td>
<td>1.43 (1.22, 1.67)</td>
<td></td>
</tr>
<tr>
<td>Reduction in functional disability</td>
<td>54.0</td>
<td>48.0</td>
<td>4.5</td>
<td>1.08 (1.09, 1.49)</td>
<td></td>
</tr>
<tr>
<td>Transient triptan sensations</td>
<td>4.3</td>
<td>5.2</td>
<td>4.7</td>
<td>0.73 (0.61, 1.14)</td>
<td></td>
</tr>
<tr>
<td>Central nervous system AEs</td>
<td>5.3</td>
<td>4.5</td>
<td>4.2</td>
<td>1.11 (0.92, 1.51)</td>
<td></td>
</tr>
<tr>
<td><em>Chest-related</em> AEs</td>
<td>5.8</td>
<td>2.1</td>
<td>4.0</td>
<td>2.93 (2.04, 4.20)</td>
<td></td>
</tr>
</tbody>
</table>

### Odds Ratio Supporting Studies for Headache Relief

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study drug # events</th>
<th>Study drug N</th>
<th>Comparator # events</th>
<th>Comparator N</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>100/22</td>
<td>347</td>
<td>531</td>
<td>372</td>
<td>530</td>
<td>0.80</td>
<td>(0.62 - 1.04)</td>
<td>4</td>
</tr>
<tr>
<td>100/27</td>
<td>87</td>
<td>174</td>
<td>94</td>
<td>174</td>
<td>0.85</td>
<td>(0.56 - 1.30)</td>
<td>3</td>
</tr>
<tr>
<td>300/46</td>
<td>294</td>
<td>498</td>
<td>307</td>
<td>504</td>
<td>0.92</td>
<td>(0.72 - 1.19)</td>
<td>3</td>
</tr>
<tr>
<td>100/19</td>
<td>196</td>
<td>306</td>
<td>198</td>
<td>305</td>
<td>0.96</td>
<td>(0.69 - 1.34)</td>
<td>4</td>
</tr>
<tr>
<td>100/21</td>
<td>338</td>
<td>508</td>
<td>338</td>
<td>514</td>
<td>1.04</td>
<td>(0.80 - 1.34)</td>
<td>5</td>
</tr>
<tr>
<td>100/23</td>
<td>304</td>
<td>498</td>
<td>288</td>
<td>491</td>
<td>1.10</td>
<td>(0.86 - 1.42)</td>
<td>4</td>
</tr>
<tr>
<td>100/26</td>
<td>230</td>
<td>359</td>
<td>226</td>
<td>376</td>
<td>1.18</td>
<td>(0.88 - 1.59)</td>
<td>5</td>
</tr>
<tr>
<td>100/24</td>
<td>206</td>
<td>292</td>
<td>193</td>
<td>289</td>
<td>1.19</td>
<td>(0.84 - 1.69)</td>
<td>3</td>
</tr>
<tr>
<td>100/26</td>
<td>266</td>
<td>360</td>
<td>226</td>
<td>376</td>
<td>1.88</td>
<td>(1.37 - 2.57)</td>
<td>5</td>
</tr>
</tbody>
</table>
### Preference weighting from different stakeholder

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Outcome</th>
<th>Risk Difference (per 1,000 Person-Years)</th>
<th>Patient Preference Weight*</th>
<th>Physician Preference Weight*</th>
<th>Regulator Preference Weight*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rapid onset (1 hour)</td>
<td>23</td>
<td>0.87</td>
<td>0.89</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>Headache relief (2 hours)</td>
<td>10</td>
<td>0.84</td>
<td>0.86</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>Pain free response</td>
<td>34</td>
<td>0.90</td>
<td>0.92</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>Sustained response (24 hours)</td>
<td>-10</td>
<td>0.92</td>
<td>0.94</td>
<td>0.88</td>
</tr>
<tr>
<td>Other</td>
<td>Reduced sensitivity to sound and light</td>
<td>25</td>
<td>0.95</td>
<td>0.97</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>Reduction in nausea or vomiting</td>
<td>88</td>
<td>0.88</td>
<td>0.90</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>Reduction in functional disability</td>
<td>61</td>
<td>0.64</td>
<td>0.69</td>
<td>0.50</td>
</tr>
</tbody>
</table>

| Risks    |Transient triptans sensations                | -8                                       | 0.98                        | 0.94                        | 0.91                        |
|          |CNS AEs                                       | 8                                        | 0.90                        | 0.86                        | 0.83                        |
|          |“Chest-related” AEs                           | 38                                       | 0.96                        | 0.92                        | 0.89                        |
|          |Intensification of migraine symptoms          | -                                        | 0.97                        | 0.93                        | 0.90                        |
|          |Myocardial infarction                         | -                                        | 0.40                        | 0.20                        | 0.33                        |

- **Advantage to study drug**
- **Advantage to placebo**
Calculate the risk difference

- Reduction in nausea or vomiting
- Reduction in functional disability
- Pain-free response
- Reduced sensitivity to sound and light
- Rapid onset
- Headache relief
- Sustained response

Risk difference (per 1,000 patients)

- Favors comparator
- Favors study drug

Legend:
- Mean
- Efficacy 95% CI
- Safety 95% CI

Transient triptans sensation

CNS AEs

“Chest-related” AEs
What can we learn from healthcare databases?

• Evidence regarding the benefit and safety issue
  Developing precise measure

http://www.tourolawreview.com/evidence/
http://www.iajjc.org/evidence.php
Type of Health Care Databases

- Claims data
- Electronic medical record
- Laboratory/diagnostic testing
- Surveillance data
- Prospective cohorts
- Prescription data
- Cross-sectional studies
- Registries
- Linked National Databases
- etc...
Particular application

- Uncommon outcomes
- Background incidence
- Short-term drug effects
- Recall bias or interviewer bias could influence the associations
- Time is limited
- Budget is limited
- etc
Probably problematic situations...

- Illnesses that do not reliably come to medical attention
- Inpatient drug exposure
- Outcomes are poorly defined by the ICD code
- Delayed drug effects
- Important confounders about which information cannot be obtained without accessing the patients, such as cigarette smoking, occupation, menarche, menopause, etc.
When designing a pharmacoepidemiological study...

- Guidelines for good pharmacoepidemiology practices (GPP)
- The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)
  - Guide on Methodological Standards in Pharmacoepidemiology (Revision 3)
- Agency for healthcare research and quality (AHRQ)
  - Developing a Protocol for Observational Comparative Effectiveness Research: A User's Guide
- STrengthening the Reporting of OBservational studies in Epidemiology (STROBE Statement)
  - http://www.strobe-statement.org
The way forward

• Good drug regulation is more than just minimizing risks; it is about maximizing gains in public health

Stakeholders, including those who are critical of regulatory standards, should be aware that a drive towards an excessive focus on avoiding risks and uncertainties will mean that patients pay a price: delay in accessing therapeutics and lost therapeutic options.
Future challenge for the regulatory affair

- The availability of evidence on the benefits and risks of a medicine
  - Promptly revise the decision based on new information
- Align acceptance of risks and uncertainty by regulators with the interests of public health
  - Capture patients value and preferences
- Engage with patients and health care providers to seek ways to further optimize the use of medicines and improve adherence to treatment.
  - Explain benefit-risk decisions to stakeholders

Regulatory and methodological standards to improve benefit-risk evaluation of medicines EMA/141854/2014
Conclusion

- During decision making process
  - Transparency
  - Communicability

- No 'One-size-fits-all method' in benefit risk assessment

- Is the benefit-risk modeling desirable?
  - No single best answer
  - The science used to support the decisions should be optimized
Thank you!

Question?

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