Benefit Risk Analysis

Experience in using the BRAT framework

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Disclaimers

“The processes described and conclusions drawn from the work presented herein relate solely to the testing of methodologies and representations for the evaluation of benefit and risk of medicines.

This report neither replaces nor is intended to replace or comment on any regulatory decisions made by national regulatory agencies, nor the European Medicines Agency.”
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Regulatory activities on structured BR assessment

- EMA Benefit-Risk Methodology Project
- FDA Grid
- ICH – Periodic Benefit-Risk Evaluation Report

- The benefit-risk evaluation should be presented in a **structured manner**.

- Provide a clear explanation of the methodology and reasoning used to develop the benefit-risk evaluation: The **assumptions, considerations, and judgment or weighting** that support the conclusions of the benefit-risk evaluation should be clear.
IMI (Innovative Medicines Initiative) PROTECT

- PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium)
  - Collaborative European project coordinated by the EMA
  - Multi-national consortium of 32 partners including academics, regulators, and pharmaceutical companies
- Work program 5 is focusing on Benefit-Risk integration and representation
What Structured Benefit-Risk Assessment is NOT about

B:R = 2.5
95% CI = [1.3, 3.7]
What Structured Benefit-Risk Assessment is about

- 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 “model”, but a quantitative model may be applied within the framework
Benefit-risk is about communication

*It’s not about not about getting a number*

- Structured Benefit-Risk analysis does not give you the answer.
- It is a framework for decomposing and understanding a problem.
- Assesses the main value drivers of the Benefit-risk.
- Communicate issues in a transparent, rational and consistent way to aid decision making.
Background

- Tysabri (natalizumab) was approved in 2004 by the FDA for the treatment of relapsing remitting multiple sclerosis (RRMS).
- In 2005 the drug was suspended because of an associated incidence of progressive multifocal leukoencephalopathy (PML), a rare neurological disorder.
- In 2006 it was re-introduced, precipitated by patient demand, but with strict risk minimization measures.
- In 2009, due to occurrence of further PML in monotherapy post marketing, CHMP reassessed the PML risk of Tysabri and confirmed the current approval.
BRAT Framework

- PhRMA Benefit Risk Action Team
Step 1: Define the decision context

Identify the fundamental problem

- Decision question:
  - Should Tysabri be given marketing approval at the time of first registration?
  - Should Tysabri be kept on the market given that episodes of PML are observed at the time that these episodes were observed?
- Indication: Relapsing remitting multiple sclerosis
- Drug to compare
  - Tysabri (Natalizumab), Avonex (Interferon beta-1a), Copaxone (Glatiramer acetate), Placebo
- Decision perspective: EMA, taking the patient perspective.
  - The regulator makes the decision, but using the values and weights of a patient.
- Time frame: two-years
  - This is the time frame of the pivotal studies, but the time frame for safety events may be longer as these take longer to manifest.
Step 2: Identify benefit and risk outcomes

Benefits

- Relapse -> 2-year relapse rate
- Disability Progression -> % w/event in 2yrs
- Convenience -> Oral od, s.c od, l.m. qw, iv. qm

Infection

- Reactivation of serious herpes viral infections -> % w/event in 2yrs
- PML -> % w/event in 2yrs

Reproductive Toxicity

- Congenital abnormalities -> % w/event in 2yrs

Liver Toxicity

- Transaminases elevation -> % w/event in 2yrs

Neurological

- Seizures -> % w/event in 2yrs
- Infusion/injection reactions -> % w/event in 2yrs
- Hypersensitivity reactions -> % w/event in 2yrs
- Flu-like reactions -> % w/event in 2yrs

Risks

- Liver Toxicity
- Neurological
- Other

Treatment (t)
Points to consider

• For gathering outcomes, leverage
  – The Target Product Profile (TPP) and Safety Profiling Plan (SPP) or Risk Management Plan (RMP) for your drug.
  – Expert knowledge on comparators profiles.

• Regarding inclusion/exclusion of outcomes
  – Keep the decision context in mind (e.g. decision maker’s perspective, time horizon)
  – Document all decisions to include/exclude

• Outcomes to consider excluding are:
  – Outcomes that are part of another included outcome.
  – Outcomes that are very similar to another included outcome.

Important to have preference independence
Step 3: Extract source data

Identify
Search strategy
Search query

Select
Study eligibility criteria

Extract
Extraction guidelines

Aggregate
e.g. meta-analysis, placebo-calibration

Study worksheet
one row per study

Data source table
one row per study/treatment/outcome

Data summary table
one row per outcome

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**Step 3: Extract source data**

Perform an indirect treatment comparison, by calibrating on a common placebo (Use the Tysabri placebo arm)

<table>
<thead>
<tr>
<th>Category</th>
<th>Outcome</th>
<th>Type of Estimate</th>
<th>Placebo</th>
<th>Tysabri</th>
<th>Avonex</th>
<th>Copaxone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease Activity</td>
<td>Relapse</td>
<td>2-year Relapse Rate</td>
<td>1.46</td>
<td>0.47</td>
<td>1.19</td>
<td>1.04</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td><strong>Risks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver Toxicity</td>
<td>ALT &gt; ULN</td>
<td>% w/ event in 2 yrs</td>
<td>4%</td>
<td>5%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>...</td>
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</tr>
</tbody>
</table>
Step 4: Value tree needs to be “tuned”

- The literature review or clinical expertise leads to the value tree being modified
  - The tree is pruned because the data are not available to populate it
  - The outcome measures may be refined in response to how data are measured
  - Some outcomes are not considered relevant
- This is closely linked with step 3 and iteration between steps 3 and 4 is common
Step 5: Assess outcome importance

*Linear Additive models with Swing Weights*

- Linear Additive Models with Swing Weights
  - Value functions: Within outcome importance
  - Swing weights: Between outcome importance

Outcome: 2-year relapse rate

Measure = 0.47

Value(measure) = 0.77

Elicited Weight = 8%

BR Contribution = 0.062

Value = 0.77

2-year relapse rate

0% - 2

Value function graph
**Step 5: Assess outcome importance**

*Linear Additive models with Swing Weights*

For each outcome category:

1. **Rank outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion/injection reactions</td>
<td>1</td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
<td>2</td>
</tr>
<tr>
<td>Flu-like reactions</td>
<td>3</td>
</tr>
</tbody>
</table>

2. **Relative importance**

How much more **important** it is to avoid the top-ranked event compared to the others?

- **Infusion/injection reactions**
- **Hypersensitivity reactions**
- **Flu-like reactions**
Repeat this process all the way up the value tree

*The top ranked outcome in each category is carried up the tree*

- Move bottom-up through the tree and compare the **top-ranked** outcomes from each category
- Finally, the top-ranked benefit is compared to the top-ranked risk
- The individual weights for each outcome can then be calculated
BRAT step 5: Assess outcome importance

Note that as the weight for a relapse is for a value function with the measure scale with a range from 0 to 2, then actual weight of a single relapse is half that shown here.

PML is 10x worse than disease progression
BRAT Step 6: Display and interpret key metrics

*Incremental Benefit-Risk of Tysabri – Placebo: Waterfall plot*

- The length of each bar gives the contribution to the overall BR.
- End of the last bar gives the overall benefit-risk.
  - Denominated in the BR of one EDSS progression
- Green = positive BR
- Red = negative BR
- The contribution to the overall BR of PML is very small
Drill down to the values and the weights

*Incremental Benefit-Risk of Tysabri – Placebo*

- This shows which outcomes are contributing most to the total benefit-risk.
- Even though the weight given to PML is large, the incidence is small, leading to a small contribution to the BR.
Sensitivity analysis on the weights

Incremental Benefit-Risk of Tysabri – Placebo

- The weights are shown under each bar.
  - The base case weight is shown in the middle, with a +/- 30% range given at the ends.
- The weights are changed one at a time.
- The most important weight is the one given to relapses.
Two way sensitivity analysis on PML

Incremental Benefit-Risk of Tysabri – Placebo

- Vary the Tysabri PML incidence (x-axis) and PML weight (each line).
- Increase the weight of PML so that it is 6x larger (to the inferred regulator weight).
- Increase the incidence of PML so that it is twice that observed.
- See that the BR is robust to these changes.
Two way sensitivity analysis on weights

*Incremental Benefit-Risk of Tysabri – Placebo*

- Vary the PML weight (x-axis) and the relapse weight (each line).
- Green line in the middle is the elicited weight. Change by +/- 30%.
- Again the BR is robust to these changes.
Take home message

- The BRAT is a framework well suited to benefit-risk analysis
- Benefit-risk analysis is conceptually easy but hard to operationalize – in particular:
  - To define consistent criteria across decision options, find data matching these criteria, and elicit value judgments
  - Squash the messy complexity of real life into a simple model
- A BR assessment does not necessarily give you the answer
  - It is a framework for decomposing and understanding a problem
  - Assesses the main value drivers of a decision
  - Communicates issues in a transparent, rational and consistent way
  - Allows sensitivity analysis around different perspectives (industry, regulator, patient, payer, prescriber)