An Overview of Benefit-Risk Assessment in Drug Development

Rebecca Noel, DrPH, MSPH
Global Benefit-Risk Leader
Eli Lilly and Company

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Executive Summary: Take Aways

• Changing drug development, regulatory, policy and patient engagement landscape pointed to a need for increased consistency and transparency in benefit-risk evaluation

• Benefit-risk frameworks are a useful tool to guide and enhance decision making

• A simple, but not simplistic, framework composed of 5 steps
Across the lifespan of a drug, we ask one fundamental question…

Do the benefits of the drug exceed the risks for the indication and its expected use?
Benefit and Risk: Pillars of Regulatory Decision-Making

To be approved for marketing, a drug must be **safe and effective** for its intended use

- The meaning of “safe” is not explicitly defined in the statutes or regulations that govern approval
- Recognizing that all drugs have some ability to cause adverse effects, the safety of a drug is assessed by determining whether its benefits outweigh its risks
- **This benefit-risk assessment is the basis of pre-market and post-market regulatory decisions**
Frameworks Support Decision-Making

Having said the safety of a drug is assessed by whether its benefits outweigh its risks, just how should we make that determination?

Historic reliance on expert judgment, but moving toward use of expert judgment + structured benefit-risk assessment

Structured benefit-risk assessment uses the concept of quality decision-making via “frameworks”

A benefit-risk framework is a systematic, consistent, and transparent approach (e.g., process and tools) that guides the assessment
**B-RA Frameworks: Support for Decision-Making and Communication**

<table>
<thead>
<tr>
<th>Decision Factor</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
</tr>
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<tbody>
<tr>
<td>Analysis of Condition</td>
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<td>Current Treatment Options</td>
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**PhRMA BRAT**

**Table 1: Steps in applying the BRAT Framework**

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
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<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>
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<tr>
<td>2. Identify outcomes</td>
<td>Select all important outcomes and create the initial value tree. Define a preliminary set of outcomes/end points for each. Document rationale for outcomes included/excluded.</td>
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<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 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>
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</tbody>
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**EMA**

- **Favourable effects**
- **Unfavourable effects**

**PRoACT-URL**

- **Uncertainty of favourable effects**
- **Uncertainty of unfavourable effects**

**BRAT = B-R action team; EMA = European Medicines Agency; FDA = Food and Drug Administration; PhRMA = Pharmaceutical Research and Manufacturers of America**
## FDA Benefit-Risk Framework

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### Benefit-Risk Summary Assessment

### Five Decision Factors
- Analysis of condition
- Current treatment options
- Benefit
- Risk
- Risk management

### Two levels of consideration
- Evidence and uncertainties
- Conclusions and reasons

### Summary
- Benefit-risk summary assessment
So Which Framework?: Global Guidance Emerges

International Council on Harmonization (ICH): Presentation of Benefit-Risk in Submissions and for Post-Marketing Surveillance
Guiding Principles

• Espouses a framework, not specific methods
• Benefit-risk assessments is based on a weighing of key benefits and key risks
  • Weighing implies judgment and allows for quantitative approaches, where useful
• “Key benefits” and “key risks” are those that contribute most importantly to the benefit-risk profile
• A descriptive (qualitative) approach is usually sufficient
  • Critical to communicate the implicit thinking behind what is assessed as being important and why
Guiding Principles (2)

- Why begin with a qualitative assessment?
  - Concern about reducing a complex decision into a single, summary statistic
  - Some quantitative methods obscure expert judgment
  - Regulatory review is characterized as a qualitative exercise grounded in the quantification of various data
  - Provides the flexibility to accommodate quantitative analyses if warranted
So Let’s Dig In!
ICH Guidance (Framework) for Benefit-Risk Assessment

Therapeutic Context: Disease/Condition + Treatment Alternatives

Key Benefits
- Consideration-1
- Consideration-2
- Consideration-3

Key Risks
- Consideration-1
- Consideration-2

Weighing the benefits and risks
Steps 1 & 2: Analysis of the Condition and Treatments Options

- Sets the stage by creating the context for the weighing of benefits and risks
  - How serious is the condition and why?
  - Who, how many and to what degree affected?
  - How well is the patient population’s medical need being met by available therapies?
- Focus on aspects with the greatest relevance and impact (e.g., incidence, morbidity, mortality, QoL)
- Public health and societal implications should also be addressed where relevant
Step 2: Assess Key Benefits

• A presentation of a factual summary of the data, i.e., *without interpretation*

• Typically primary and other clinically important endpoints (secondary and exploratory endpoints)
  – May use combination of study endpoints
  – Show ability of surrogate to predict clinical benefits
  – May include convenience (e.g., dosing regimen or route of administration) that may lead to improved patient compliance or benefits that affect those other than the patient (e.g., population benefits of a vaccine due to herd immunity)

• Discussion of strengths, limitations and uncertainties of benefit data
Identifying and Describing Key Benefits

• Clinical importance of the benefit
• Magnitude of the absolute difference in effect vs comparator; in some cases, also expressing the difference in relative terms may be informative
• Time course of the key benefit
• Variability, particularly in relevant subpopulations
• Study design considerations
• Completeness
• Number of clinical studies and consistency of results across studies
• Dose-response
• Generalizability of the clinical study result to clinical practice
• Uncertainties around surrogate endpoints predicting benefit
Step 3: Assess Key Risks

• Similar to key benefits, key risks are a presentation of a factual summary of the data, i.e., *without interpretation*

• Risks include adverse events and other unfavourable effects associated with the product

• Discussion of strengths, limitations and uncertainties of risk data
Identifying and Describing Key Risks

- Seriousness and/or severity, frequency, reversibility, and tolerability
- Frequencies as the absolute difference relative to the comparator in the context of the background frequency in the patient population
- Ability to monitor, minimize, or manage the risk
- Variability of the key risk across relevant subpopulations
- Time course of the risk
- Study design considerations
- Adequacy of assessment of risk
- Investigation(s) to address safety issues
- Completeness of data collection and duration of follow-up
Step 4: Integrated Benefit-Risk Assessment

- A benefit-risk conclusion, provided via a succinct explanation of the reasoning and judgment used in assessing and weighing the key benefits and key risks
- Explanation of how any uncertainties affected the interpretation of the evidence and their impact on the benefit-risk assessment
Aspects to Consider in Reaching a Benefit-Risk Conclusion

- The impact of the therapeutic context on the BR assessment
  - How the severity of disease and expected benefit influence the acceptability of the risks of the therapy
  - How the new medicinal product addresses a medical need
- Key aspects of risk management that are important in reaching a favorable benefit-risk assessment:
  - Whether nonresponders can be readily identified, allowing them to discontinue treatment
  - Other risk management activities, such as registries or restricted distribution systems
- Remember: Methods that quantitatively express the underlying judgments and uncertainties in the assessment can be used
Hepatic Toxicity through the Lens of Benefit-Risk: Real World Example

- **Ribociclib** was approved for treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer
  - Grade 3 or 4 increases in ALT (10% versus 1%) and AST (7% versus 2%) were reported in ribociclib and placebo arms, respectively
  - Concurrent elevations in ALT or AST greater than three times the ULN and total bilirubin greater than two times the ULN, with normal alkaline phosphatase, in the absence of cholestasis occurred in 4 (1%) patients
Discussion: Ribociclib

- Key benefits: PFS
- Key risks: QT interval prolongation, neutropenia and hepatobiliary toxicity
- Four patients (1.2%) in the ribociclib plus letrozole Group met the biochemical definition of Hy’s law;
  - Despite the availability of hormone directed therapies for treatment of first-line Hr positive advanced breast cancer, patients ultimately develop resistance and progression of disease and go on to receive multiple additional therapies. In light of the high burden of disease, there remains a clear medical need to develop new therapies for the treatment of advanced breast cancer to extend life, delay disease progression and/or lessen breast cancer related symptoms. The risk of QT interval prolongation, hepatobiliary toxicity and neutropenia and dose modifications to address safety will be communicated in labeling in the Warnings and Precautions section of the label.
Discussion: Ribociclib (2)

- [https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209092Orig1s000RiskR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209092Orig1s000RiskR.pdf)
Selected Readings

• FDA Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making:


• Revision of M4E Guideline on Enhancing the Format and Structure of Benefit-Risk Information:
  http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4E_R2_Efficacy/M4E_R2_Step_4.pdf
We are responsible for reaching good decisions by helping each other think through all the information we have.