Key Sources of Uncertainty in the Assessment of Benefits and Risks of Pharmaceuticals and Associated Challenges

Institute of Medicine Workshop: Characterizing and Communicating Uncertainty in the Assessment of Benefits and Risks of Pharmaceutical Products
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Disclaimer

- The views expressed in this talk are mine, and as such, the principles, ideas, and perspectives provided here do not necessarily reflect those of my employer

The Roadmap...

1. What we are dealing with: Decision dimensions in drug development (context)
2. What we are talking about: Population-based benefit-risk assessment throughout the drug lifecycle
3. Going back to the basics: Key sources of uncertainty
4. Considerations for the optimal approach to address uncertainty around BR assessment
The Roadmap...

1. What we are dealing with: Decision dimensions in drug development (context)

Decision Dimensions in Drug Development...

EVIDENCE
- Exposure
- Drugs, biologics, devices
- Nature

Outcomes
- Effect
- Modifiers

BELIEF
- Magnitude of effect
- Natural
- Measurement

UNBUNDLING INFORMATION
- Threshold for concern
- Sense of uncertainty
- The ugly

Our common interest is to evaluate association vs. causality?
Are all drugs’ benefit created equal?

Well, perhaps not...
How about risk?

Are all adverse events created equal?

**Domains of Adverse Events in Drug Development:**

Not All AEs Are Created with Equal Uncertainty…!

- Inherent uncertainty about source, timing, and nature of safety information

- Premarketing
  - Supported by several streams
  - Biologically plausible

- Postmarketing
  - Counter-intuitive

**In a Nutshell…**

- What we are dealing with:
  - A complex decision-making process that has inherent quantitative and qualitative dimensions, reflecting the interaction between multiple streams of evidence with many stakeholders
  - Drugs with benefits and risks that are not created equal

  - Context matters significantly in the evaluation process — the same set of facts might lead to a different course of action!
The Roadmap…

- What we are dealing with: Decision dimensions in drug development (context)
- What we are talking about: Population-based benefit-risk assessment throughout the drug lifecycle

Which Drugs Might NOT Need BR Assessment?

The message: BR assessment is a moving target because of the dynamic nature of the information...

However, Regulatory Time Is the Product of the Information and the Calendar Times

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\[ RR = 2 \]

We cannot have it BOTH ways

Information Time

Calendar Time

Drug Use

Adverse Events

Information about benefit

Efficacy

Uncertainty

Effectiveness

Time of approval

Missing piece of the puzzle

Premarket phases

Information about benefit

Precautionary

Postmarket/Real World Use

Information about risk

Current Realities Regarding the Population-based Benefit-risk Assessment Throughout the Drug Lifecycle

Hammad et al., 2013. Clinical Pharmacology & Therapeutics. doi:10.1038/clpt.2013.118
In a Nutshell…

- We are talking about:
  - A dynamic benefit-risk assessment process in which we superimpose group experience on individual patients
  - An imbalance in the sources, timing, and nature of information on benefit and risk in the pre- and post-marketing periods

The Roadmap…

1. What we are dealing with: Decision dimensions in drug development (context)
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3. Going back to the basics: Key sources of uncertainty

The Three Domains of BR Assessment: Almost Three Different Fields of Science…

1- Benefit

2- Risk

3- Approaches to put them together
Breaking it down to the basic elements...

To make it more manageable...

Challenges and knowledge gaps, underlying uncertainties in BR assessment, have three unique, yet intertwined sources...

Transcending issues

Clinical

Uncertainty in benefits and risk

Methodological

Statistical

Volunteer effect, indication vs. off-label use, inclusions and exclusions, case definition, surrogate outcomes, AE with long latent period, lack of MCID, no true comparativeness... etc.

RCTs vs. observational design and conduct limitations, e.g. randomized withdrawals, ecological fallacy, measurement errors, selection and channeling bias, approach to evaluate BR, etc.

Knowledge gaps

Challenges

System is designed for drugs to pass a test, sampling approaches, residual errors, rare events challenge, programs with small size... etc.
Clinical Methodological Statistical System is designed for drugs to pass a test, sampling approaches, residual errors, rare events challenge, programs with small size … etc.

Volunteer effect, indication vs. off-label use, inclusions and exclusions, case definition, surrogate outcomes, AE with long latent period, lack of MCID, no true comparativeness … etc.

Operational aspects: The “Fourth” Dimension
1. Need more info: can not coerce patients to participate post-market
2. Benefit: system not designed to quantify it, no MICD
3. Risk: lack of “threshold of risk tolerance” (regulators vs. payers vs. healthcare providers vs. patients)
4. Surveillance effort:
   - “Time trend bias” related to the dynamic nature of all the pieces
   - Unknown impact of regulatory actions on BR balance
   - Impact of “Confounding by Information” on BR balance
   - “Volume” bias due to large number of small negative studies
   - Need for true EHR/big data infrastructure
5. …

Classification adopted from Berlin et al. Clinical Trials 2012; 10: 20 –31
Uncertainties in BR assessment, have three unique, yet intertwined sources…

The Roadmap…
1. What we are dealing with: Decision dimensions in drug development (context)
2. What we are talking about: Population-based benefit-risk assessment throughout the drug lifecycle
3. What the debate is all about: Scientific thought process and the core debates in BR
4. Considerations for the optimal approach to address uncertainty around BR assessment

What is the "Status Quo"?
The “Precautionary Principle”...

- A strategy to cope with possible risks in which scientific understanding is incomplete...
  - “A need to err on the side of caution because of uncertainties about the safety of technologies or infrastructure”
  - “When human activities may lead to morally unacceptable harm that is scientifically plausible but uncertain, actions shall be taken to avoid or diminish that harm”
  - “Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent [environmental] degradation”

What is at stake?

What About the Patient Perspective: How Does It Relate to Uncertainty?

- In practice, the “Precautionary Principle” might conflate uncertainty about the extent of the risk with the uncertainty about the willingness of patients to accept the risk.

- Patient perspective is likely to change over time depending on stage of life and disease severity, adding to the uncertainty.

- Group experience vs. individual decisions.

In Short, the Optimal Approach to Address Uncertainty in BR Assessment Should Take Into Consideration...

- The complexity of the decision-making process: quantitative and qualitative dimensions, not all drugs created equal, context matters, sources of uncertainties (clinical, methodological, and statistical), operational challenges.

- The dynamic nature of the BR assessment with clear imbalance in the sources, timing, and nature of information on benefit and risk.

- The goal of addressing uncertainty is to improve our judgment, not to replace it with an automatic process....

- Identify and address knowledge gaps to achieve quick wins, while minding the scientific boundaries of our tools.

- The need for a better way to truly characterize and incorporate pertinent patient prospective.