FORUM:
Patient-Focused Benefit-Risk Analysis to Inform Regulatory Decisions
Moderator
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Value in Health Themed Sections

Scheduled Themed Sections for 2016

- **July/August 2016:**
  - Cost-Effectiveness And Clinical Practice Guidelines: Have We Reached A Tipping Point?
    - Guest Editor: Lou Garrison

- **September/October 2016:**
  - Patient-Focused Benefit-Risk Analysis to Inform Regulatory Decisions
    - Guest Editor: Shelby Reed

- **December 2016:**
  - Economics on Making Choices on the Journey of Universal Health Care Coverage
    - Guest Editor: Kalipso Chalkidou
Value in Health Themed Sections

Themed Sections in Process

- Value to Decision Makers of Evaluations of Personalized/Precision Medicine: Applications to Other Emerging Technologies
  - Guest Editor: Kathryn Phillips
- Rare Diseases: Road to Approval and Patient Access
  - Guest Editor: Kati Copley-Merriman
- Affordability
  - Guest Editors: Adrian Towse & Josephine Mauskopf
- Improving the Methods and Processes for Conducting Value Assessments of Health Care Interventions
- Improving the Methods and Processes for Conducting Value Assessments of Health Care Interventions
  - Guest Editor: Jalpa Doshi

Value in Health Themed Issue

Patient-centered movement

Quantitative benefit-risk

Regulators
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Regulatory Decision-making in Canada – Exploring New Frontiers in Patient Involvement

Deborah A Marshall
University of Calgary

Agnes V Klein, Stephanie Hardy, Robyn Lim
Health Canada
Background to Regulatory Review

- Health Canada’s Health Products and Food Branch (HPFB) is the national regulatory authority responsible for evaluating and monitoring the quality, safety, and efficacy of therapeutic products in Canada.
- Regulatory benefit-risk assessments underpin Health Canada’s decisions across the life-cycle of a therapeutic product.
- Canada has an established practice, albeit implicit and often *ad hoc*, for including patient perspectives in both operational and policy-based regulatory decision-making.

Recent Changes (1)  
Transparency and Openness

- Recent legislative amendments and Health Canada’s Regulatory Transparency and Openness Framework aim to:
  - enhance the transparency of the regulatory review processes, and
  - provide public information about review decisions
- Opportunities to advance in the area of seeking and considering patient perspectives throughout the lifecycle of therapeutic products.
Amendments to *Food and Drugs Act* to improve Health Canada’s ability to collect post-market safety information, and take appropriate action when a serious risk to health is identified.

Key amendments include:
- Power to require information, tests or studies
- Power to require a label change/package modification
- Power to recall unsafe therapeutic products
- Ability to disclose information in certain circumstances
- Tougher measures for those that do not comply
- Mandatory reporting of serious adverse drug reactions and medical device incidents by healthcare institutions

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**2) Protecting Canadians from Unsafe Drugs Act**
*Vanessa’s Law (Bill C-17) Nov 2014*

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**Canadian Examples of Patient Involvement**

**Scientific/Expert Advisory Committees**
- Patient advocates serve as members of Health Canada’s standing Scientific and Expert Advisory Committees to provide medical, technical, and/or scientific advice, practical and contextual perspectives, to help resolve issues
- Patient advocates on ad hoc Expert Advisory Panels as-needed to provide advice on specific drug submissions or on emerging and/or controversial issues post-market.
- Examples include:
  1) panel on use of insulin of animal origin and its place in the treatment of Type 1 diabetes mellitus;
  2) public forum on selective Cox-2 inhibitor NSAIDS;
  3) focused consultation with patient safety groups to discuss risk minimization options regarding acetaminophen overdose and liver injury.
Canadian Examples of Patient Involvement

**Patient Involvement Pilot Project (2014)**

- Explored the value and feasibility of patient involvement in the orphan drug context as starting point for systematic, structured opportunities to inform benefit-risk assessment and management
- Simulated how input from patients, their caregivers, healthcare professionals and patient groups could be collected and incorporated in the drug submission review process.
- Online questionnaires were designed to gather qualitative information on the following (examples of one biologic and one pharmaceutical):
  - the impact on individual patient’s quality of life;
  - experience with currently available therapies;
  - unmet medical need; and
  - the patient’s level of risk tolerance

**Results from the Pilot Project:**

- Patient education on regulatory review and decision-making processes and reviewer training on when and how to best consider patient input in these processes is needed;
- Timing of when reviewers receive patient input is important;
- Additional experience needed.

**Opportunities and Future Prospects**

- Determining the best ways to elicit and consider patient input in a systematic manner and exploring the scope and nature of patient input of highest value.
- Assessing the overall suitability and feasibility of adopting, modifying or collaborating with other existing models such as those used by the FDA and EMA, and HTA bodies
Patient Involvement - Further Exploration

a) Who is best situated to provide input?
b) At what stage(s) in the regulatory process is it most feasible, or valuable, for patient input to be collected?
c) Is there information to enhance the regulator’s understanding of patient drug experiences that could be gleaned from within data collected during clinical trials and submitted as part of the traditional data package?
d) What are the most appropriate and effective formats for patient input?
e) How should patient input be considered and captured in the regulatory assessment and decision-making processes?

Patient-Focused Benefit-Risk Analysis to Inform Regulatory Decisions: The EU perspective

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Hochschule Neubrandenburg, Germany

Andrea R. Beyer
University of Groningen, The Netherlands

Sarah Garner
National Institute for Health and Care Excellence (NICE), London, UK
Assessment of benefits and risks

• In Europe marketing approval is granted by The European Medicines Agency (EMA), a decentralized agency of the European Union (EU).
  – Most approvals are valid EU-wide.
  – National regulatory authorities are not included in the approval process unless they are the ‘rapporteur’ doing the evaluation.

• Added value of including patients’ perspectives within EMA benefit-risk assessments has been widely discussed.

European Medicines Agency (EMA)
EMA Benefit-Risk Methodology Project

- Quantitative approaches that are sufficiently comprehensive to numerically represent the benefit-risk balance by incorporating the value of favorable and unfavorable effects:
  – Bayesian statistics
  – Decision trees and influence/relevance diagrams
  – Multi criteria decision analysis (MCDA)

- In addition, specific methods that are more restricted in scope but can be used for particular cases:
  – Probabilistic simulation
  – Markov simulations
  – Kaplan-Meier estimates
  – QALY/ DALY
  – Conjoint analysis
- IMI-PROTECT project ("Pharmacoepidemiological research on outcomes of therapeutics by a European consortium")
  - Aim: Strengthening the monitoring of pharmacovigilance of medicines in Europe.
  - Several methods for eliciting preferences among various stakeholders have been evaluated: DCE, AHP, and MCDA (MACBETH approach).
  - Results of the studies were distilled into a set of practical recommendations for benefit-risk decision processes and supporting tools.

- Conclusions:
  - No single benefit-risk methodology can fully capture all aspects of a benefit-risk assessment.
  - Choice of a single approach or combination of methodologies should be matched to the complexity of the problem.

→ 13 benefit-risk assessment methods/frameworks were recommended for further appraisal for the use in real benefit-risk assessment

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**Table:** Practical recommendations for the benefit-risk decision processes and the supporting tools according to IMI

<table>
<thead>
<tr>
<th>Stages of benefit-risk assessment</th>
<th>Useful methods/frameworks</th>
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<tbody>
<tr>
<td>Planning</td>
<td>Benefit-Risk Action Team (BRAT)</td>
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<tr>
<td></td>
<td>Problem, Objectives, Alternatives, Consequences, Trade-offs, Uncertainty, Risk and Linked decisions (PROACT-URL)</td>
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<tr>
<td>Evidence gathering and data preparation</td>
<td>Indirect Treatment Comparison (ITC)</td>
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<td>Mixed Treatment Comparison (MTC)</td>
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<td>Probabilistic Simulation Method (PSM)</td>
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<tr>
<td>Analysis</td>
<td>Metric indices/numerical representations of benefits and risks</td>
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<td>Number Needed to Treat (NNT)</td>
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<td></td>
<td>Impact numbers</td>
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<td></td>
<td>Quantitative frameworks to model benefit-risk trade-off and balance benefits and risks</td>
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<tr>
<td></td>
<td>Multi-Criteria Decision Analysis (MCDA)</td>
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<td></td>
<td>Stochastic Multi-criteria Acceptability Analysis (SMAA)</td>
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<td></td>
<td>Utility survey techniques</td>
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<td></td>
<td>Discrete Choice Experiment (DCE)</td>
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<td>Stochastic Multi-criteria Acceptability Analysis (SMAA)</td>
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<tr>
<td>Conclusion and Dissemination</td>
<td>Results and consensus from the benefit-risk assessment are communicated to a wider audience</td>
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Germany: IQWiG-Pilots on AHP and DCE


NICE: Social Value Judgements

- NICE has explicitly defined information by the type, format, and sources of evidence in its guidelines for assessment and testing of eligibility (appraisal).

- Appraisal is usually based on evidence from patients with a condition.

- Citizens characterise an overall societal perspective on what should be taken into account in decision-making related to distributive justice.

- Views of citizens’ conferences are published in “Social Value Judgements”.

Future Prospects

- Range of participation efforts on European level extends from qualitative surveys of patients' needs to approaches of science-based documentation of quantitative patient preferences.

- European pilot projects have shown that modeling of the benefit-risk assessment for medicines is possible.

- More research projects are needed to design the tools that are accessible to patients and other stakeholders, appropriate to the needs of the regulators/assessors and that can be integrated into the current processes in benefit-risk evaluation.

Patient Preferences in Regulatory Benefit-Risk Assessments: A U.S. Perspective

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Duke University

Mo Zhou
Bloomberg School of Public Health
Johns Hopkins University

Acknowledgement
Anindita Saha
Center for Devices and Radiological Health
U.S. Food and Drug Administration

This presentation reflects the views of the authors and should not be construed to represent the policies of the U.S. FDA.
Patient-Focused Decision Making

- Center for Drug Evaluation and Research
    - PDUFA V amendments (2012)
    - Public meetings being conducted in 24 priority disease areas
    - Information obtained to inform drug-development and regulatory-review processes

- Center for Devices and Radiological Health
  - 2012 Guidance: “FDA would consider evidence relating to patients’ perspective of what constitutes a meaningful benefit.”
  - Patient Preference Initiative to incorporate patient preferences on the benefit-risk tradeoffs in CDRH decision making
  - 2015 draft guidance on submitting preference data
  - 2016-2017 Strategic Priorities

Qualitative and Quantitative Approaches

- CDER qualitative and CDRH quantitative approaches complementary
  - Structured public meetings elicit direct patient feedback
  - Quantifying preferences helps integrate patient concerns with existing clinical data.

- Type of information needed could vary in product lifecycles
  - Discovery and ideation phases of product development: qualitative information on unmet needs, feasibility constraints, and human-factors considerations
  - Quantitative patient-preference information for conducting structured regulatory benefit-risk

Center for Devices Preference Study

CDRH-sponsored study cited as an example that “followed many of the recommendations listed.”

Regulatory Impact of the Study

- Used study’s decision aid tool to evaluate EnteroMedics’s Maestro Rechargeable System
- Device failed to meet its co-primary trial endpoints
- Approved in January 2015 based on patients’ benefit-risk tradeoff preferences
  - First new obesity device approved by FDA since 2007
  - First approval to result from CDRH's patient-centered regulatory initiative

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm430223.htm
Patient Organization Preference Study

Duchenne Muscular Dystrophy Preferences

- Study demonstrated community-engaged process to understand treatment preferences
- "Submitted patient-initiated FDA draft guidance to inform drug development and regulatory review
- CDER invited public comment on report and draft guidance
- Not used in recent reviews
Challenges

- When is it in society’s best interest to approve novel health technologies that offer promising therapeutic benefits, but also have worrisome side effects?
- CDER: how to integrate qualitative data from public meetings into existing evidence-based decision making
- CDRH: how to build capacity to implement ambitious strategy to quantify patient benefit-risk tradeoff preferences

Dr. Rob Califf, FDA Commissioner

You don’t know people’s preferences unless you ask them. ... To the extent that FDA takes preferences seriously, I think it’s a great day.
The MDIC Framework for Patient-centered Benefit-Risk Assessment

ISPOR Forum on Patient-Focused Benefit-Risk Analysis to Inform Regulatory Decisions
May 24, 2016

*Bennett Levitan, MD-PhD*
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**FDA CDRH 2012 guidance on B-R assessment raised a critical question**

- FDA guidance recognizes that patients will vary in how they value benefits and tolerate risks
  - “FDA realizes that some patients are willing to take on a very high risk to achieve a small benefit, whereas others are more risk averse.”
  - “FDA would consider evidence relating to patients' perspective of what constitutes a meaningful benefit when determining if the device is effective, as some set of patients may value a benefit more than others.”

→ Guidance suggests that FDA would consider patient perspective and preferences on benefits and risks

But it did not say how…
Medical Device Innovation Consortium (MDIC)

- 55 Members
- 6 Projects
- Leading resource on issues important to the Medtech innovation ecosystem
- Congressional testimony on modernizing clinical trials
- $500k funding from FDA for Patient-Centered Benefit-Risk Framework - Project Completed
- $643k funding from FDA for Quality Engagement Forum
- $300k+ of industry funding + member dues

A 501(c)3 - Public-Private Partnership collaborating on Regulatory Science to make patient access to new medical device technologies faster, safer, and more cost-effective

WORKING COOPERATIVELY
to re-engineer pre-competitive technology innovation

REDUCING TIME
and resources needed for new technology development, assessment, and review

HELPING PATIENTS
gain access to new medical technologies sooner

www.MDIC.org

Vision for Patient-Centered Benefit-Risk Project

To establish a credible framework for assessing patient preferences regarding the probable benefits and risks of a proposed medical device and for incorporating this patient preference information into pre-market and post-market regulatory submissions and decisions
The other reasons for a framework on patient preference studies

- Do we really need it?
- When should we do it?
- Work with a patient group?
- Who is involved?
- Will regulators pay attention?
- What can we do with it?
- How long will it take?
- Can we publish?
- How much does it cost?
- Whose preferences?
- Who can help us?
- Can we trust the results?

MDIC PCBR Project Components

- Framework
  - Framework for Patient Centered Benefit-Risk Assessment
- Catalog
  - Catalog of Patient Preference Assessment Methods
- Future Work
  - Agenda for Future Research in Patient Preferences
Key Topics in the Framework

• Definitions and core concepts
• When is collecting patient preference information potentially valuable for B-R assessment?
• Use and value of patient preference information throughout the lifecycle
• How patient preference information may be useful in the regulatory process
• Potential value of patient preference information beyond the regulatory process
• Methods for preference assessment and factors to consider in their use

When is Patient Preference Information Potentially Valuable in Regulatory Review?

• Factors related to the patient perspective
  – Patients willing to accept a different degree of risk than regulators
  – Important differences in the preferences of subgroups of patients
  – Understanding the clinical experience requires considerable familiarity with the disease (e.g. highly subjective endpoints, lifestyle indication, rare diseases)

• Factors related to benefit-risk tradeoffs
  – Clear benefit with rare serious risks compared to alternatives
  – Modest benefit but considerably less risk than alternatives
  – Harms occur early/benefits occur later (e.g. Tx to delay disease onset)
  – Considerable uncertainty on whether a patient will realize the benefit or risks

• Factors related to novelty
  – New technology or mechanism of action
  – Lack of device precedent in indication or technology
What Can a Sponsor Learn from a Patient Preference Study?

- **Trial design**: What endpoints do patients care most about?
- **TPP**: What is the relative importance of benefits, risks and other treatment features to patients?
- **Approval for subgroups, payer assessment, adaptive licensing**: How do patients vary in these properties (heterogeneity)? Are there distinct subgroups?
- **Ph 2a/b**: What level/rate of endpoints are critical to patients?
- **Ph 3**: Maximum acceptable risk, minimum required benefit?
- **Reg**: Are there important differences between stakeholders?
- **Post-approval**: Shared decision-making

Incorporating Patient Preferences into the Medical Device Product Lifecycle

- **Patient-Informed Needs**
- **Pre-clinical**: Patient Preference Benefit-Risk Information
- **Clinical**: Patient-Centered Outcomes
- **Regulatory Decision**: Patient-Informed Clinical Trial Design, Patient Reported Outcomes
- **Product Launch**: Communicating Benefit-Risk Information to Patients

Source: FDA Center for Devices and Radiological Health (CDRH)
## Methods Included in the Catalog

<table>
<thead>
<tr>
<th>Group*</th>
<th>Method</th>
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</table>
| Structured-weighting | • Simple direct weighting  
| | • Ranking exercises  
| | • Swing weighting  
| | • Point allocation  
| | • Analytic hierarchy process  
| | • outranking methods  
| Health-state utility | • Time tradeoff  
| | • Standard gamble  
| Stated-preference | • Direct-assessment questions  
| | • Threshold technique  
| | • Conjoint analysis and discrete-choice experiments  
| | • Best-worst scaling exercises  
| Revealed-preference | • Patient-preference trials  
| | • Direct questions in clinical trials  

* Grouping scheme meant only to facilitate discussion of methods. Some methods could be assigned to multiple groups

## Questions Considered

### Methodology-Related Questions
- How are the data acquired?
- Are hypothetical scenarios required?
- How are attributes/levels determined and defined?
- Is the method experimental?

### Analysis-Related Questions
- Does the method require statistical analysis?
- Does the method require specialized software?
- Can the results be described and interpreted easily?

### Sample-Related Questions
- What is the minimum sample size required?
- What is the reasonable maximum sample size?
- What is the time commitment required of patients?
- Cognitive and knowledge requirements of patients?

### Output-Related Questions
- Can the method be used to identify attributes that are important to patients?
- Can the method be used to estimate weights for attributes?
- Can the method be used to estimate the tradeoffs that patients are willing to make among attributes?
- Can the method be used to detect, describe, or quantify heterogeneity in preferences across patients and across time?

### General Questions
- Representativeness and generalizability?
- Validity?
- Resource requirements?
Questions for Future Research in Patient Preferences

- Can patients do these surveys reliably?
- Stated choice is not actual choice
- Choosing the right method
- Industry can bias these surveys
- Selecting the attributes
- Sample selection – whose preferences and when?
- Sample size
- Formal assessments of validity
- Regulatory requirements

Sites for MDIC Framework and FDA CDRH Draft Patient Preference Guidance

www.mdic.org/PCBR