STATED PREFERENCES IN DRUG EVALUATION: A COMPARATIVE ASSESSMENT OF THE USE OF STATED PREFERENCE IN THE US, CANADA, AND THE EUROPEAN UNION

Prepared by:
Kevin Marsh, PhD

ISPOR, Boston, 23rd May 2017

Stated Preference SIG
Workshop objective

- To compare decision makers’ use of stated preference research in the medical technology approval and reimbursement in the US, EU and Canadian regulatory environment drawing good practice lessons from the best elements of each

Our panel

- Deborah Marshall, PhD, Professor, O’Brien Institute for Public Health, University of Calgary, Calgary, AB, Canada
- Axel C. Mühlbacher, PhD, MBA, Professor, Health Economics and Health Care Management, Institute Health Economics and Health Care Management, IGM, Hochschule Neubrandenburg, Neubrandenburg, Germany
- F. Reed Johnson, PhD, Professor, Duke School of Medicine, Preference Evaluation Research Group, Duke Clinical Research Institute, Durham, NC, USA
Questions/discussion

● Do you know of examples of the use of stated preference in decision making that we have not mentioned?
  ○ What lessons can we learn from this example?

● What do you see as the future direction for the use of stated preferences in decision making?

Use of Patient Preferences in the Canadian Context

Deborah A Marshall, PhD
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Outline

• What do we mean by patient preferences?
• Do we need patient preferences in drug evaluation?
• Brief overview of situation in Canada

MDIC Framework for Patient-Centered Benefit-Risk Assessment

Medical Device Innovation Consortium:

• Defines ‘preferences’ as:
  • “Qualitative or quantitative statements of the relative desirability or acceptability of attributes that differ among alternative health interventions”

• Define ‘patient-preference methods’ as:
  • “Methods for collecting and analyzing data that allow quantitative assessments of the relative desirability or acceptability to patients of attributes that differ among alternative medical treatment approaches”
MDIC Methods for Patient-Centered Benefit-Risk Assessment

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

Step 1
- Regulatory Approval: Evaluate quality, safety, and efficacy

Step 2
- Listing and Reimbursement:
  - clinical
  - cost-effectiveness
  - budget impact
Simplified Steps in Drug Review and Approval

Step 1
- Regulatory Approval: Evaluate quality, safety, and efficacy

Step 2
- Listing and Reimbursement:
  - Clinical
  - Cost-effectiveness
  - Budget impact
  - Patient input

Why are we doing this?

Beyond clinical and economic data = Patient Input

What is the best approach?

Patient-focused benefit-risk analysis to inform regulatory decisions

Guest Editor: Shelby Reed

Value in Health Themed Issue, October, 2016

Regulatory Review in Canada

- 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.
- 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 that Support Patient Engagement (1)

1) Transparency and Openness
- 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.
Recent Changes that Support Patient Engagement (2)

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

- 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

Health Canada Regulatory Process

1) Patient Involvement on Advisory Committees

- Patient 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
Health Canada Regulatory Process

2) Patient Involvement in Pilot Project

• 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 designed to gather qualitative information on:
  • The impact on individual patient’s quality of life
  • Experience with currently available therapies
  • Unmet medical need
  • 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

Health Canada Patient Involvement - Future

Assess best approaches systematically - what can we learn from existing models (e.g. FDA and EMA)?

1. Who is best situated to provide input?
2. At what stage(s) in the regulatory process is it most feasible, or valuable, for patient input to be collected?
3. 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?
4. What are the most appropriate and effective formats for patient input?
5. How should patient input be considered and captured in the regulatory assessment and decision-making processes?
Canadian Process for Patient Input

- CADTH: Canadian Agency for Drugs and Technologies in Health
- New drugs and existing drugs being proposed for new indications reviewed through Common Drug Review (CDR)
  - Then provides reimbursement recommendations/advice to federal and provincial governments/health plans
- Input from patient groups to “ensure that issues important to patients are incorporated into the CDR process in a formal and meaningful way”
- Canadian Drug Expert Committee (CDEC; independent advisory body) reviews and makes formulary listing recommendations
- Patient input submitted through organized patient group

https://cadth.ca/about-cadth/what-we-do/products-services/cdr/patient-input
Process and Template for Patient Input

Patient Group Activities

- Create and send survey to patients and caregivers
- Analyze data internally

Interview patients with experience with drug in question if possible
Complete template

Sections in Submission
6 pages, 3500 words

1. Background Info on Patient Group
2. Experience of patients and caregivers with condition and current therapy
3. Expectations and expectations for the new drug under review
4. Additional information and Conflict of interest declarations

https://www.cadth.ca/about-cadth/what-we-do/products-services/cdr/patient-input

Thank you!
STATED PREFERENCES IN DRUG EVALUATION: THE USE OF STATED PREFERENCE IN THE EUROPEAN UNION

Axel Mühlbacher
Tuesday, May 23, 2017 - W11
ISPOR Boston

Preference studies in the context of HTA
ISPOR Special Interest Group

• “Stated Preference Research in the European Union Working Group”

• Aim:
  – to map which stated preference methods are being used in the European regulatory environment.
  – facilitate a more systematic consideration of preferences as part of regulatory decisions – approval, reimbursement and pricing.
  – describe the use of preference in regulatory decision-making contexts based on the EU initiatives and pilot projects
Declaration of Alma Ata

Article IV of the Declaration of Alma Ata (1978):

"...it is a basic right—even the duty—for the people to participate in the
planning and implementation of health services."

Patients: Rhetoric?
Perspective: citizen, insured or patient?
Decision: form of participation?
Type of decision: approval, appraisal & reimbursement?
Evidence on priorities/preferences?

Level of involvement

- Macro level – political decision-making
- Meso level – organisational
- Micro level – research and care
Type of involvement

- Information and Communication
- Consultation
- Participation

Decision-making in health care
Developments on the EU level

Preference studies in the context of HTA
Development at the EMA

Preference studies in the context of HTA
Development at the EMA: Benefit-Risk Methodology

• Aim of the project:
  – Improve the consistency, transparency, and communication of the benefit-risk assessment in assessment reports
  – Development and Testing of tools for weighing multiple benefits and risks to support regulatory decisions at the EMA level

• Three quantitative approaches to numerically represent the benefit-risk balance (as a difference or a ratio)
  – Bayesian statistics
  – Decision trees and influence/relevance diagrams
  – Multi criteria decision analysis (MCDA)

Preference studies in the context of HTA
Development at the EMA: Benefit-Risk Methodology

• Five specific methods that are more restricted in scope but can be used for particular cases
  – **Probabilistic simulation**, when the focus is aligned on the uncertainty of effects
  – **Markov simulations**: Markov processes extend a decision tree to include the movement between health states over time. According to the EMA report these may be most relevant for post-approval decisions.
  – **Kaplan-Meier estimates** of changes in health conditions over time
  – **Quality-adjusted life years / Disability-adjusted life years** for the modelling of multiple endpoints. According to EMA, the current focus on health outcomes restricts the relevance of both DALYs and QALYs, but as they are multi-criteria metrics, they could be developed for both regulators and health technology assessors.
  – **Conjoint analysis** to illustrate trade-offs between effects between favorable and unfavorable effects, especially to determine patient preferences. According to EMA conjoint analysis is “particularly relevant to eliciting patients’ preferences but doesn’t consider uncertainty”.
Preference studies in the context of HTA
Development in the EU: IMI Protect

• 5-year research project
  – funded equally by the Innovative Medicines Initiative and by industry as in-kind contributions.
  – builds upon the experiences and outcomes of previous initiatives, e.g., from the US FDA, EMA, previous IMI projects such as PROTECT, and the MDIC

• Main aim:
  – strengthen patient-centric decision making throughout the life cycle of medicinal treatments
  – developing expert and evidence-based recommendations on how patient preferences should be assessed and inform decision making.

Developments in EU member countries

Preference studies in the context of HTA
Development in Lombardy, Italy

- Lombardy Region developed an HTA framework („Valuta zione delle Tecnologie Sanitarie“) incorporating and adapting elements from the EUnetHTA Core Model and the EVIDEM framework
  - Maps EUnetHTA domains into dimensions that Lombardy Region set up to legitimize the prioritization of technologies
  - Includes criteria from the EVIDEM framework to support the systematic appraisal of the assessment report into a final decision.

- The framework has been used in Lombardy Region since 2011 to decide on the introduction and delisting of health technologies

Preference studies in the context of HTA

Development in Lombardy, Italy

Framework is applied in a three-step process comprising

(1) Prioritization of requests, grounded on a “quick and dirty” assessment limited to dimensions;

(2) Full assessment of the prioritized technologies, provided by answering EUnetHTA-based issues;

(3) Appraisal of the assessed technologies, grounded on the analysis of multiple criteria, using the EVIDEM framework (quantitative result (score for 15 criteria) and 6 qualitative evaluations).

Preference studies in the context of HTA

Development in Hungary

- Formal guideline for conducting economic evaluation of health care interventions in Hungary

- As a part of the application dossier, one must submit a formal HTA report (including a health-economics analysis), clinical evaluation, clinical expert opinion, and detailed cost calculation.

- MDCA was introduced by a ministerial decree in 2010 for the evaluation of new hospital medical technologies applied in hospital care.
Preference studies in the context of HTA

Development in Germany: IQWiG-Pilot project


Preference studies in the context of HTA

Development in Belgium

Preference studies in the context of HTA

Belgian Healthcare Knowledge Centre (KCE)

• KCE focuses on an increased participation of patients and citizens in decision-making; "Get involved" initiative

• The KCE distinguishes between
  (1) citizens (representatives) who represent the taxpayer,
  (2) patient representatives who represent (potential) patients and consumers of health services
  (3) patients who represent experts through their own experiences

• Feasibility study to assess the acceptance of different models for citizen and patient participation using a two-stage Delphi survey
  – study shows a high degree of consensus regarding the importance of citizen/patient participation

Conclusion

• European developments show that the idea of patient participation is playing an increasingly important role.
  • Currently, a paradigm shift is taking place where citizens no longer act as merely passive players in the health sector, but increasingly interact as partners with regulatory authorities.

• It seems that there is a bottom up recognition of the value of including patients in the regulatory processes.

• The range of participation efforts extends from qualitative surveys of patients' needs to approaches of science-based documentation of quantitative patient preferences
### Tysabri History

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>2003</td>
<td>Multiple-sclerosis trial indicated 66% fewer relapses and over 90% fewer lesions compared to placebo</td>
</tr>
<tr>
<td>November 2004</td>
<td>FDA approval</td>
</tr>
<tr>
<td>February 2005</td>
<td>3 cases of progressive multifocal leukoencephalopathy (PML), 2 fatal. Product withdrawn.</td>
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<tr>
<td>2005-2006</td>
<td><em>MS patient risk-tolerance study</em></td>
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<td>June 2006</td>
<td>FDA re-approval for MS with black-box warning</td>
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<tr>
<td>2006-2007</td>
<td><em>Patient, physician, and parent risk-tolerance studies for Crohn’s disease</em></td>
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<tr>
<td>November 2007</td>
<td>EMA rejection for Crohn’s disease</td>
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<tr>
<td>January 2008</td>
<td>FDA approval for Crohn’s disease</td>
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</tbody>
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Selected Patient-Centric Events

PDUFA V
- MDIC co-founded by FDA CDRH and Industry
- Center for Devices obesity preference study
- Center for Devices draft guidance and MDIC framework on patient preferences in regulatory review
- Center for Devices Strategic Priorities – patient engagement
- PDUFA VI

FDA CDRH Patient Preference Initiative
- FDA CDRH Patient-focused Drug Development Meetings

2012 | 2013 | 2014 | 2015 | 2016 | 2017

Patient
- PPMD policy forum on MD (19 FDA officials)
- PPMD monograph on B-R in rare diseases
- PPMD publishes B-R preference study in Duchenne MD
- PPMD submits draft guidance on Duchenne MD to FDA
- Diabetes groups/FDA forum on study endpoints
- BIO/PPMD Best Practices Toolkit for patient preference studies
- NHC/GA draft guidance for FDA on patient perspective in development
- PatientsLikeMe/Margolis Center Patient-Reported Data

Adapted from B. Levitan, NIH HCS Collaboratory and PCORnet Grand Rounds, 3/4/2016

Patient-Focused Decision Making at FDA

- Center for Drug Evaluation and Research (CDER)
  - PDUFA V amendments (2012)
  - Public meetings being conducted in 24 priority disease areas
  - Semi-quantitative benefit-risk evaluation framework
  - PDUFA VI amendments (2016)

- Center for Devices and Radiological Health (CDRH)
  - 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
  - 2016 guidance on submitting preference data
  - 2016-2017 Strategic Priorities
### Decision Framework

<table>
<thead>
<tr>
<th>Decision Factor</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis of Condition</td>
<td>Summary of evidence</td>
<td>Conclusions (implications for decision)</td>
</tr>
<tr>
<td>Current Treatment Options</td>
<td>Summary of evidence</td>
<td>Conclusions (implications for decision)</td>
</tr>
<tr>
<td>Benefit</td>
<td>Summary of evidence</td>
<td>Conclusions (implications for decision)</td>
</tr>
<tr>
<td>Risk</td>
<td>Summary of evidence</td>
<td>Conclusions (implications for decision)</td>
</tr>
<tr>
<td>Risk Management</td>
<td>Summary of evidence</td>
<td>Conclusions (implications for decision)</td>
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<td>Benefit-Risk Summary and Assessment</td>
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### Center for Drugs Duchenne Approvals

- **September 2016**—Exondys 51 for 15% of patients with dystrophin mutation (accelerated approval)

- **February 2017**—Emphlaza corticosteroid
  - Fast track review
  - Rare pediatric disease priority review
  - Orphan-drug designation
Weight-Loss Device Decision Tool

Regulatory Impact of the Study

- EnteroMedics’s Maestro Rechargeable System for weight loss
- Device failed to meet its original trial endpoints
- Device was approved in January 2015
  - First new obesity device approved by FDA since 2007
  - First approval to result from CDRH’s patient preference initiative

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm430223.htm
FDA’s guidance on benefit-risk determinations for device approvals describes patient tolerance for risk and perspective on benefit as an explicit factor the agency may consider in approval decisions.
“FDA understands that patients and care-partners who live with a disease or condition on a daily basis and utilize devices in their care may have developed their own insights into and perspectives on the benefits and risks of devices reviewed...”

- Voluntary submission of patient-preference data
- Recommendations for collecting patient-preference data for FDA reviews
- Recommendations for including patient-preference information in labeling

Center for Devices 2016-2017 Strategic Priorities

**Patient Engagement**

Promote a culture of meaningful patient engagement by facilitating CDRH interaction with patients

*By December 31, 2017, 90% of CDRH employees will interact with patients as part of their job duties.*

Increase use and transparency of patient input as evidence in our decision making

*By September 30, 2017, 100 percent of PMA, de novo and HDE decisions will include a public summary of available and relevant patient perspective data considered.*
Prescription Drug User Fee Act (PDUFA) VI

- PDUFA V sunsets in September 2017
- More support for rare diseases, innovative trial designs, real-world evidence, safety monitoring
- Patient engagement
  - More public meetings in disease areas
  - Guidance for collecting patient input on
    - disease burden,
    - treatment impact, and
    - outcomes assessment

Be careful what you wish for…?

- Impact of obesity-device study and Duchenne engagement
- Are methods and researchers ready?
  - Limited expertise
  - Limited understanding of validity and reliability of methods
- Is the Agency ready?
  - Limited expertise
  - Limited understanding of validity and reliability of methods
- Needs for training and resources
  - CDRH training program
  - CDRH case studies
  - CDRH/Duke validity study
Questions/ discussion

- Do you know of examples of the use of stated preference in decision making that we have not mentioned?
  - What lessons can we learn from this example?

- What do you see as the future direction for the use of stated preferences in decision making?