Incorporating quantitative patient preference information into healthcare decision-making processes

*Is HTA falling behind?*

**Panellists:** David Mott, Deborah Marshall & Brett Hauber  
**Moderator:** Paula Lorgelly

Issue Panel at ISPOR 2018, Baltimore, USA  
Monday 21st May

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**Context**

- The role of patients in decision making has changed over time
Patient’s roles

• Patient-level trial data (clinical outcomes, quality of life and resource use) as evidence tabled at decision making committee
• Patient/consumer representative or patient advocacy organisations on decision making committees
  • Information role vs
  • Voting rights

Qualitative preferences

Quantitative Patient Preferences

• Quantitative statements of the relative desirability or acceptability of attributes that may differ by intervention
• Considerable range of methodologies exist to elicit these preferences
Different levels of decision making

• Regulator – quality, safety and efficacy
• Adoption decision – cost effective / efficiency
• Reimbursement/funder – budget impact

Panel Discussion

• Use of quantitative patient preference information (PPI) in regulatory decision-making is growing, but
• Application in health technology assessment (HTA) is less frequent

• *Aim is to debate whether there are opportunities for increased use of quantitative PPI in HTA*
Panel Process

David Mott will provide an overview of the use of quantitative PPI and posit why HTA appears to be falling behind

Brett Hauber will discuss the recent progress in the regulatory space, explaining how PPI in regulatory decisions has become better defined

Deborah Marshall will consider the challenge for HTA assessment processes in incorporating and weighing PPI with clinical, cost-effectiveness and budget impact information

Discussion and debate from the audience with voting

Polling and Q&A

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Poll: Before we begin, do you think that HTA is falling behind?

The Use of Quantitative PPI in Health Care Decision-Making: Methods and Issues

David J. Mott, PhD

Issue Panel Presentation, ISPOR 2018, Baltimore Monday 21st May
Aims

The aims of this presentation are:

- To provide an overview of the methods that can be used to generate quantitative patient preference information (PPI).
- To describe how quantitative PPI can be used to inform healthcare decision-making, primarily focusing on health technology assessment (HTA).
- To set out the debate: is HTA falling behind the regulatory space in this area?

Methods

There are a range of different methodologies that can be used to generate different types of quantitative PPI.

<table>
<thead>
<tr>
<th>Group Method</th>
<th>Method</th>
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<tbody>
<tr>
<td>Structured-weighting</td>
<td>Simple direct weighting</td>
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<td>Ranking exercises</td>
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<td></td>
<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 trade-off (TTO)</td>
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<td>Standard gamble (SG)</td>
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<td>Stated-preference</td>
<td>Direct-assessment questions</td>
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<td></td>
<td>Threshold technique</td>
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<td>Conjoint analysis and discrete-choice experiments (DCE)</td>
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<td>Best-worst scaling exercises</td>
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<td></td>
<td>Contingent valuation (CV)</td>
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<tr>
<td>Revealed-preference</td>
<td>Patient-preference trials</td>
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<td></td>
<td>Direct questions in clinical trials</td>
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</tbody>
</table>

Table adapted from MDIC Report (2015)
Quantitative PPI in Regulatory Decision-Making

- In the regulatory space, it is important to understand the trade-offs between benefits and risks that patients might be willing to make.
- Quantitative PPI regarding maximum acceptable risk, or minimum acceptable benefit is of particular interest.
- The European Medicines Agency (EMA) has recently conducted a multi-criteria decision-analysis (MCDA) pilot study that incorporated quantitative PPI (Postmus et al., 2017).
- Projects by the Innovative Medicines Initiative (IMI) such as PROTECT and PREFER have, and will, explore this further in the context of regulatory decisions.

Quantitative PPI in HTA Overview

<table>
<thead>
<tr>
<th>Setting</th>
<th>Purpose of Quantitative PPI</th>
<th>Key Methods</th>
<th>Key Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost/Comparative-Effectiveness Analyses (CEAs)</td>
<td>To provide experienced health state utilities for use in quality-adjusted life year (QALY) calculations.</td>
<td>TTO, SG, DCE, Hybrid Methods</td>
<td>Brazier et al. (2017)</td>
</tr>
<tr>
<td></td>
<td>To generate uptake estimates for use as model parameters.</td>
<td>DCE</td>
<td>Terris-Presthoit et al. (2016)</td>
</tr>
<tr>
<td>Other Economic Evaluation Methods</td>
<td>To provide willingness to pay (WTP) estimates for use in cost-benefit analyses (CBAs).</td>
<td>CV, DCE</td>
<td>McIntosh et al. (2010)</td>
</tr>
<tr>
<td>Multi-Criteria Decision-Analysis (MCDA)</td>
<td>To provide information on the relative importance of a range of criteria relating to the intervention.</td>
<td>Structured Weighting Techniques, DCE</td>
<td>Marsh et al. (2017)</td>
</tr>
</tbody>
</table>
Quantitative PPI in HTA
Health State Utilities

- This method allows for patient preferences to be considered without a significant move away from the status quo.
- It is possible to generate experienced health state utilities from individuals experiencing the health state that is being valued (e.g. patients).
  - An experienced value set exists for Sweden (Burström et al., 2014).
- However, whilst it is possible, there are practical challenges (Brazier et al., 2017):
  - It is difficult to access very unhealthy patients.
  - There are ethical concerns with tasks such as time trade-off.

Quantitative PPI in HTA
Uptake Parameters

- Estimates of user uptake are sometimes used as parameters in model-based economic evaluations.
- Expert opinion is often used to generate estimates, however it has been argued that this is suboptimal (Terris-Prestholt et al., 2016).
- An alternative is to estimate user uptake rates using stated-preference methods such as discrete choice experiments (DCE).
- These methods could allow for greater consideration of preference heterogeneity within patient groups and could be more accurate than using expert opinion alone.
Several preference elicitation methods allow for willingness to pay (WTP) to estimated.

These can be used in traditional forms of economic evaluation, such as cost-benefit analysis, which often express benefits in monetary terms.

There are several examples of WTP estimates generated from discrete choice experiments being used in HTAs in the UK.

- The UK National Institute for Health Research (NIHR) has funded several, with the results published in its journal Health Technology Assessment (e.g. Watson et al., 2017).
- There are also some unpublished examples from PhD projects.

There has been increasing interest in the use of MCDA in HTA, given its flexibility and ability to take into account a larger set of benefits than standard approaches (Marsh et al., 2018).

In an MCDA, the various alternatives must be scored in terms of their performance in relation to a set of criteria that are determined to be important to the decision at hand.

The relative importance of the criteria must also be determined, possibly using the likes of structured weighting methods or DCE.

A range of stakeholders could provide this information, including patients if considered desirable.
Recent Progress in HTA (Europe)

- In the UK, NICE currently recommend in their reference case that health state utilities are generated from samples of the general population.
- However, NICE have recently collaborated with Myeloma UK to explore how patient preferences might be able to inform HTA decision-making.
- In Germany, IQWiG have conducted several case studies to incorporate quantitative PPI into decision-making (Danner et al., 2011; Mühlbacher et al., 2017)
- The IMI PREFER project will also provide information on incorporating patient preferences into HTA.

Future Challenges for HTA

There has arguably been less commitment from HTA agencies on the importance, and incorporation, of quantitative PPI relative to regulatory bodies worldwide. Some of the challenges might include (Mott, 2018):

1. **The Prevailing Methodology.** The focus on cost-effectiveness analysis using QALYs potentially limits opportunities.

2. **Normative Issues.** Rejection of experience-based utilities; the importance of citizens or payees in resource allocation decision-making.

3. **The Use of Qualitative PPI.** Patient involvement in HTA is considered important by most agencies; typically patient reps are involved in appraisals.
Conclusion

- There are a range of methods that can be used to generate quantitative PPI.
- There are also a number of ways to incorporate quantitative PPI directly into economic analyses.
- However, thus far the commitment from HTA agencies has been somewhat lacking in this area.
- HTA does appear to be falling behind the regulatory space, where there is a clearer appetite from regulators for this type of data.
- Going forward, there are a number of challenges when it comes to the use of quantitative PPI in HTA.
Regulators’ Use of Patient Preference Information

Some of What Has Happened in the US

- CDRH Obesity Preference Study (2015)
- CDRH Patient Preference Final Guidance (2016)
- PFDD Guidance Plan (2018)
- PDUFA V (2012)
- Maestro VBLOC System Approved (2016)
- Rituxan HYCELA receives FDA approval (2017)
- PDUFA VI (2017)

PDUFA – Prescription Drug User Fee Act
CDRH – FDA Center for Devices and Radiological Health
PFDD – Patient Focused Drug Development

CDRH Guidance on Patient Preferences

First US Regulatory Guidance Specific to the Use of Patient Preference Information

- Objectives:
  1. to encourage submission of PPI, if available, by sponsors or other stakeholders to FDA and to aid in FDA decision making;
  2. to outline recommended qualities of patient preference studies, which may result in valid scientific evidence;
  3. to provide recommendations for collecting and submitting PPI to FDA; and
  4. to discuss FDA’s inclusion of PPI in its decision summaries and provide recommendations for the inclusion of such information in device labeling.
FDA Developing Guidance on Using Patient Experience Data in Benefit-Risk Assessments

Most Recent Effort to Address Patient Preference Information from FDA

Four Examples of Regulatory Use of Patient Preference Information

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Disease or Condition</th>
<th>Study Type</th>
<th>Study Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDRH¹</td>
<td>Obesity</td>
<td>Discrete-Choice Experiment (DCE)</td>
<td>Regulatory decision⁴</td>
</tr>
<tr>
<td>EMA²</td>
<td>Melanoma and Myeloma</td>
<td>Multi-Criteria Decision Analysis (MDCA)</td>
<td>Pilot study</td>
</tr>
<tr>
<td>Genentech³</td>
<td>Blood cancers</td>
<td>Cross-over trial</td>
<td>Labeling⁵</td>
</tr>
<tr>
<td>CDRH / MDIC</td>
<td>Parkinson’s</td>
<td>Threshold technique</td>
<td>Clinical trial design⁶</td>
</tr>
</tbody>
</table>

¹ CDRH = Center for Devices and Radiological Health  
² EMA = European Medicines Agency  
³ MDIC = Medical Device Innovation Consortium  
⁴ http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm430223.htm  
⁶ http://www.imi-prefer.eu/events/event/?eventId=33454
CDRH Obesity Study

- DCE of patient choices among hypothetical device profiles, each defined by varying levels of 8 attributes

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of operation</td>
<td>(1) endoscopic; (2) laparoscopic; (3) open surgery</td>
</tr>
<tr>
<td>Diet restrictions</td>
<td>(1) Eat ½ cup at a time; (2) Weight 4 hours between eating; (3) Can’t eat hard-to-digest foods</td>
</tr>
<tr>
<td>Average weight loss</td>
<td>(1) 5% body weight; (2) 10% body weight; (3) 20% body weight; (4) 30% body weight</td>
</tr>
<tr>
<td>How long weight loss lasts</td>
<td>(1) 6 months; (2) 1 year; (3) 5 years</td>
</tr>
<tr>
<td>Comorbidity improvement</td>
<td>(1) None; (2) Reduce risk (or current dosage) by half; (3) Eliminate risk (or current dosage)</td>
</tr>
<tr>
<td>How long side effects last</td>
<td>(1) None; (2) 1 month; (3) 1 year; (4) 5 years</td>
</tr>
<tr>
<td>Chance of a serious side effects requiring hospitalization</td>
<td>(1) None; (2) 5% chance of hospitalization, no surgery; (3) 20% chance of hospitalization, not surgery; (4) 5% hospitalization for surgery</td>
</tr>
<tr>
<td>Chance of dying from getting a weight loss device</td>
<td>(1) None; (2) 1%; (3) 3%; (4) 5%; (5) 10%</td>
</tr>
</tbody>
</table>

Obesity Decision Tool

- Results used to create a decision tool to evaluate alternative device profiles
VBLOC Maestro® Rechargeable System

- First new obesity device approved by FDA since 2007
- The clinical study did not meet its original endpoint

- However, “the Agency looked at an FDA-sponsored survey relating to patient preferences of obesity devices that showed a group of patients would accept risks associated with this surgically implanted device for the amounts of weight loss expected to be provided by the device”

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm430223.htm

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Worst Level</th>
<th>Best Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-month survival probability</td>
<td>45%</td>
<td>65%</td>
</tr>
<tr>
<td>Probability of a moderate toxicity</td>
<td>20%</td>
<td>5%</td>
</tr>
<tr>
<td>Probability of a severe toxicity</td>
<td>35%</td>
<td>15%</td>
</tr>
</tbody>
</table>

*Swing weighting and discrete-choice experiments can both use choice scenarios to elicit weights; however, the procedures for achieving this are different between the two methods.

EMA Melanoma/Myeloma Pilot Study

- MCDA with patients and carers, regulators, and healthcare professionals.
- Swing weighting for 3 changes in cancer treatment attributes

Postmus et al., Clinical Pharmacology & Therapeutics, 2016
Relative Weights for Treatment Outcomes

Average Value Weights

Example Result: PCAs are willing to accept a 2% increase in the probability of moderate toxicity for every 1% increase in the 12-month survival probability

EMA Pilot Study: Conclusions

• “If based on robust scientific evidence it can be shown that a significant group of reasonable well-informed patients accepts a trade-off between benefits and risks, this may provide support for a claim of a favorable benefit-risk and inform the regulators’ decision in situations where the balance of benefits and risks is not self-evident.”
Rituxan HYCELA Preference Study

- Open-label cross-over study of patient preferences for subcutaneous injection over intravenous infusion

Rummel et al., Annals of Oncology, 2017

Preferences for SC and IV in Label

Rummel et al., Annals of Oncology, 2017

1.4 Patient Experience
Previously untreated adult patients outside of the United States with CD20+ diffuse large B-cell lymphomas (DLBCL) or CD20+ follicular non-Hodgkin’s lymphoma (FL) Grades 1, 2, or 3b were randomized to receive a standard chemotherapy regimen (CHOP, CVP, or bendamustine) and either RITUXAN HYCELA or

1,400mg/23.400 Unit at Cycles 1-4 (after the first cycle with intravenous rituximab) or a rituximab product by intravenous infusion at Cycles 1-4. After the fourth cycle, patients were crossed over to the alternative route of administration for the remaining 4 cycles. After Cycle 8, 477 of 432 patients (77%) reported preferring subcutaneous administration of RITUXAN HYCELA over intravenous rituximab and the most common reason was that administration required less time in the clinic. After Cycle 8, 69 of 432 patients (21%) preferred intravenous rituximab administration and the most common reason was that it felt more comfortable during administration. Forty-eight of 600 patients (7.7%) had no preference for the route of administration. Twenty-eight subjects of 600 (4.7%) received Cycle 9 but did not complete the preference questionnaire.

Patient Preference Study

• Elicit Parkinson’s disease patients’ preferences for benefits and burdens of device treatments using the threshold technique

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Burdens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in daily “on time”</td>
<td>Risk of (worsening) depression or anxiety</td>
</tr>
<tr>
<td>(50% decrease in “off time”)</td>
<td></td>
</tr>
<tr>
<td>50% decrease in motor symptoms</td>
<td>Risk of serious adverse event (brain bleed)</td>
</tr>
<tr>
<td>50% decrease in PD pain</td>
<td>Increase in 1-year mortality risk</td>
</tr>
<tr>
<td>50% decrease in cognitive impairment</td>
<td>Increase in wait time (discounting)</td>
</tr>
<tr>
<td>50% in medication and side effect burden</td>
<td></td>
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</tbody>
</table>
Parkinson’s Device – Maximum Acceptable Risk

- Results will be used in a model of optimal clinical trial design that incorporates patient preferences

Regulatory and HTA Bodies Face Different Decisions

- Patient preferences are useful in regulatory decision making because they can demonstrate:
  - What treatment attributes are important to patients
  - How important different treatment attributes are to patients
  - The tradeoffs that patients are willing to make among benefits and risks
- Patient preferences are appropriate because they reflect decisions among individual patients when faced with a treatment choices
  - Can incorporate patient values into benefit-risk assessments.
- HTA decisions are essentially budget allocation decisions
  - Considering preferences for a single product does not provide insight into the choice of whether to reimburse that product when budgets could be better allocated to products in a different disease area.
Challenges to Using Quantitative Patient Preferences Information in HTA

Deborah A Marshall, PhD
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Outline

- Why should we include patient preferences in HTA?
- Where are the potential opportunities using the Canadian context as an example?
- Patient Values Project in Colorectal Cancer
Why Patients Should be Involved in HTA

1. Patient’s Rights Perspective
   - Alma Ata Declaration (1978) – “…people have the right and duty to participate individually and collectively in the planning and delivery of their health care”
   - WHO resolution on health intervention and HTA in support of universal health coverage

2. Need for Value Determination
   - Value determinations and value judgements needed beyond cost-effectiveness

3. Evidentiary Contributions
   - Patients provide the ‘lived experience’ that reflects benefits (and harms) to the patient that may be broader than the outcomes reflected in trials or traditional quality of life data

4. Methodological Perspective
   - New approaches for obtaining timely evidence
   - Patient input on design and relevant endpoints for clinical studies


Physicians overestimated impact of effectiveness and underestimated the impact of side effects/treatment effects as well as their quality of life...

<table>
<thead>
<tr>
<th>Type of Conclusion</th>
<th>Number of Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferences and judgements show no meaningful or significant difference</td>
<td>11</td>
</tr>
<tr>
<td>Preferences and judgements show no meaningful or significant difference in the ranking of attributes, but <strong>meaningful differences of strengths</strong></td>
<td>11</td>
</tr>
<tr>
<td>Preferences and judgements show meaningful or significant differences</td>
<td>23</td>
</tr>
<tr>
<td>No conclusions on agreement</td>
<td>1</td>
</tr>
</tbody>
</table>

N=46 studies using discrete-choice experiments, conjoint analyses, standard gamble, time trade-offs and paired comparisons to compare patient preferences with doctor judgements (1985 and 2011).

- Muhlbacher A and Juhnke C. Appl Health Econ Health Policy, 2013.
Discordance Amongst Patient and Provider Preferences in Discrete Choice Experiments

Providers rank structure and outcome attributes more highly than patients. Patients rank process attributes more highly than providers.

Based on systematic review: n=38 papers, n=16 interventions, n=26 conditions.

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

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

CADTH Common Drug Review (CDR) Process for Patient Input

Canadian Process for Patient Input

- Canadian Agency for Drugs and Technologies in Health (CADTH)
- 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 (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
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

Beyond clinical and Economic Data + Patient Input

What is needed to inform the specific decision?
What is the best approach?
Why are we doing this?

Patient Values Project
Colorectal Cancer Canada

Broader definition of Patient Values and determining the appropriate metrics to measure these Values, Patient Groups will be better able to:

- Provide objective input to assist expert committees in the evaluation of patient group input.
- Include measurable values of the patient perspective allowing for better quality submissions in addition to anecdotal evidence.
- Allow a more reasoned and balanced assessment of the patient perspective when evaluating drugs.
- Provide objective and quantifiable input of patient Values based on validated research techniques.
Phases of the Patient Values Project

**Phase 1**
- Scoping review of literature to inform survey development;
- Survey will contain:
  - Demographic and experience questions;
  - Discrete choice experiment;
  - Quality of life measures.
- Consultations with experts;
- Focus groups meetings;
- Interviews with stakeholders.

**Phase 2**
- Key metric and indicator development to measure preferences captured in survey data.

**Phase 3**
- Framework draft;
- Review based on discussions, meetings and inputs from stakeholders;
- Validation using three case-based scenarios.

Polling and Q&A

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**Poll:** Following the presentations, do you think that HTA is falling behind?

**Live Content Slide**
*When playing as a slideshow, this slide will display live content*

**Poll:** If you do think that HTA is falling behind, what are the main reasons?
Thank you!
Questions?