The Science of Eliciting Patient Preferences in Benefit-Risk

Objective: Provide a common understanding of methods used to understand patient preferences for benefit expectations and risk tolerance, how preferences can inform product development, and current gaps in the knowledge base.
speakers

John F P Bridges
PhD
Associate Professor, Johns Hopkins Bloomberg School of Public Health

Bennett Levitan
MD, PhD
Director, Quantitative Safety Research, Janssen R&D of Johnson & Johnson

Bill Murray
President & CEO, Medical Device Innovation Consortium

Marilyn Metcalf
PhD
Senior Director, Benefit-Risk Evaluation, GSK

MODERATOR
Patient Preferences: What and Why?

*Bennett Levitan, MD-PhD*

Department of Epidemiology
Janssen Research & Development LLC,
Pharmaceutical Companies of Johnson & Johnson
The views and opinions expressed in the following slides are those of the individual presenter and should not be attributed to Janssen R&D, its directors, officers, employees, volunteers, members, chapters, councils, Special Interest Area Communities or affiliates, or any organization with which the presenter is employed or affiliated.
Example 1

- **Skin disease**
  - Generally progressive → leads to mild itching and rashes

- **Treatments available**
  - Not always effective – works for 25% of patients

- **New treatment is developed**
  - Much more effective – works for 75% of patients
  - But also discover that it causes a rare (1/1000) but generally fatal side effect

Would you use the new treatment?
How might patients balance benefits and risks in example 1?

- Rare fatal side effect
- Mild side effects
- Prevents itching and rashes
Example 2

- **Very debilitating nervous system disease**
  - Generally progressive → leads to serious disability

- **Treatments available**
  - Not always effective – works for 25% of patients

- **New treatment is developed**
  - Much more effective – works for 75% of patients
  - But also discover that it causes a rare (1/1000) but generally fatal side effect

Would you use the new treatment?
How might patients balance benefits and risks in example 2?

- Rare fatal side effect
- Mild side effects
- Prevents debilitating nervous system disease
What’s the Difference?

- No difference in chances of benefit or harm / statistics
- No difference in time course of symptoms

- Difference is due to **values** placed on the benefit and harm
Real Example: Tysabri for Multiple Sclerosis
agree on facts

physician

disagree on values

patient
Cautionary Note: Many Roles for the Patient Perspective Other Than Preferences

- Defining medical context
  - Nature of illness
  - Medical need
- Prototyping a device
- Study design
  - Designing recruitment
  - Endpoint selection
  - Peer advocate during informed consent
  - Reduce trial burden and time → reduced dropout
- Preference studies for benefit-risk
- Reporting results to patient community
- ...

Thanks to Bray Patrick-Lake (Duke) and CTTI
What are Preferences?

- Measures of the relative importance of benefits, harms and other characteristics of treatments
  - Allows for characterizing preferences for desirable features and acceptability of undesirable features
  - Includes the relative nature of preferences
  - Can be qualitative or quantitative
  - Can also apply to judgments (for another, vs. preferences for oneself)
Using Preferences

To use preference information in a regulatory context requires more than expressions of feelings or opinions – it needs hard core data.

Preference studies can obtain this data in a reliable and validated manner.
Maximum Acceptable Risk for Stroke or Permanent Severe Disability in Alzheimer’s Patients

Improvement in Disease Progression

Hauber, et. al., Alh Dz Assoc Disord, 23(1), 2009
Identifying Differences Between Key Stakeholders

Preferences for Anticoagulants in Atrial Fibrillation

US Physician

- Death
- Disabling Stroke
- Non-Disabling Stroke
- Major Bleeding
- Heart Attack
- Blood Clot

US Patient

- Death
- Disabling Stroke
- Non-Disabling Stroke
- Major Bleeding
- Heart Attack
- Blood Clot

Levitan, Yuan, González, et al., ISPOR 18th Ann Int Mtg, 2013
Applying Preferences - Determining Which Endpoints are Most Critical

Benefits

↓ Pain
- Rapid onset
- Headache relief
- Pain-free response
- Sustained response

↓ Sensitivity
- Reduced sensitivity to sound & light

↓ Other
- Patients regarded pain-free status as unrealistic

Risks

↑ Individual Risks

Benefit-Risk Balance

* Major bleeding excluding death and stroke

Physician: “I was really struck that you threw out the parameter that we focused the most on. We thought that if you were going to have the risk of a heart attack, you should really get rid of your migraine, period.”

Applying Preferences - Differences Between Treatments Sorted by Preference / Clinical Impact (mock data for an atrial fibrillation drug)

- Death: -21
- Disabling stroke: -30
- Clot in GI system: -16
- Non-disabling stroke: -20
- Heart attack: 3
- Non-fatal/stroke major bleeding*: 12

* Major bleeding excluding death and stroke

Risk Difference (per 10,000 patients)

Favors Study Drug  Favors Comparator

Most severe  Least severe
Applying Preferences - Differences Between Treatments Sorted by Preference / Clinical Impact (mock data for an atrial fibrillation drug)

- Death: Favors Comparator (-46)
- Disabling stroke: Favors Comparator (+2)
- Non-disabling stroke: Favors Comparator (+1)
- Heart attack: Favors Comparator (-13)
- Non-fatal/stroke major bleeding*: Favors Study Drug (+17)
- Moderate bleeding: Favors Comparator (+72)

* Major bleeding excluding death and stroke
A Goal

*agree on facts*

*understand values*
Measuring patient-preferences for benefit-risk analysis

John F P Bridges PhD
Associate Professor
Department of Health Policy and Management

JOHNS HOPKINS
BLOOMBERG SCHOOL of PUBLIC HEALTH
My recent research on preferences from benefit risk has been funded by:

- **Parent Project Muscular Dystrophy (PPMD),** where I was a paid consultant.
- **Food and Drug Administration** to explore methods for incorporating preferences into benefit risk analysis (#FDA HHSF22320100007, Segal PI).
- I am currently supported by grants from the **Center for Medicine in the Public Interest (CMPI)** (supported by InterMune Inc.) and the **Patient-Centered Outcomes Research Institute (PCORI) Methods Program Award** (ME-1303-5946).
Overview

There are three broad aims of the presentation today:

1. To discuss why studying stated preferences is central to benefit-risk analysis
2. To discuss methodological developments to advance and apply stated-preference methods in the evaluation of health and healthcare
3. To present a case study on how we quantified preferences of caregivers of a child with Duchenne muscular dystrophy (DMD) for the benefits and risk of potential treatments
Engaging patients and the public

• Two schools of thought have emerged to engage patients and the public in decision making:
  
  ‣ Direct engagement via representation, consultation and/or testimony.
  
  ‣ Formal study of the priorities and preferences of patients and the public.

• “When asking the public to assist in determining health priorities, we should use techniques that allow people to reveal their true preferences. If not, why bother asking them at all?” Gafni, 1995
Motivation to measure stated-preferences

- A movement to advance and apply stated-preference methods in healthcare emerged in the 1990s. This was in part:
  - A backlash against payer-centered approaches to evaluation (e.g. cost-effectiveness analysis)
  - As a means to incorporate “process attributes” as well as outcomes (e.g. risk, staff attitudes, etc)
  - An approach to place the patient at the center of the evaluation evaluation paradigm
  - To move away from narrow “extra-welfarist” definitions of health, such as the QALY
Stated-preference methods – Popular techniques

- Early stated-preferences methods included:
  - Qualitative research
  - Willingness to pay (contingent valuation)
  - Conjoint analysis

- More modern techniques have also emerged
  - Discrete-choice experiments (DCE)
  - Best-worst scaling (BWS)
  - Analytic hierarchy process (AHP)
  - Threshold techniques
  - Ranking techniques
Increasing use of stated-preference methods

- 5 recent systematic reviews have documented the increase in the applications of conjoint analysis and discrete-choice experiments in healthcare.

- Joy et al (2013) present a scoping review of all preference studies (n=61) focused on diabetes.
  - 2 further diabetes review have been published – Purnell et al (2014); von Arx and Kjær (2014)

Effort to standardize methods and approaches

- The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) published the first methodological standards (The ISPOR Checklist) for conjoint analysis (Bridges et al 2011).
- These were followed up by further standards on:
  - Experimental design (Johnson et al, 2013)
  - Statistical analysis – draft (Hauber et al, 2014)
- In 2008, Johns Hopkins and ADIS publishing founded The Patient – Patient-centered Outcomes Research as the medical journal to focus on the patient's perspective. Published 6 times a year, the impact factor is now 1.98.
Case study – Duchenne muscular dystrophy?
Duchenne muscular dystrophy (DMD)

- Duchenne muscular dystrophy (DMD) is the most common fatal genetic disorder diagnosed in children, affecting 1 in every 3,500 live male births.
- As DMD is found on the X-chromosome, it primarily affects boys, but it occurs across all races.
- DMD causes progressive loss of skeletal muscle and weakness, with a resulting loss of motor function over time, leading to loss of ambulation and then cardiac and respiratory compromise, with death typically in the late 20s.
- There is no FDA approved treatment for DMD.
Treatment preferences

- A pool of treatment features (attributes) identified and refined in consultation with parents, clinicians, and industry
- Six attributes were chosen to cover the potential benefits, risks and other features, each varying across three levels each.
- A main-effects orthogonal array was used as the basis of the experimental design - identifying 18 potential treatments that systematically varied across the six chosen attributes.
Attributes and levels

- **Effect on muscle function** (none, slows, stops)
- **Gain in expected lifespan** (none, 2, 5 years)
- **Post-approval information** (none, 1, 2 years)
- **Nausea** (none, loss of appetite, loss of appetite and occasional vomiting)
- **Risk of bleeds** (none, risk of bleeding gums and increased bruising, risk of hemorrhagic stroke)
- **Risk of heart arrhythmia** (none, risk of harmless heart arrhythmia, risk of dangerous heart arrhythmia and sudden death)
Choose the best thing in this treatment by clicking the circle under “best” and choose the worst thing by clicking the circle under “worst”. You have to choose a best thing and worst thing to move on. Remember that a computer chose the combinations to make the experiment work, and some may seem bad. Even so, please pick the best and worst thing.

<table>
<thead>
<tr>
<th>Best</th>
<th>Treatment</th>
<th>Worst</th>
</tr>
</thead>
<tbody>
<tr>
<td>○</td>
<td>Slows the progression of weakness</td>
<td>○</td>
</tr>
<tr>
<td>○</td>
<td>2 year gain in expected lifespan</td>
<td>○</td>
</tr>
<tr>
<td>○</td>
<td>1 year of post-approval drug information available</td>
<td>○</td>
</tr>
<tr>
<td>○</td>
<td>Causes loss of appetite</td>
<td>○</td>
</tr>
<tr>
<td>○</td>
<td>Increased risk of bleeding gums and increased bruising</td>
<td>○</td>
</tr>
<tr>
<td>○</td>
<td>Increased risk of harmless heart arrhythmia</td>
<td>○</td>
</tr>
</tbody>
</table>
## Results – Treatment Preferences

<table>
<thead>
<tr>
<th>Treatment benefits and risks</th>
<th>Best</th>
<th>Worst</th>
<th>Utility</th>
<th>SE</th>
<th>T-test</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stops progression of weakness</td>
<td>628</td>
<td>2</td>
<td>0.877</td>
<td>0.01</td>
<td>69.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Slows progression of weakness</td>
<td>571</td>
<td>0</td>
<td>0.800</td>
<td>0.02</td>
<td>53.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Does not change progression of weakness</td>
<td>68</td>
<td>125</td>
<td>-0.080</td>
<td>0.02</td>
<td>-4.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5 year gain in expected lifespan</td>
<td>348</td>
<td>17</td>
<td>0.464</td>
<td>0.02</td>
<td>22.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2 year gain in expected lifespan</td>
<td>299</td>
<td>8</td>
<td>0.408</td>
<td>0.02</td>
<td>21.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No extra gain in expected lifespan</td>
<td>12</td>
<td>93</td>
<td>-0.113</td>
<td>0.01</td>
<td>-8.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2 years of post-approval drug info available</td>
<td>109</td>
<td>69</td>
<td>0.056</td>
<td>0.02</td>
<td>3.0</td>
<td>0.001</td>
</tr>
<tr>
<td>1 years of post-approval drug info available</td>
<td>20</td>
<td>4</td>
<td>0.022</td>
<td>0.01</td>
<td>3.3</td>
<td>0.001</td>
</tr>
<tr>
<td>No post-approval drug info available</td>
<td>41</td>
<td>56</td>
<td>-0.021</td>
<td>0.01</td>
<td>-1.5</td>
<td>0.064</td>
</tr>
<tr>
<td>No increased chance of nausea</td>
<td>19</td>
<td>26</td>
<td>-0.010</td>
<td>0.01</td>
<td>-1.0</td>
<td>0.148</td>
</tr>
<tr>
<td>Causes loss of appetite</td>
<td>1</td>
<td>95</td>
<td>-0.132</td>
<td>0.01</td>
<td>-10.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Causes loss of appetite with occasional vomiting</td>
<td>17</td>
<td>217</td>
<td>-0.280</td>
<td>0.02</td>
<td>-15.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No increased risk of bleeds</td>
<td>3</td>
<td>11</td>
<td>-0.011</td>
<td>0.01</td>
<td>-2.1</td>
<td>0.016</td>
</tr>
<tr>
<td>Increased risk of bleeding gums and increased bruising</td>
<td>0</td>
<td>190</td>
<td>-0.266</td>
<td>0.02</td>
<td>-16.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Increased risk of hemorrhagic stroke and lifelong disability</td>
<td>0</td>
<td>514</td>
<td>-0.720</td>
<td>0.02</td>
<td>-42.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No increased risk of heart arrhythmia</td>
<td>5</td>
<td>32</td>
<td>-0.038</td>
<td>0.01</td>
<td>-4.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Increased risk of harmless heart arrhythmia</td>
<td>1</td>
<td>122</td>
<td>-0.169</td>
<td>0.01</td>
<td>-11.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Increased risk of dangerous heart arrhythmia and sudden death</td>
<td>0</td>
<td>561</td>
<td>-0.786</td>
<td>0.02</td>
<td>-51.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Results – Treatment preferences (2)

<table>
<thead>
<tr>
<th>Levels</th>
<th>Stops</th>
<th>Slows</th>
<th>None</th>
<th>5 yr</th>
<th>2 yr</th>
<th>None</th>
<th>2 yr</th>
<th>1 yr</th>
<th>None</th>
<th>Mild</th>
<th>Mod</th>
<th>None</th>
<th>Mild</th>
<th>Sev</th>
<th>None</th>
<th>Mild</th>
<th>Sev</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.877</td>
<td>0.800</td>
<td>-0.08</td>
<td>0.464</td>
<td>0.408</td>
<td>-0.11</td>
<td>0.056</td>
<td>0.022</td>
<td>-0.02</td>
<td>-0.01</td>
<td>-0.13</td>
<td>-0.28</td>
<td>-0.01</td>
<td>-0.26</td>
<td>-0.72</td>
<td>-0.03</td>
<td>-0.16</td>
</tr>
</tbody>
</table>
### Conditional attribute importance

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Max</th>
<th>Min</th>
<th>Diff</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect on muscle function</td>
<td>0.877</td>
<td>-0.08</td>
<td>0.957</td>
<td>28.7</td>
</tr>
<tr>
<td>Lifespan</td>
<td>0.464</td>
<td>-0.113</td>
<td>0.577</td>
<td>17.3</td>
</tr>
<tr>
<td>Knowledge about the drug</td>
<td>0.056</td>
<td>-0.021</td>
<td>0.077</td>
<td>2.3</td>
</tr>
<tr>
<td>Nausea</td>
<td>-0.01</td>
<td>-0.28</td>
<td>0.27</td>
<td>8.1</td>
</tr>
<tr>
<td>Risk of bleeds</td>
<td>-0.011</td>
<td>-0.72</td>
<td>0.709</td>
<td>21.2</td>
</tr>
<tr>
<td>Risk of heart arrhythmia</td>
<td>-0.038</td>
<td>-0.786</td>
<td>0.748</td>
<td>22.4</td>
</tr>
<tr>
<td>Sum</td>
<td>3.4</td>
<td></td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

- Effect on muscle function, 28.7
- Lifespan, 17.3
- Knowledge about the drug, 2.3
- Nausea, 8.1
- Risk of bleeds, 21.2
- Risk of heart arrhythmia, 22.4
Protecting Health, Saving Lives—

_Millions at a Time_
A Public-Private Partnership
collaborating on Regulatory Science
to make patient access to new medical device technologies
faster, safer and more cost-effective
MDIC: Partnering to Achieve Results

- 43 Members  
- 5 Projects

Case for Quality | Clinical Trial Innovation & Reform | Clinical Diagnostics
Computer Modeling & Simulation | Patient Centered Benefit-Risk Assessment

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-efficient

MDIC: Partnering to Achieve Results

Align Resources

Accelerate Progress

Achieve Results

WORKING COOPERATIVELY
with FDA 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

ALIGN | ACHIEVE | ACCELERATE
Patient-Centered Benefit-Risk Assessment in Medical Devices

- FDA CDRH 2012 guidance on factors to consider for B-R assessment in devices
- Landmark policy statement:
  - First regulatory guidance on B-R worldwide
  - Still the only regulatory guidance for development worldwide
Implications?

• Benefit-risk assessment is currently a key component for regulatory review, but it traditionally has been based on the regulatory/physician perspective

• CDRH B-R guidance suggests a much more critical role for the patient perspective
  ➔ Some regulatory reviews may require a formal understanding of the patient view on B-R

• Treatments are currently approved based on efficacy and safety for subgroups defined by demographic or medical properties
  ➔ Potential future where approval may include subgroups based on patient view of B-R
MDIC Patient-Centered Benefit-Risk Assessment: Project Overview

Vision
To establish a credible framework for assessing patient preferences regarding 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.

Approach
− Develop credible methods for collecting patient preference benefit-risk information for a disease or condition and
− Establish a credible framework to include patient preference of probable benefits and probable risks of a proposed medical device
− Provide suggestions to FDA that FDA can then choose to use in future guidance documents and regulatory decisions
Preference Methodology Catalog

Objectives
- Assess the methods that are currently available to quantify patients’ benefit-risk preferences
- Evaluate the applicability of available methods to benefit-risk assessments at different stages in the product lifecycle
- Identify gaps in the availability of methods or the ability of existing methods to support benefit-risk assessment

Project Overview
- Phase 1: Develop a Preference-Methodology Catalog
- Phase 2: Evaluate Methods Across the Product Lifecycle
- Phase 3: Conduct a Gap Analysis
# Methods to be included in the catalog

<table>
<thead>
<tr>
<th>Qualitative</th>
<th>Stated-preference</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Structured interviews or discussions</td>
<td>• Rating questions</td>
</tr>
<tr>
<td>• Ranking exercises</td>
<td>• Direct assessment questions</td>
</tr>
<tr>
<td>• Sentiment analysis (web trolling)</td>
<td>• Stated behavior</td>
</tr>
<tr>
<td></td>
<td>• Threshold techniques</td>
</tr>
<tr>
<td></td>
<td>• Conjoint analysis and discrete-choice experiments</td>
</tr>
<tr>
<td></td>
<td>• Best-worst scaling</td>
</tr>
<tr>
<td>Structured weighting</td>
<td></td>
</tr>
<tr>
<td>• Swing weighting</td>
<td></td>
</tr>
<tr>
<td>• Point allocation or “100 coins”</td>
<td></td>
</tr>
<tr>
<td>approaches</td>
<td></td>
</tr>
<tr>
<td>• Analytical hierarchy process, MACBETH,</td>
<td></td>
</tr>
<tr>
<td>and variants</td>
<td></td>
</tr>
<tr>
<td>• Outranking methods</td>
<td></td>
</tr>
<tr>
<td>Health-state utility</td>
<td></td>
</tr>
<tr>
<td>• Standard gamble</td>
<td>• Patient preference trials</td>
</tr>
<tr>
<td>• Time tradeoff</td>
<td>• Direct questions in clinical trials</td>
</tr>
<tr>
<td></td>
<td>• “Norton method”</td>
</tr>
<tr>
<td></td>
<td>• Informed consent</td>
</tr>
</tbody>
</table>
To be valuable for both FDA staff and industry, the Patient-Centered Benefit-Risk Framework should improve the understanding of CDRH staff and of applicants on how to identify the potential value of patient preference information in CDRH benefit-risk determinations for PMA or *de novo* 510k approval.

The framework should be balanced, transparent, and useful.
Key Challenges in Developing the Framework

• Developing an Approach to Assessing the Value of Patient Preference Information for Specific Situations
• Recognizing and Reconciling the Perspectives of Multiple Stakeholders
• Characterizing the Value of Preference Information Over Time – Regulatory Novelty and Product Lifecycle Considerations
• Maximizing the Utility of Patient Preference Information
Collecting patient preference information

• The timing for collection of patient preference information should be assessed when the sponsor believes there is a sufficient understanding of the particular benefits and risks expected with the treatment
  − Preference studies conducted early in development may not include risks or benefits, identified later in development
  − Conducting preference studies after pivotal trials are completed may be challenging due to limited time between unblinding of the results and the submission to FDA
  − Discussions between the sponsor and FDA can help assess whether the current understanding of benefits and risks is sufficient to guide patient preference studies about a technology.
Other regulatory considerations

• The collection and submission of patient preference information should be optional for the sponsor, not a requirement for FDA approval.

• If patient preference information proves important in helping to guide an FDA approval decision, that patient preference information should be reflected in the product labeling.

• The collection and analysis of patient preference information may be valuable as a part of post-market study requirements, but should be optional on the part of sponsors.
A Public-Private Partnership collaborating on Regulatory Science to make patient access to new medical device technologies faster, safer and more cost-effective

FasterCures Benefit-Risk Boot Camp
Bill Murray, MDIC President & CEO
September 23, 2014
Questions?