Benefit-Risk Preference Methods: What Makes Rare Disease Unique?

Brett Hauber, PhD
Senior Economist and Vice President
Health Preference Assessment

Annual Rare Disease Scientific Workshop
Workshop 7: "Incorporating the Patient Perspective in Rare Disease Drug Development"
MDIC Catalog of Methods

- Formal title is “Catalog of Methods for Assessing Patient Preferences for Benefits and Harms of Medical Technologies”

- Primary objective was to provide an overview of a range of available patient-preference methods
  - Focused on benefit-risk preferences
    - But patient-preference methods can be used for multiple purposes
  - Focused on medical technologies
    - But patient-preference methods can be applied to any health care intervention or health service
Patient Preference Methods

• Quantitative assessments of the relative desirability or acceptability of features that differ among alternative medical technologies

Source: MDICx Webinar, January 22,2015  http://mdic.org/mdicx/#archive
Patient Preference Methods

Quantitative assessments of the relative desirability or acceptability of features that differ among alternative medical technologies

Methods in the catalog are limited to quantitative assessments

Source: MDICx Webinar, January 22, 2015 http://mdic.org/mdicx/#archive
Patient Preference Methods

- Quantitative assessments of the relative desirability or acceptability of features that differ among alternative medical technologies

Methods in the catalog are limited to quantitative assessments

Qualitative information may be useful in certain circumstances, but often are not sufficient to conduct a formal benefit-risk assessment

Source: MDICx Webinar, January 22, 2015  http://mdic.org/mdicx/#archive
Patient Preference Methods

• Quantitative assessments of the relative desirability or acceptability of features that differ among alternative medical technologies

Benefit-risk preference measures are most useful when preferences are “relative” meaning that preferences for one feature can be directly compared to preferences for all other features.

Source: MDICx Webinar, January 22, 2015 http://mdic.org/mdicx/#archive
Patient Preference Methods

- Quantitative assessments of the relative desirability or acceptability of features that differ among alternative medical technologies

Acceptability indicates aversion to negative outcomes or features (i.e., harms)

Desirability indicates preferences for positive outcomes or features (i.e., benefits)

Source: MDICx Webinar, January 22, 2015 http://mdic.org/mdicx/#archive
Patient Preference Methods

- Quantitative assessments of the relative desirability or acceptability of features that differ among alternative medical technologies

The ultimate purpose of benefit-risk analysis is to evaluate the benefit-risk balance between alternatives

Source: MDICx Webinar, January 22, 2015 [http://mdic.org/mdicx/#archive](http://mdic.org/mdicx/#archive)
Benefit-Risk Assessment

1. Assess benefits and harms
2. Elicit weights for benefits and harms from patient perspective
3. Apply weights to assessed benefits and harms

Source: MDICx Webinar, January 22, 2015
http://mdic.org/mdicx/#archive
Benefit-Risk Assessment

1. Assess benefits and harms
2. Elicit weights for benefits and harms from patient perspective
3. Apply weights to assessed benefits and harms

Some preference methods are typically used as part of multi-criteria decision making.

Source: MDICx Webinar, January 22, 2015
http://mdic.org/mdicx/#archive
Benefit-Risk Assessment

Assess benefits and harms

Elicit weights for benefits and harms from patient perspective

Apply weights to assessed benefits and harms

Some preference methods are typically used as part of multi-criteria decision making

Examples include structured weighting methods such as swing weighting or direct weighting used in multi-criteria decision analysis

Source: MDICx Webinar, January 22, 2015
http://mdic.org/mdicx/#archive
Benefit-Risk Assessment

Assess benefits and harms

Elicit weights for benefits and harms from patient perspective

Apply weights to assessed benefits and harms

Some methods focus only on eliciting weights

Source: MDICx Webinar, January 22, 2015
http://mdic.org/mdicx/#archive
Benefit-Risk Assessment

- Assess benefits and harms
- Elicit weights for benefits and harms from patient perspective
- Apply weights to assessed benefits and harms

Some methods focus only on eliciting weights
Some methods are used to elicit one weight at a time
Examples include methods used to elicit health-state utilities

Source: MDICx Webinar, January 22, 2015
http://mdic.org/mdicx/#archive
Benefit-Risk Assessment

1. Assess benefits and harms
2. Elicit weights for benefits and harms from patient perspective
3. Apply weights to assessed benefits and harms

Some methods focus only on eliciting weights

Some methods are used to elicit multiple weights simultaneously

Examples include stated preference methods such as conjoint analysis and discrete-choice experiments

Source: MDICx Webinar, January 22, 2015
http://mdic.org/mdicx/#archive
Benefit-Risk Assessment

Assess benefits and harms

Elicit weights for benefits and harms from patient perspective

Apply weights to assessed benefits and harms

Some methods look at actual decisions…

Source: MDICx Webinar, January 22, 2015
http://mdic.org/mdicx/#archive
Benefit-Risk Assessment

Assess benefits and harms

Elicit weights for benefits and harms from patient perspective

Apply weights to assessed benefits and harms

Some methods look at actual decisions…

…and infer weights based on differences in alternatives

Source: MDICx Webinar, January 22, 2015
http://mdic.org/mdicx/#archive
## Methods Included in the MDIC Catalog

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

Source: MDIC Framework Report
http://mdic.org/framework-report/
What Makes Rare Disease Unique?

• What happens when we have very small populations?

• Are we measuring what matters to patients?

• How big do improvements need to be to be worthwhile?
Small Populations

- Rhizomelic chondrodysplasia punctate (RCDP) affects fewer than 1 in 100,000 people worldwide (ghr.nlm.nih.gov)

  - ‘…whether a drug is having an effect “can be really difficult to tease out if your working population is 10 or 20 patients,” Dr. Bober added. “It’s not like we can give this drug to 20,000 people and see what happens.”’ (http://www.nytimes.com/2015/09/07/us/flicker-of-hope-for-children-with-rare-and-devastating-disease.html*)

- Quantitative patient preference methods which require large sample sizes, may not be feasible (or even necessary)

  - Simpler mixed-methods (qualitative research with quantitative outputs) may be most appropriate

*Flicker of Hope for Children With Rare and Devastating Disease - The New York Times
By ABBY GOODNOUGH SEPT. 6, 2015
What matters to patients and their families

Again, consider the case of RCDP

Biologic Endpoint Approach → Increased plasmalogen levels

*Flicker of Hope for Children With Rare and Devastating Disease - The New York Times
By ABBY GOODNOUGH SEPT. 6, 2015
What matters to patients and their families

Again, consider the case of RCDP

Biologic endpoint Approach → Increased plasmalogen levels

Patient-preference approach → ‘…Dr. Bober asked about the clinical trial: What kind of improvement would the parents most like to see in Jude?’

*Flicker of Hope for Children With Rare and Devastating Disease - The New York Times
By ABBY GOODNOUGH SEPT. 6, 2015
What matters to patients and their families

Again, consider the case of RCDP

Biologic endpoint Approach  →  Increased plasmalogen levels

Patient-preference approach  →  ‘...Dr. Bober asked about the clinical trial: What kind of improvement would the parents most like to see in Jude?’

‘Stronger respiratory and immune systems, she replied. The ability to “talk to us, reach for us, hug us.”’

*Flicker of Hope for Children With Rare and Devastating Disease - The New York Times
By ABBY GOODNOUGH SEPT. 6, 2015
What matters to patients and their families

Again, consider the case of RCDP

Biologic endpoint Approach → Increased plasmalogen levels

Patient-preference approach

“One of the biggest challenges … would be figuring out “end points”: ways to evaluate whether the drug was providing any benefit.”

“Knowing why she’s in pain,” … “Not having to troubleshoot everything.”

“To even think he could communicate with us, or reach for things”

“..improvements… in Marley’s respiratory function and in her vision, because she is going blind”

*Flicker of Hope for Children With Rare and Devastating Disease - The New York Times By ABBY GOODNOUGH SEPT. 6, 2015*
What matters to patients and their families

Again, consider the case of RCDP

Dr. Bober conducted an informal preference study to identify what matters to these parents.

*Knowing why she’s in pain,“ … “Not having to troubleshoot everything.”*

“To even think he could communicate with us, or reach for things”

“..improvements… in Marley’s respiratory function and in her vision, because she is going blind”

*Flicker of Hope for Children With Rare and Devastating Disease - The New York Times By ABBY GOODNOUGH SEPT. 6, 2015*
What matters to patients and their families

Again, consider the case of RCDP

Dr. Bober conducted an informal preference study to identify what matters to these parents.

Before we can measure what matters, we need to determine what matters and how much each of these things matter

*Flicker of Hope for Children With Rare and Devastating Disease - The New York Times By ABBY GOODNOUGH SEPT. 6, 2015*
Measuring What Matters: Alzheimer’s Disease

Hauber et al., 2014
Measuring What Matters: Alzheimer’s Disease

Not all things that we can measure are of equal importance

Hauber et al., 2014
Patient and Parent input in Drug Development: Fragile X

Fragile X Syndrome

- Serious disease features
- Heterogeneous presentation
- Unmet medical need

Clinical development challenges

- No established endpoints
- No established effect sizes
- Need rationale for drug development design

Cross (2012), CNS Summit presentation
Patient and Parent Input in Drug Development: Fragile X

Thinking about Quality of Life for a Person with Fragile X

Now we would like you to compare Medicine A and Medicine B that affect all six abilities we have described.

1. In your opinion, which medicine would result in a better overall quality of life for a person with fragile X?

<table>
<thead>
<tr>
<th>Ability</th>
<th>Medicine A</th>
<th>Medicine B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Learn and apply new skills</td>
<td>Somewhat hard</td>
<td></td>
</tr>
<tr>
<td>Explain needs</td>
<td>Very hard</td>
<td>Not hard</td>
</tr>
<tr>
<td>Control own behavior</td>
<td>Somewhat hard</td>
<td>Very hard</td>
</tr>
<tr>
<td>Take part in new social activities</td>
<td>Somewhat hard</td>
<td></td>
</tr>
<tr>
<td>Care for self</td>
<td>Somewhat hard</td>
<td>Not hard</td>
</tr>
<tr>
<td>Pay attention</td>
<td>Somewhat hard</td>
<td>Very hard</td>
</tr>
</tbody>
</table>

Which medicine do you think would result in the better quality of life? 

---

Cross (2012), CNS Summit presentation
Patient and Parent Input in Drug Development: Fragile X

Cross (2012), CNS Summit, presentation
Patient and Parent Input in Drug Development: Fragile X

Small changes in things that matter more may be more important than big changes in things that matter less.

Cross (2012), CNS Summit, presentation
Three Types of Patient Preference Information

- **Attributes:**
  - *What matters*
    - Can often be obtained using qualitative methods;
    - Simple quantitative methods can be used to separate those attributes that matter to patients from those attributes that do not.

- **Relative importance:**
  - *How much it matters*
    - Requires using quantitative methods that provide a weight for each attribute.

- **Tradeoffs:**
  - *How much it matters and what tradeoffs are patients willing to make*
    - patients are willing to make to obtain or avoid a given attribute.
    - can be approximated by comparing the weights that patients assign to each attribute, obtaining accurate trade-off information may require quantitative methods designed explicitly for this purpose.
Patients Preference in Rare Diseases

• Formal quantitative preference analysis underutilized in rare disease
  – Small populations
  – Little demand (but this is changing)

• Patient preferences are important at all phases of drug and device development
  – Identifying unmet needs
  – Identifying endpoints
  – Quantifying relative importance of endpoints
  – Demonstrating importance of endpoints measured in trials

• Understanding patients’ benefit-risk tradeoff matters
  – Demonstrating how much risk patients are willing to accept in order to achieve benefits
  – Critical to communicating the patient perspective