Patient-focused Benefit-Risk Assessment

March 4, 2016

NIH HCS Collaboratory and PCORnet Grand Rounds

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<table>
<thead>
<tr>
<th>Outcome</th>
<th>Drug A</th>
<th>Drug B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relief of pain</td>
<td>![Severity Scale](none, mild, moderate, severe)</td>
<td>![Severity Scale](none, mild, moderate, severe)</td>
</tr>
<tr>
<td>Ability to perform work/school and social activities</td>
<td>No limitations</td>
<td>Cannot work, difficulty with chores and shopping</td>
</tr>
<tr>
<td>Annual chance of a heart attack</td>
<td>1 in 10,000</td>
<td>No chance</td>
</tr>
<tr>
<td>Which medicine would you choose if these were the only medicines available?</td>
<td><img src="false" alt="Choose Drug A" /></td>
<td><img src="true" alt="Choose Drug B" /></td>
</tr>
<tr>
<td>Outcome</td>
<td>Drug C</td>
<td>Drug B</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>--------------------------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>Relief of pain</td>
<td>None, Mild, Moderate, Severe</td>
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<tr>
<td>Which medicine would you choose if these were the only medicines available?</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Outcome</td>
<td>Drug D</td>
<td>Drug B</td>
</tr>
<tr>
<td>-------------------------------</td>
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<td>Annual chance of a heart attack</td>
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<td>No chance</td>
</tr>
<tr>
<td>Which medicine would you choose if these were the only medicines available?</td>
<td>□</td>
<td>□</td>
</tr>
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</table>
agree on facts

physician

patient

may disagree on values
What Did Migraine Patients Say?

Stated choice conjoint preference survey of 200 adult migraine patients

- Relieving all functional limitations was twice as important as relieving all migraine pain

Maximum Acceptable Risk = maximum level of treatment-related 1-year heart attack risk patients would accept for a given improvement in migraine symptoms

- Patients would accept up to a 2/1000 (95% CI 1.6 – 2.4) annual heart attack risk in exchange for restoring their ability to function during migraines

Benefit-risk Assessment

- Evaluation of medical products considering both benefits and harms
  - Not simply the union of efficacy and safety data

- Key component of FDA, EMA and other health authority regulatory decisions
  - Unstructured in the past, becoming more formal

- A growing field combining regulatory, clinical, decision, behavioral economics and risk communication sciences
Patient Engagement, Patient-focused B-R and Patient Preferences
Main patient-focused aspects of benefit-risk

- Characterizing burden of disease and unmet need
- Developing novel endpoints and PRO instruments
- Determining which endpoints/rates/levels are most important
- Assessing preference tradeoffs between endpoints
- Identifying preference heterogeneity and subgroups
Growing Regulatory and Patient Momentum for Patient-focused Drug Development / B-R

Regulatory (selected)

FDA CDER Patient-focused Drug Development Meetings
# FDA CDER B-R 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>
</tr>
</tbody>
</table>

Benefit-Risk Summary and Assessment
The Voice of the Patient

A series of reports from the U.S. Food and Drug Administration’s (FDA’s) Patient-Focused Drug Development Initiative

Chronic Fatigue Syndrome and I

Public Meeting: Ag Report Date: Sept

The Voice of the Patient

A series of reports from the U.S. Food and Drug Administration’s (FDA’s) Patient-Focused Drug Development Initiative

Lung Cancer

Public Meeting: June 28, 2013 Report Date: December 2013

Center for Drug Evaluation U.S. Food and Drug Adminstration (FDA)

Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) U.S. Food and Drug Administration (FDA)
Growing Regulatory and Patient Momentum for Patient-focused Drug Development / B-R

Regulatory (selected)

- CDHR pilot obesity pref study 4/2014
- FDA CDRH Patient Preference Initiative
- FDA CDER Patient-focused Drug Development Meetings

FDA CDRH Obesity Device Preference Study

Risks

Δ Risk

New Device

Δ Benefit

Weight Loss

Δ Benefit

Diet & Exercise

Gastric Banding

Gastroplasty

Detailed Thresholds for Maximum Acceptable Risk: Can Inform Development Strategy and Regulatory Requirements

FDA CDRH/RTI Obesity Device Preference Study

Results for average obese patient (243lbs and 5'10")

Irony and Ho, DIA/FDA Statistics Forum, Feb, 2015
Better outcomes have significantly higher weights

Worse outcomes have significantly lower weights
Mortality Risk, Weight Loss, and Weight-Loss Duration are the most important attributes.

Side Effect is the least important attribute.

Irony and Ho, DIA/FDA Statistics Forum, Feb, 2015
No difference between diet restrictions. *Wait 4 hours and Eat 1/4 cup* but *No sweets or hard to digest foods* is worse.
FDA Weighs Patients' Risk Tolerance in Approving Obesity Device

By Ferdous Al-Faruque / Email the Author / View Full Issue

The agency approved EnteroMedics’ *Maestro* neuromodulator to treat obesity despite the device not meeting endpoints in its pivotal trial. The agency relied in part on a survey that found obese patients willing to take more risks in exchange for weight loss.

In making the decision the agency took into consideration patients’ willingness to accept higher potential risk of the device which failed to meet its co-primary endpoints in a pivotal study. It is the first approval to result from CDRH's pilot program to formally incorporate patient preference into risk-benefit determinations for obesity devices, and it is the first new obesity device approved by FDA since 2007.
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- CDRH Strategic Priorities – patient engagement 1Q/2016

FDA CDRH Patient Preference Initiative

FDA CDER Patient-focused Drug Development Meetings

FDA CDRH Patient Preference Initiative: Collaborative Building Blocks

MDIC Methodology Catalog

MDIC Framework: PPI in Lifecycle

FDA CDRH Draft Guidance: PPI in Benefit-Risk

FDA CDRH Obesity Case Study

Device Patient Preference Initiative

Patient Reported Outcomes

PPI = Patient Preference Information
Regulatory Guidance in Benefit-Risk Assessment for Medical Devices

- FDA CDRH 2012 guidance on factors to consider for B-R assessment in devices
- Landmark regulatory policy statement on benefit-risk
- Impetus for MDIC patient-centered B-R project
Patient-Centered B-R Assessment

• FDA CDRH 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

- 48 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
MEDICAL DEVICE INNOVATION CONSORTIUM

FDA
CMS NIH

industry
Nonprofits
- Patients
- Providers
- Academics

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

www/mdic.org
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
Key Components of MDIC Patient-centered Benefit-risk 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
What are “Preferences”? 

Qualitative or quantitative statements of the relative desirability or acceptability of attributes that differ among alternative health interventions

Definition applies equally well to preferences of caregivers, physicians, payers and regulators.

Which Treatment is Best?

Reduction in days hospitalized (benefit)

Probability of infection (risk)

Treatment C is superior on both benefit and risk

Preference information is not needed to determine the best treatment

Now Which Treatment is Best?

Preference information is needed to choose between devices A and Cs

This is a “Preference Sensitive Decision”
How Do Preferences Help Us Choose?

- In many cases, the decision is clear over a plausible range of preferences → clinical judgment is sufficient to assess the tradeoff.
- But not always …
How Do Preferences Help Us Choose?

- Preference studies give the maximum additional risk that patients would accept for this increase in benefit.

Maximum acceptable additional risk is much larger than $\Delta$ Risk.
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- CDRH Strategic Priorities – patient engagement 1Q/2016
Objectives of FDA CDRH Draft Guidance on Patient Preference Information

- Encourage voluntary submission of patient preference information
- Provide recommendations for collecting patient preference information to FDA
- Provide recommendations for including patient preference information in labeling
CDRH Strategic Priorities 2016-2017

- Establish a National Evaluation System for medical devices
- Promote a culture of quality and organizational excellence
- Partner with patients

Patient Engagement

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

Science of Patient

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

CDRH Strategic Priorities 2016-2017

- Establish a National Evaluation System for medical devices
- Promote a culture of quality and organizational excellence
- Partner with patients

‘Goal: Increase use and transparency of patient input as evidence in our decision making
- By 9/30/17, 100% of … decisions will include a public summary of available and relevant patient perspective data
- By 9/30/17, increase the number of patient perspective studies (e.g., PROs or patient preferences) used in support of … regulatory decisions’
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FDA CDRH Patient Preference Initiative

FDA CDER Patient-focused Drug Development Meetings
- 2012
- 2013
- 2014
- 2015
- 2016
- 10/2013 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
- 2Q/2014
- 11/2014 Diabetes groups/FDA forum on study endpoints
- 9/2014 FasterCures B-R “Boot Camp”
- 3Q/2015 BIO/PPMD Best Practices Toolkit for pat pref studies
- 4Q/2015 NHC/GA draft guidance for FDA on pat perspective in development

Patient (selected)
- PPMD – Parent Project Muscular Dystrophy
- BIO – Biotechnology Innovation Organization
- NHC/GA – National Health Council / Genetic Alliance
Sites for MDIC Framework and FDA CDRH Draft Patient Preference Guidance

www.mdic.org/PCBR

Roles for patient preferences in regulatory review and post-approval
Patient Perspective: Determining Which Endpoints are Most Critical

Benefit-Risk Balance

Benefits

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

- ↓ Sensitivity
  - Reduced sensitivity to sound & light

- ↓ Other
  - Reduced sensitivity to sound & light
  - Reduced sensitivity to sound & light

Risks

↑ Individual Risks

Patient: "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."

Patients regarded pain-free status as unrealistic

Fragile-X Syndrome

• Rare genetic condition impacting development
  ▸ Learning and intellectual disabilities, cognitive impairment, behavioral challenges (ADHD, autism, social anxiety), physician features
  ▸ No cure – educational, therapeutic support

• Preference study conducted to prepare for phase 3 study
  ▸ No established endpoints or effect sizes
  ▸ Intent was to identify which endpoints or components of existing instruments were most important to patients
  ▸ Survey administered to family members, given patient cognitive limitations
Preference Survey Identified Large Gap Between Clinician and Patient Caretaker Beliefs on Endpoint Importance

Clinical and commercial perspective of the most important endpoints

Caretaker perspective of the most important endpoints

Ability/outcome

N = 614

J. Cross, CNS Summit, Nov, 2012
### Risk Differences by Clinical Severity/Impact†

**Atrial Fibrillation Example**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th># of Events (/10,000 patient-years)</th>
<th>Risk difference /10,000 patient-yrs (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>Study Drug 188 Comparator 222</td>
<td></td>
</tr>
<tr>
<td>Disabling stroke</td>
<td>Study Drug 38 Comparator 50</td>
<td></td>
</tr>
<tr>
<td>Non-CNS systemic embolism</td>
<td>Study Drug 4 Comparator 19</td>
<td></td>
</tr>
<tr>
<td>Non-disabling stroke</td>
<td>Study Drug 79 Comparator 77</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Study Drug 91 Comparator 112</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>Study Drug 360 Comparator 345</td>
<td></td>
</tr>
<tr>
<td>Non-major clinically-relevant bleeding</td>
<td>Study Drug 1180 Comparator 1137</td>
<td></td>
</tr>
</tbody>
</table>

† Endpoints in order of health state utility, a value that reflects preference for health states relative to perfect health and death.
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
Maximum Acceptable Risk of treatment-related death or permanent severe disability due to stroke

A Key Idea

To use patient viewpoints in a regulatory context requires more than expressions of feelings or opinions – it needs defensible **data**

Preference studies **have** the potential to obtain these data reliably
A Goal

agree on facts
understand values