FORUM: Patient-Focused Benefit-Risk Analysis to Inform Regulatory Decisions

Moderator
Shelby Reed, PhD, RPh, Professor in Medicine,
Duke Clinical Research Institute, Durham, NC, USA

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Value in Health Themed Sections

Scheduled Themed Sections for 2016

- **July/August 2016**:
  - *Cost-Effectiveness And Clinical Practice Guidelines: Have We Reached A Tipping Point?*
  - Guest Editor: Lou Garrison
- **September/October 2016:**
  - *Patient-Focused Benefit-Risk Analysis to Inform Regulatory Decisions*
  - Guest Editor: Shelby Reed
- **December 2016:**
  Economics on Making Choices on the Journey of Universal Health Care Coverage
  - Guest Editor: Kalipso Chalkidou

Value in Health Themed Sections

Themed Sections in Process

- *Value to Decision Makers of Evaluations of Personalized/Precision Medicine: Applications to Other Emerging Technologies*
  - Guest Editor: Kathryn Phillips
- *Rare Diseases: Road to Approval and Patient Access*
  - Guest Editor: Kati Copley-Merriman
- *Affordability*
  - Guest Editors: Adrian Towse & Josephine Mauskopf
- *Improving the Methods and Processes for Condu Assessments of Health Care Interventions*
- *Improving the Methods and Processes for Condu Assessments of Health Care Interventions*
  - Guest Editor: Jalpa Doshi

Two headlines / doupl

Value in Health Themed Issue

Patient-centered movement

Quantitative benefit-risk

Regulators

FDA working with Patients to explore Benefit/Risk: Opportunities & Challenges

Health Canada

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Presenters

Deborah A. Marshall, PhD

- Canada Research Chair, Health Services and Systems Research, Professor, Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Health Research Innovation Centre, Calgary, Alberta, Canada

Axel C. Mühlbacher, PhD

- Professor of Health Economics and Health Care Management, Institute Health Economics and Health Care Management, IGM, Hochschule Neubrandenburg, Neubrandenburg, Germany

F. Reed Johnson, PhD

- Senior Research Scholar, Department of Medicine, Do-Director, Preference Evaluation Research (PrefER) Group, Duke Clinical Research Institute, Duke University, Durham, NC, USA

Bennett Levitan, MD, PhD

- Senior Director, Epidemiology, Janssen R&D, LLC, Titusville, NJ, USA

5

Regulatory Decision-making in Canada – Exploring New Frontiers in Patient Involvement

Deborah A Marshall
University of Calgary

Agnes V Klein, Stephanie Hardy, Robyn Lim
Health Canada

6

Background to Regulatory Review

- 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 of a therapeutic product.
- 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 (1) Transparency and Openness

- Recent 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.

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

9

Canadian Examples of Patient Involvement

Scientific/Expert Advisory Committees

- Patient advocates 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.

10

Canadian Examples of Patient Involvement

Patient Involvement Pilot Project (2014)

- Explored the 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 were designed to gather qualitative information on the following (examples of one biologic and one pharmaceutical):
  - the impact on individual patient's quality of life;
  - experience with currently available therapies;
  - unmet medical need; and
  - 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.

Opportunities and Future Prospects

- Determining the best ways to elicit and consider patient input in a systematic manner and exploring the scope and nature of patient input of highest value.
- Assessing the overall suitability and feasibility of adopting, modifying or collaborating with other existing models such as those used by the FDA and EMA, and HTA bodies

Patient Involvement - Further Exploration

a) Who is best situated to provide input?
b) At what stage(s) in the regulatory process is it most feasible, or valuable, for patient input to be collected?
c) 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?
d) What are the most appropriate and effective formats for patient input?
e) How should patient input be considered and captured in the regulatory assessment and decision-making processes?

Patient-Focused Benefit-Risk Analysis to Inform Regulatory Decisions: The EU perspective

Axel C. Mühlbacher, Christin Juhnke
Hochschule Neubrandenburg, Germany

Andrea R. Beyer
University of Groningen, The Netherlands

Sarah Garner
National Institute for Health and Care Excellence (NICE), London, UK

Assessment of benefits and risks

- In Europe marketing approval is granted by The European Medicines Agency (EMA), a decentralized agency of the European Union (EU).
  - Most approvals are valid EU-wide.
  - National regulatory authorities are not included in the approval process unless they are the 'rapporteur' doing the evaluation.
- Added value of including patients' perspectives within EMA benefit-risk assessments has been widely discussed.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/

Reference: Hockley, K. (2013): IMI Protect WP5: Eliciting patient preferences in the benefit-risk assessment of medicines. Dec. 13th 2013, Berlin (unpublished).

15

European Medicines Agency (EMA)

EMA Benefit-Risk Methodology Project

- Quantitative approaches that are sufficiently comprehensive to numerically represent the benefit-risk balance by incorporating the value of favorable and unfavorable effects:
  - Bayesian statistics
  - Decision trees and influence/relevance diagrams
  - Multi criteria decision analysis (MCDA)

- In addition, specific methods that are more restricted in scope but can be used for particular cases:
  - Probabilistic simulation
  - Markov simulations
  - Kaplan-Meier estimates
  - QALY/ DALY
  - Conjoint analysis

European Medicines Agency (EMA)
IMI- Innovative Medicines Initiative

- IMI-PROTECT project ("Pharmacoepidemiological research on outcomes of therapeutics by a European consortium")
  - Aim: Strengthening the monitoring of pharmacovigilance of medicines in Europe.
  - Several methods for eliciting preferences among various stakeholders have been evaluated: DCE, AHP, and MCDA (MACBETH approach).
  - Results of the studies were distilled into a set of practical recommendations for benefit-risk decision processes and supporting tools.

- Conclusions:
  - No single benefit-risk methodology can fully capture all aspects of a benefit-risk assessment.
  - Choice of a single approach or combination of methodologies should be matched to the complexity of the problem.

→ 13 benefit-risk assessment methods/frameworks were recommended for further appraisal for the use in real benefit-risk assessment

European Medicines Agency (EMA)
IMI- Innovative Medicines Initiative

Table.: Practical recommendations for the benefit-risk decision processes and the supporting tools according to IMI

Stages of benefit-risk assessment	Useful methods/frameworks
Planning	– Benefit-Risk Action Team (BRAT) – Problem, Objectives, Alternatives, Consequences, Trade-offs, Uncertainty, Risk and Linked decisions (PrOACT-URL)
Evidence gathering and data preparation	– Indirect Treatment Comparison (ITC) – Mixed Treatment Comparison (MTC) – Probabilistic Simulation Method (PSM)
Analysis	*Metric indices/ numerical representations of benefits and risks* – Number Needed to Treat (NNT) – Number Needed to Harm (NNH) – Impact numbers *Quantitative frameworks to model benefit-risk trade-off and balance benefits and risks* – Multi-Criteria Decision Analysis (MCDA) – Stochastic Multi-criteria Acceptability Analysis (SMAA) *Utility survey techniques* – Discrete Choice Experiment (DCE)
Exploration	– Indirect Treatment Comparison (ITC) – Mixed Treatment Comparison (MTC) – Utility survey techniques (DCE, AHP, Swing-weighting, MACBETH) – Probabilistic Simulation Method (PSM) – Stochastic Multi-criteria Acceptability Analysis (SMAA)
Conclusion and Dissemination	– results and consensus from the benefit-risk assessment are communicated to a wider audience

Hughes, D., E.A.J. Waddingham, S. Mt-Isa, A. Goginsky, E. Chan, G. Downey, C.E. Hallgreen, K.S. Hockley, J. Juhaeri, A. Lieftucht, M.A. Metcalfe, R.A. Noel, L. Phillips, D. Ashby, and A. Micaleff, RECOMMENDATIONS REPORT: Recommendations for the methodology and visualisation techniques to be used in the assessment of benefit and risk of medicines, IMI-PROTECT Work Package 5, 2013.

Germany: IQWiG-Pilots on AHP and DCE

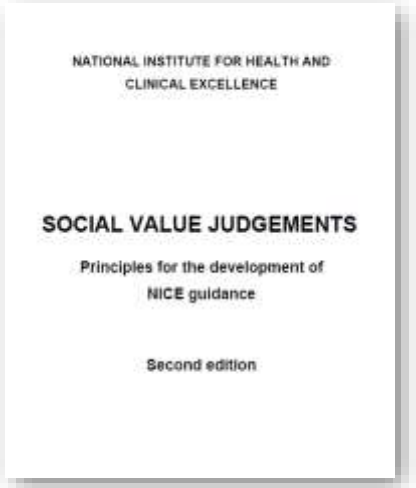
Reference : IQWiG, IQWiG-Berichte – Nr. 163: Analytic Hierarchy Process (AHP) – Pilotprojekt zur Erhebung von Patienten-präferenzen in der Indikation Depression, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2013: Köln.

Reference : IQWiG, IQWiG-Berichte – Nr. 227: Wahlbasierte Conjoint-Analyse – Pilotprojekt zur Identifikation, Gewichtung und Priorisierung multipler Attribute in der Indikation Hepatitis C, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2014: Köln.

Reference: Mühlbacher, A., Bridges, J. F. P., Bethge, S., Dintsios, C. M., Schwalm, A., Gerber-Grote, A., Nübling, M.: Preferences for antiviral therapy of chronic hepatitis C: A discrete choice experiment. In: European Journal of health economics, 2015. online first(DOI: 10.1007/s10198-016-0763-8).

NICE: Social Value Judgements

- NICE has explicitly defined information by the type, format, and sources of evidence in its guidelines for assessment and testing of eligibility (appraisal).
- Appraisal is usually based on evidence from patients with a condition.
- Citizens characterise an overall societal perspective on what should be taken into account in decision-making related to distributive justice.
- Views of citizens' conferences are published in “Social Value Judgements”.



Future Prospects

- Range of participation efforts on European level extends from qualitative surveys of patients' needs to approaches of science-based documentation of quantitative patient preferences.
- European pilot projects have shown that modeling of the benefit-risk assessment for medicines is possible.
- More research projects are needed to design the tools that are accessible to patients and other stakeholders, appropriate to the needs of the regulators/ assessors and that can be integrated into the current processes in benefit-risk evaluation.

Patient Preferences in Regulatory Benefit-Risk Assessments: A U.S. Perspective

Reed Johnson
Duke Clinical Research Institute
Duke University

Mo Zhou
Bloomberg School of Public Health
Johns Hopkins University

Acknowledgement
Anindita Saha
Center for Devices and Radiological Health
U.S. Food and Drug Administration

This presentation reflects the views of the authors and should not be construed to represent the policies of the U.S. FDA.

Patient-Focused Decision Making

- Center for Drug Evaluation and Research http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHVisionandMission/UCM481588.pdf
  - PDUFA V amendments (2012)
  - Public meetings being conducted in 24 priority disease areas
  - Information obtained to inform drug-development and regulatory-review processes
- Center for Devices and Radiological Health
  - 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
  - 2015 draft guidance on submitting preference data
  - 2016-2017 Strategic Priorities

http://www.gpo.gov/fdsys/pkg/FR-2015-07-02/pdf/2015-16359.pdf
http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm.
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM296379.pdf
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM446680.pdf
http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHVisionandMission/UCM481588.pdf

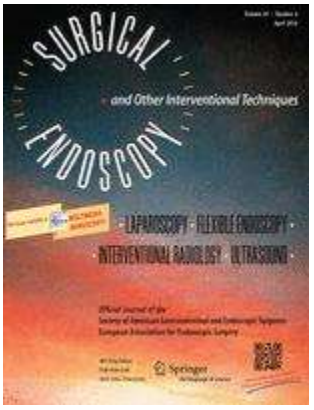
Qualitative and Quantitative Approaches

- CDER qualitative and CDRH quantitative approaches complementary
  - Structured public meetings elicit direct patient feedback
  - Quantifying preferences helps integrate patient concerns with existing clinical data.
- Type of information needed could vary in product lifecycles
  - Discovery and ideation phases of product development: qualitative information on unmet needs, feasibility constraints, and human-factors considerations
  - Quantitative patient-preference information for conducting structured regulatory benefit-risk

Hammad TA, Neyarapally GA. In: Jiang Q, He W, eds. *Benefit-Risk Assessment Methods in Medicinal Product Development: Bridging the Qualitative and Quantitative Assessments*. Boca Raton, FL: CRC Press Taylor and Francis Group; 2016

Center for Devices Preference Study

CDRH-sponsored study cited as an example that “followed many of the recommendations listed.”



Incorporating patient-preference evidence into regulatory decision making

Martin P. Ho · Juan Marcos Gonzalez · Herbert P. Lerner · Carolyn Y. Neuland · Joyce M. Whang · Michelle McMurry-Heath · A. Brett Hauber · Telba Irony

Abstract

Ho MP, Gonzalez JM, Lerner HP, et al. Incorporating patient-preference evidence into regulatory decision making. *Surg Endosc*. 2015.

Regulatory Impact of the Study

- Used study’s decision aid tool to evaluate EnteroMedics’s Maestro Rechargeable System
- Device failed to meet its co-primary trial endpoints
- Approved in January 2015 based on patients’ benefit-risk tradeoff preferences
  - First new obesity device approved by FDA since 2007
  - First approval to result from CDRH's patient-centered regulatory initiative

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

Patient Organization Preference Study

LEADING ARTICLE

Caregiver Preferences for Emerging Duchenne Muscular Dystrophy Treatments: A Comparison of Best-Worst Scaling and Conjoint Analysis

Hollin, et al. The Patient - Patient-Centered Outcomes Research. February 2015, Volume 8, Issue 1, pp 19-27

27

Duchenne Muscular Distrophy Preferences

- Study demonstrated community-engaged process to understand treatment preferences
- “Submitted patient-initiated FDA draft guidance to inform drug development and regulatory review
- CDER invited public comment on report and draft guidance
- Not used in recent reviews

Parent Project Muscular Dystrophy. Guidance for Industry: Duchenne Muscular Dystrophy Developing Drugs for Treatment over the Spectrum of Disease. Hackensack; 2014.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM450229.pdf

28

Challenges

- When is it in society's best interest to approve novel health technologies that offer promising therapeutic benefits, but also have worrisome side effects?
- CDER: how to integrate qualitative data from public meetings into existing evidence-based decision making
- CDRH: how to build capacity to implement ambitious strategy to quantify patient benefit-risk tradeoff preferences

Dr. Rob Califf, FDA Commissioner

You don't know people's preferences unless you ask them. … To the extent that FDA takes preferences seriously, I think it's a great day.

Release Event for the MDIC Framework for Integrating Patient Perspective into Medical Device Benefit-Risk Assessments and the FDA Center for Devices and Radiological Health Draft Guidance, May 13, 2015.

The MDIC Framework for Patient-centered Benefit-Risk Assessment

ISPOR Forum on Patient-Focused Benefit-Risk Analysis to Inform Regulatory Decisions
May 24, 2016

Bennett Levitan, MD-PhD
Dept. of Epidemiology
Janssen Research & Development LLC,
Pharmaceutical Companies of Johnson & Johnson

FDA CDRH 2012 guidance on B-R assessment raised a critical question

- **FDA 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**

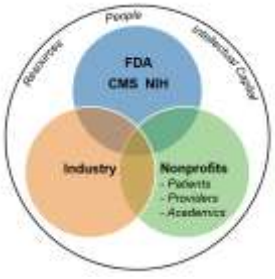
But it did not say how…

Medical Device Innovation Consortium (MDIC)

- 55 Members
- 6 Projects
- Leading resource on issues important to the Medtech innovation ecosystem
- Congressional testimony on modernizing clinical trials
- $500k funding from FDA for Patient-Centered Benefit-Risk Framework - Project Completed
- $643k funding from FDA for Quality Engagement Forum
- $300k+ of industry funding + member dues

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-effective

MDIC
MEDICAL DEVICE INNOVATION CONSORTIUM



Align Resources

Accelerate Progress

Achieve Results

WORKING COOPERATIVELY
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

33

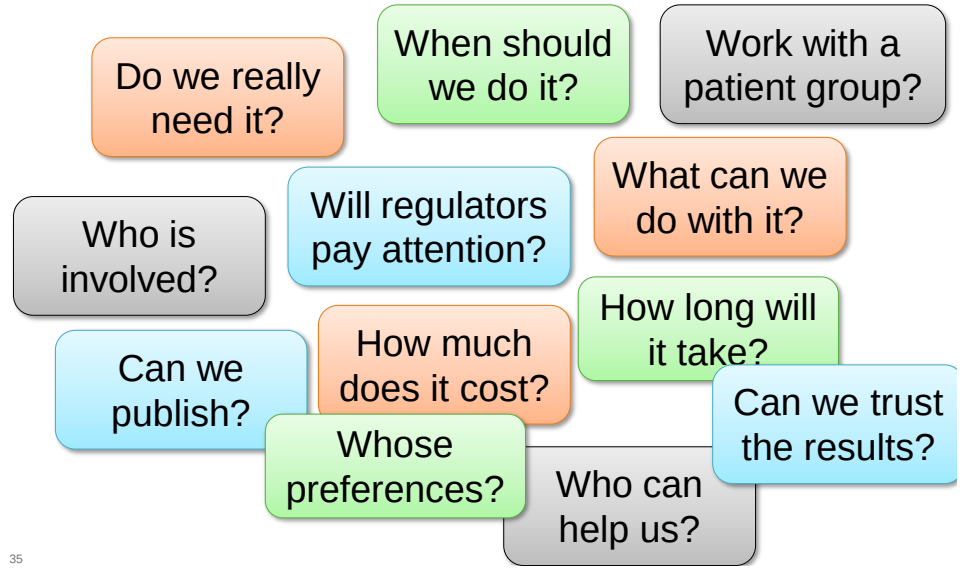
Vision for Patient-Centered Benefit-Risk Project

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

MDIC

34

The other reasons for a framework on patient preference studies



35

MDIC PCBR Project Components

Framework	Catalog	Future Work
• Framework for Patient Centered Benefit-Risk Assessment	• Catalog of Patient Preference Assessment Methods	• Agenda for Future Research in Patient Preferences

MDIC

36

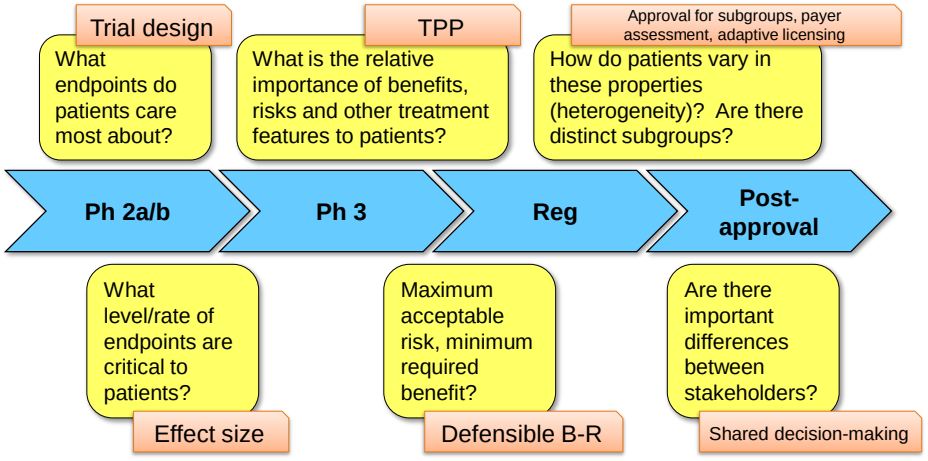
Key Topics in the Framework

- 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

When is Patient Preference Information Potentially Valuable in Regulatory Review?

- Factors related to the patient perspective
  - Patients willing to accept a different degree of risk than regulators
  - Important differences in the preferences of subgroups of patients
  - Understanding the clinical experience requires considerable familiarity with the disease (e.g. highly subjective endpoints, lifestyle indication, rare diseases)
- Factors related to benefit-risk tradeoffs
  - Clear benefit with rare serious risks compared to alternatives
  - Modest benefit but considerably less risk than alternatives
  - Harms occur early/benefits occur later (e.g. Tx to delay disease onset)
  - Considerable uncertainty on whether a patient will realize the benefit or risks
- Factors related to novelty
  - New technology or mechanism of action
  - Lack of device precedent in indication or technology

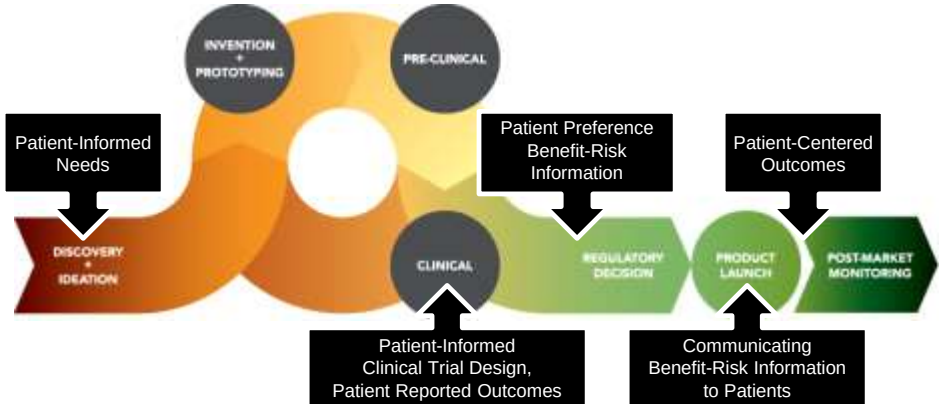
What Can a Sponsor Learn from a Patient Preference Study?



MDIC

39

Incorporating Patient Preferences into the Medical Device Product Lifecycle



Source: FDA Center for Devices and Radiological Health (CDRH)

MDIC

40

Methods Included in the Catalog

Group*	Method
Structured-weighting	• Simple direct weighting • Ranking exercises • Swing weighting • Point allocation • Analytic hierarchy process • Outranking methods
Health-state utility	• Time tradeoff • Standard gamble
Stated-preference	• Direct-assessment questions • Threshold technique • Conjoint analysis and discrete-choice experiments • Best-worst scaling exercises
Revealed-preference	• Patient-preference trials • Direct questions in clinical trials

* Grouping scheme meant only to facilitate discussion of methods. Some methods could be assigned to multiple groups

41

Questions Considered

Methodology-Related Questions
How are the data acquired?
Are hypothetical scenarios required?
How are attributes/levels determined and defined?
Is the method experimental?

Sample-Related Questions
What is the minimum sample size required?
What is the reasonable maximum sample size?
What is the time commitment required of patients?
Cognitive and knowledge requirements of patients?

General Questions
Representativeness and generalizability?
Validity?
Resource requirements?

Analysis-Related Questions
Does the method require statistical analysis?
Does the method require specialized software?
Can the results be described and interpreted easily?

Output-Related Questions
Can the method be used to identify attributes that are important to patients?
Can the method be used to estimate weights for attributes?
Can the method be used to estimate the tradeoffs that patients are willing to make among attributes?
Can the method be used to detect, describe, or quantify heterogeneity in preferences across patients and across time?

42

Questions for Future Research in Patient Preferences

- Can patients do these surveys reliably?
- Stated choice is not actual choice
- Choosing the right method
- Industry can bias these surveys
- Selecting the attributes
- Sample selection – whose preferences and when?
- Sample size
- Formal assessments of validity
- Regulatory requirements

43

Sites for MDIC Framework and FDA CDRH Draft Patient Preference Guidance

www.mdic.org/PCBR


Patient Preference Information – Submission, Review in PMAs, HDE Applications, and *De Novo* Requests, and Inclusion in Device Labeling

Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

DRAFT GUIDANCE

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM446680.pdf

44