FDA Perspective on Patient Preference Information

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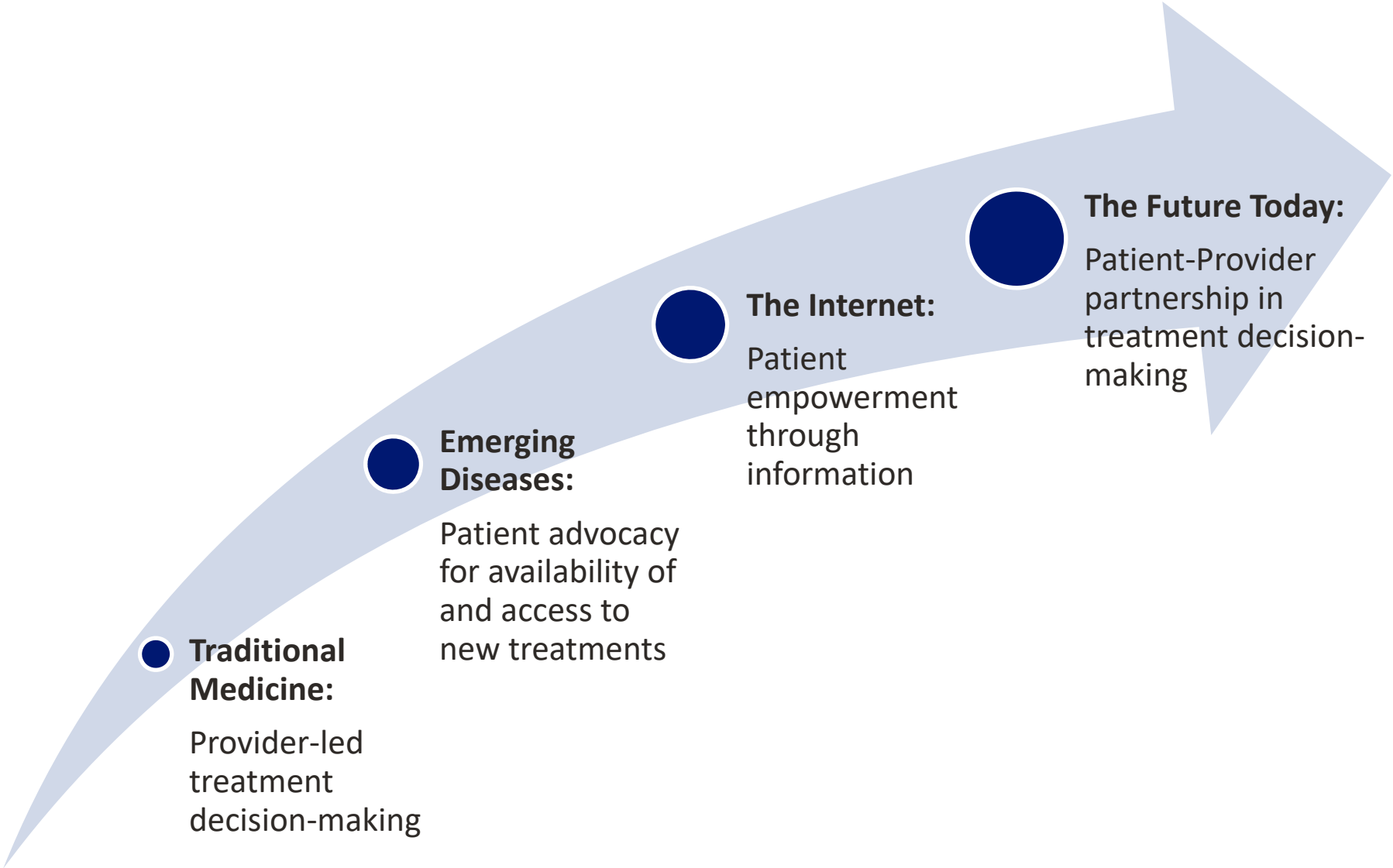
Patients are at the Heart of What We Do

CDRH Vision: Patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world

Evolution of the Role of the Patient



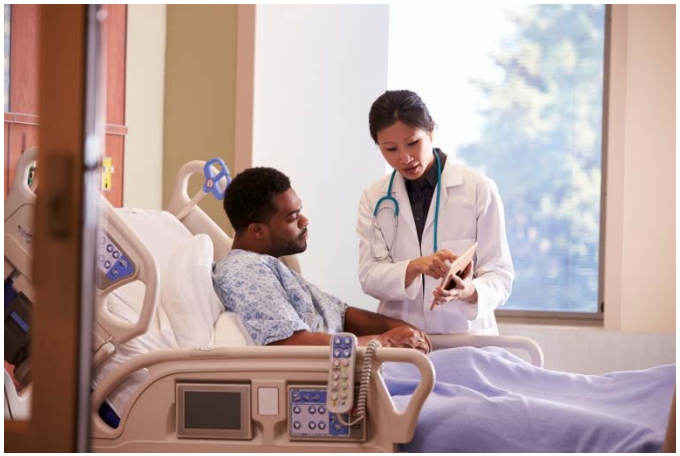
Patient Preference

- Patient preferences are defined as qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions
- Relevant preferences of care-partners (e.g., parents) and health care professionals may also be considered

Guidance: Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling

How is PPI different from PRO?

- ***Patient-reported outcome (PRO)*** is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else
- PRO instruments are designed to measure a patient's perceptions of health status before, during, and after therapy
- Patient preference studies measure what specified type of therapy or attributes of a given therapeutic or diagnostic strategy a patient might prefer



PPI Framework in Medical Product Development

Development	Clinical Trial Design	Pre-Market Benefit-Risk Assessment	Post-Market
1. Identify unmet medical need 2. Understand what matters most to patients about their disease or treatment	1. Inform endpoint selection 2. Inform performance goal	1. Analysis of condition 2. Current treatment options 3. Patient perspective on benefit-risk tradeoffs	1. Inform interpretation of new data affecting benefit-risk assessment 2. Communicate benefit-risk information to patients

Rare pediatric cancer case study

Neurodegenerative case study

Preference Sensitive Decisions for Disease Areas

- PPI may be particularly useful when diseases are “preference sensitive”
- Patient decisions regarding treatment options are preference sensitive when:
  - ❑ multiple treatment options exist and there is no option that is clearly superior for all patients;
  - ❑ when the evidence supporting one option over others is considerably uncertain or variable; and/or
  - ❑ patients’ views about the most important benefits and acceptable risks of a technology vary considerably within a population, or differ from those of healthcare professionals.

Preference Sensitive Decisions for Products

- Is a decision preference sensitive?
- Does the medical product:
  - ❑ Have a direct patient interface?
  - ❑ Intend to yield significant health and appearance benefits?
  - ❑ Intend to directly affect health-related quality of life?
  - ❑ Have certain life-saving but high-risk characteristics?
  - ❑ Fill an unmet medical need or treat a rare disease or condition?
  - ❑ Offer alternative benefits to those already marketed?
  - ❑ Represent novel technology?
- Not all decisions are preference sensitive

Recommended Qualities of Patient Preference Studies

Well-designed and conducted patient preference studies can provide valid scientific evidence regarding patients' risk tolerance and perspective on benefit.

A. All about Patients
   - Patient Centeredness
   - Sample Representativeness
   - Capturing Heterogeneous Patient Preferences
   - Comprehension by Study Participants

B. Good Study Design
   - Established Good Research Practices
   - Effective Benefit-Risk Communication
   - Minimal Cognitive Bias
   - Relevance

C. Good Study Conduct and Analysis
   - Study Conduct
   - Logical Soundness
   - Robustness of Analysis of Results

Qualities: All about Patients

Patient Centeredness

- Patients are the focus of the study
- Should measure the preferences and perspectives of well-informed patients

Representativeness of the Sample and Generalizability of Results

- Should measure preferences of a representative sample of adequate size so that the study results can be reasonably generalized to the population of interest

Capturing Heterogeneity of Patients' Preferences

- Patients' preferences may be heterogeneous even among those with the same disease or condition
- Should reflect the preferences of patients from the full spectrum of disease for which the device is intended to be used

Comprehension by Study Participants

- Ensure that study participants fully understand the harm, risk, benefit, uncertainty, and other medical information being communicated to them

Qualities: Good Study Design

Established Good Research Practices by Recognized Professional Organizations

- Quality of a study may be established if it follows guidelines for good research practices established by a recognized professional organization

Effective Communication of Benefit, Harm, Risk, and Uncertainty

- Reduce uncertainty caused by health numeracy
  - Avoid solely verbal descriptions of uncertainty; Use multiple formats simultaneously
  - Pretest the communication format

Minimal Cognitive Bias

- Minimize cognitive biases such as framing, anchoring, simplifying heuristics, or ordering effect

Relevance

- Inclusion and omission of harm, risk, benefit, and uncertainty should be well justified
- Relevance of specific endpoints to potential clinical outcomes should be clearly communicated to properly elicit preference

Qualities: Study Conduct and Analysis

Study Conduct

- Compliance of research staff and study participants with the study protocol

Logical Soundness

- Data should include internal-validity tests of logic and consistency
- Verified for conformity with logic and consistency

Robustness of Analysis of Results

- Sources of uncertainty
- Sensitivity analysis

Recommendations for PPI Collection

- Talk to FDA early and often to make sure
  - The study asks a relevant research question and includes the attributes/levels of regulatory interest
  - Ranges of levels cover results observed in clinical study
- Choose an appropriate study design
  - # of interested attribute: Single-attribute (e.g., threshold technique) vs multi-attribute (e.g., DCE, BWS) methods
  - Comparator(s)
- Stratified randomization for balanced subgroups to capture preference heterogeneity
- Encourage data quality assessment plan

Recommendations for PPI Documentation

- Development of survey instrument
  - Justification for the chosen method
  - Attribution/level generation & selection process
- Pre-test document as critical evidence to show respondents understand questions and can finish the survey
- Specify subgroups prospectively and stratified randomization for balanced subgroups to capture preference heterogeneity
- Encourage data quality assessment plan

General Steps to Measure Preferences

- Different methods, the same questions:
  - Which one would you prefer and how important is it?
- Glossary
  - Attribute: Benefits, risks, and other considerations
  - Levels: Values or categories that attributes may take (e.g., size of benefit, frequency of SAEs, device placement procedures)
- Steps (simplified)
  - Qualitative:
    - Rank outcomes or measure benefit-risk tradeoff preference?
    - Determine attributes of interest (patients, sponsors, clinicians, FDA)
    - Design survey instrument and pretest it with patients
  - Quantitative:
    - Develop experimental design and specify analysis plan
    - Analyze collected data and document study results

Innovation from Patients for Patients

Collaboration is key to building this field

Thank You

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FDA/CBER Perspective on Patient Preference Information

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Disclaimer:
'This is an informal communication and represents my own best judgment. This presentation does not bind or obligate FDA.'

Examples of source of patient input in regulatory setting

FDA

Input from a patient representative or from a patient during open public hearing at advisory committee meeting
Patient input such as comments & narrative submitted to FDA by the patient group
Patient brought by a sponsor to an FDA-sponsor review meeting
Patient-Reported Outcomes (PRO) Patient Preference Information (PPI)

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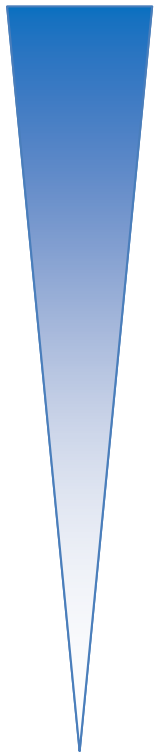
Patient-Reported Outcomes (PRO)
Patient Preference Information (PPI)

Reviewer Experience



CBER's Science of Patient Input (SPI) Initiative

- Scientifically valid, qualitative and quantitative methods for capturing patient perspective information such as **PRO & PPI** on the:
  - Benefits and risks of medical products, and
  - Incorporating this information into review and regulatory decision-making
- Supports Agency efforts to more systematically capture and incorporate the patient perspective into our regulatory framework

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- Supports Agency efforts to more systematically capture and incorporate the patient perspective into our regulatory framework
- Current focus :
  - Building internal review capacity and expertise
  - Collaborating with our colleagues in other FDA centers & external stakeholders
  - Exploring existing and new ways to effectively integrate PPI into our regulatory framework
  - Tracking our experience to inform continuous improvement of the science

Patient preference is elicited in clinical setting but use in regulatory context is new

	Clinical setting	Regulatory setting
Decision context	• Individual	• Representative sample of target population
Method & scientific rigoristic	• Qualitative • Rely on clinician knowledge & judgment	• Qualitative and/or quantitative • Rigorous method & meet regulatory standard
Preference-sensitive condition	• Existing therapies (e.g. Symptom management vs curative) • High risk & high efficacy	• Experimental therapy (e.g. Therapy X with potential for cure but significant adverse effects) • High uncertainty & high stakes
Result	• Qualitative & employ in the context of shared-decision making	• Quantitative & inform benefit-risk analysis

What resources are available?

Notable Initiative 2012-

- CDER/CBER PFDD meetings
- CDRH/CBER PPI guidance

Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and *De Novo* Requests, and Inclusion in Decision Summaries and Device Labeling

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

Document issued on August 24, 2016.
This document will be in effect as of October 25, 2016.

The draft of this document was issued on May 18, 2015.

For questions about this document regarding CDRH-regulated devices, contact the Office of the Center Director (CDRH) at 301-796-5900 or Aarathi Sasi at 301-796-2197 (Aarathi.Sasi@fda.hhs.gov).

For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

MDIC B-R Project Report

ISPOR Conjoint Analysis

ICH Format & Structure of B-R

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

REVISION OF M4E GUIDELINE ON ENHANCING THE FORMAT AND STRUCTURE OF BENEFIT-RISK INFORMATION IN ICH

EFFICACY - M4E(R2)

Current *Step 4* version
dated 15 June 2016

Example Application 2015-

- FDA CDRH/RTI obesity
- EMA cancer patients study
- Industry SC vs IV rituximab

Incorporating Patient Preferences Into Drug Development and Regulatory Decision Making: Results From a Quantitative Pilot Study With Cancer Patients, Carers, and Regulators

D Postmus[1,2], M Mavris[1], HL Hillege[2], T Salmonson[1,3], B Ryll[4], A Plate[5], I Moulon[1], H-G Eichler[1], N Bere[1] and F Pignatti[1]

Preference for subcutaneous or intravenous administration of rituximab among patients with untreated CD20+ diffuse large B-cell lymphoma or follicular lymphoma: results from a prospective, randomized, open-label, crossover study (PrefMab)

M. Rummel[1*], T. M. Kim[2], F. Aversa[3], W. Brugger[4†], E. Capochiani[5], C. Plenteda[3], F. Re[6], P. Trask[7], S. Osborne[8], R. Smith[8] & A. Grigg[9]

How to overcome some challenges ?

Challenges	What we expect from CERSI workshop?
Defining benefit and risk attributes for eliciting preference while we know less in pre-market setting	• Method of attributes selection • Scope of PPI at various stage of medical product development • Managing expectation & status of the science
Conducting scientifically valid PPI studies	• Discussion on how to minimize bias • Choice of valid method • Ideas and collaboration to generate best practice documents
Generalizing PPI studies	• Discuss preference heterogeneity & sample size • Good survey conduct & sampling practices • Good statistical analysis
Reviewing PPI submission and incorporating in regulatory decisions	• Building Capacity • Continuous collaboration to advance methods, consensus on definition & scope

U.S. FOOD & DRUG ADMINISTRATION

Thank you!

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