Science of Patient Input: Patient Reported Outcomes and Patient Preference Information

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Patients are at the heart of what we do at CDRH

**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
Partner with Patients

We interact with patients as partners and work together to advance the development and evaluation of innovative devices, and monitor the performance of marketed devices.

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

2. Increase use and transparency of patient input as evidence in our decision-making.
Evolution of the Role of the Patient

**Traditional Medicine:**
Provider-led treatment decision-making

**Emerging Diseases:**
Patient advocacy for availability of and access to new treatments

**The Internet:**
Patient empowerment through information

**The Future Today:**
Patient-Provider partnership in treatment decision-making

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Shared Goal:
Improve patient health by better understanding patient needs, experiences and preferences
Where can patient perspectives inform Medical Device development and evaluation?

- Patient-Centered Outcomes
- Patient Preference
- Benefit-Risk Information
- Patient-Informed Needs
- Patient-Informed Clinical Trial Design, Patient Reported Outcomes
- Communicating Benefit-Risk Information to Patients

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Increase in Patient Perspective Data

- 50% of PMAs received in FY15 contain PROs
- Observed a >300% increase in premarket submissions with PRO endpoints
- Identified over 600+ premarket submissions containing PROs from CY2000-2014*

*Based on search for PROs in CDRH’s historical submission archives
Building on a Strong Foundation

CDRH Vision

Patient-Centered Device Innovation & Evaluation

Patient Preferences
- Case Study in Obesity / Weight Loss Devices (2012-2015)
- Patient Preference Public Workshop (2013)
- Patient Preference Information Guidance (2016)
- Medical Device Innovation Consortium (MDIC) Patient Centered Benefit-Risk Project

Clinical Studies
- Patient Input in Clinical Trials (2016-2017)

Patient Engagement
- Patient Representatives in FDA Advisory Committee Meetings (since 1991)
- Patient Participation in Medical Product Discussions, FDASIA 1137 (2012)
- Patient Engagement Advisory Committee (2017)
- Increased Patient – Staff Interactions (2016-17)
COA Glossary & Abbreviations

Clinical Outcome Assessment (COA)
Assessment of a clinical outcome made through report by a clinician, a patient, a non-clinician observer or through a performance-based assessment

Patient Reported Outcome (PRO)
A measurement based on a report that comes directly from the patient about the status of a patient’s health condition without amendment or interpretation of the patient’s response by a clinician or anyone else.
Ex. Numeric rating scale of pain intensity

Clinician Reported Outcome (ClinRO)
A measurement based on a report that comes from trained health-care professional after observation of a patient’s health condition.
Ex. Psoriasis Area and Severity Index

Observer Reported Outcome (ObsRO)
A measurement based on a report of observable signs, events or behaviors related to a patient’s health condition by someone other than the patient or a health professional.
Ex. Observer-completed log of seizure episodes

Performance Outcome (PerfO)
A measurement based on a task(s) performed by a patient according to instructions that is administered by a health care profession.
Ex. 6-Minute Walk Test

Slide courtesy of Nikunj Patel, FDA COA Staff
Concepts a PRO Measure May Capture

• Symptoms
  – prevalence, impact, tolerability
• Functioning
• Satisfaction
• Expectations
• Health-related quality of life
• Compliance or Adherence
• Adverse Events
PRO assessments should be held to same standard as other trial measures

• Fit for purpose

• Clear statement of objectives

• Well-defined and reliable assessments
What is your PRO Trial Objective?

• What is your PRO Trial Objective?
  – Describe the patient experience on treatment?
  – Inform Safety / Tolerability?
  – Inform Effectiveness?

• What is your U.S. regulatory goal for the PRO data?
  – Supportive data for overall benefit:risk assessment?
  – Descriptive patient experience data in device label?
  – Make a claim of treatment benefit in device label?
What is a “Fit For Purpose” PRO Instrument?

1. Appropriate for its intended use
   - Study design, Patient population, Treatment/Diagnosis under study

2. Validly and reliably measures concepts that are:
   - Clinically relevant
   - Important to patients

3. Can be communicated in labeling in a way that is accurate, interpretable, and not misleading (i.e., well-defined)
Further Considerations: Strength of Endpoint Results

• **What** is being Measured? *(Endpoint Selection)*
  – Direct Benefit (Feels/Functions/Survives) or a Surrogate?

• **How** accurately is it being measured? *(Measurement Characteristics)*
  – How certain can we be regarding the result and magnitude?
  – Susceptibility to Bias
  – Accuracy of the Timing of the Event (When did the event occur?)

• **How Much** effect on the endpoint is observed? *(Magnitude of Effect)*
  – Large effects seen in trial results can mitigate uncertainty
  – Small effects may have questionable clinical relevance
Definition of Patient Preference

“Qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified choices among outcomes (or other attributes) that differ among alternative health interventions”*

• Patient preference information is useful when:
  • Multiple treatments exist but none are superior
  • Patient views about the most important benefits and acceptable risks vary within a population or differ from that of healthcare professionals
  • Evidence supporting one option over others is uncertain or variable
Patient Preference Information (PPI)

• Qualitative PPI may be useful
  – identifying which outcomes, endpoints or other attributes are valued most by patients
  – which factors affect patients’ perspectives on risk and benefit

• Quantitative PPI
  – provide estimates of how much different outcomes, endpoints or other attributes are valued by patients,
  – tradeoffs that patients state or demonstrate they are willing to make
What can PROs and PPI tell us?

Patient-Reported Outcomes (PRO)
- Endpoints in regulatory studies
- Outcomes to monitor postmarket
- Interest to payers, providers, patients

Patient Preference Information (PPI)
- Inform endpoints or effect size for regulatory studies
- Inform subgroup considerations
- Labeling changes / expanded indications
Patient Preference Studies

- FDA’s guidelines on patient preference information were finalized on August 24, 2016

- Guideline notes that “Evaluations of patient-centered variations in tolerance to risks and perspective on benefits may, in the aggregate, reveal a population-level assessment of patient benefit-risk preference for that device, which may be considered valid scientific evidence”*§

## CDRH Guidance on Factors to Consider for Benefit – Risk Determinations (2016)

- Worksheet with questions to guide evaluation of each factor
- Patient Preference Information (PPI) as important factor:

<table>
<thead>
<tr>
<th>Factors</th>
<th>Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-Reported Outcomes</td>
<td>• Do benefit(s) and risk(s) include effects on patients’ health-related quality of life?</td>
</tr>
<tr>
<td>Benefit-Risk Considerations</td>
<td>• Which benefits and risks are most important to affected patients?</td>
</tr>
<tr>
<td></td>
<td>• What benefit-risk tradeoffs are acceptable from the patient perspective?</td>
</tr>
<tr>
<td></td>
<td>• Are there clinically-relevant subgroups of patients that would choose a particular benefit-risk profile over other alternatives?</td>
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<tr>
<td></td>
<td>• Does PPI capture diverse preference across the spectrum of indicated population and thus, generalizable?</td>
</tr>
</tbody>
</table>
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. This may inform FDA’s evaluation of a device’s benefit-risk profile during the PMA, HDE application, and de novo request review processes.

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
FDA News Release

FDA approves first-of-kind device to treat obesity

For Immediate Release
January 14, 2015

The U.S. Food and Drug Administration today approved the Maestro Rechargeable System for certain obese adults, the first weight loss treatment device that targets the nerve pathway between the brain and the stomach that controls feelings of hunger and fullness.

The Maestro Rechargeable System, the first FDA-approved obesity device since 2007, is approved to treat patients aged 18 and older who have not been able to lose weight with a weight loss program, and who have a body mass index of 35 to 45 with at least one other obesity-related condition, such as type 2 diabetes.

BMI, which measures body fat based on an individual’s weight and height, is used to

NxStage Medical Announces FDA Clearance for Solo Home Hemodialysis Using NxStage® System One™

First clearance of its kind gives trained NxStage patients freedom to dialyze without a care partner

LAWRENCE, Mass., Aug. 28, 2017 /PRNewswire/ -- NxStage Medical, Inc. (Nasdaq: NXTM), a leading medical technology company focused on advancing renal care, today announced that the U.S. Food and Drug Administration (FDA) has cleared its System One for solo home hemodialysis, without a care partner, during waking hours.
Regulatory Impact

• Advance research and regulatory science towards outcomes that are most important to patients

1) To inform clinical trial design

2) To inform FDA evaluation

MDUFA IV Commitment: Patient Engagement & the Science of Patient Input

- Develop clinical, statistical, and scientific expertise to evaluate PRO & PPI in submissions
- Public meetings to discuss approaches of incorporating PPI and PRO as evidence in device submissions
- Flexible framework for PROs
- Develop a model for bridging studies

https://www.fda.gov/ForIndustry/UserFees/MedicalDeviceUserFee/ucm454039.htm
Challenges and Advancing Science

- Preference elicitation approaches that are fit-for purpose
  - Benefit-risk tradeoffs
  - Endpoint identification
  - Development of patient-reported outcomes

- Validity criteria, standards, and quality metrics

- Bias minimization

- Building capacity, training, resources, and value proposition
Take Home Points

• Patient input is a CDRH priority and integral to medical product evaluation
• Content validity of PRO measure should be established prior to use in clinical studies and is informed by clinical judgment and patient input
• Validity is **not** a fixed property of a questionnaire
  – The questionnaire is valid (i.e., fit for purpose) in a given context of use which includes the intended use population
• At a minimum, the questionnaire should be relevant to the clinical condition, be understandable to patients, and have an appropriate recall period for the trial and condition
• Voluntary submission of PPI may be informative during benefit-risk determination
• May be informative earlier in device development (to inform clinical study parameters such as endpoint selection and effect size)
• **RECOMMEND EARLY INTERACTIONS WITH FDA REVIEW STAFF IF PLANNING TO USE EITHER IN TRIAL**
Innovation from Patients for Patients
PRO Resources

• Guidance on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

• Clinical Outcome Assessment (COA): Recommended Publications

• Clinical Outcome Assessment Glossary of Terms

• Social Research Methods
  (https://www.socialresearchmethods.net/kb/measval.php)
PPI Examples and Resources

• CDRH Patient Preference Obesity Study

• Guidance for Industry and Food and Drug Administration Staff: Factors to Consider for Benefit Risk Determinations in Medical Device Premarket Approval and De Novo Classifications


• MDIC Patient-Centered Benefit Risk Project: A Framework for Incorporating Information on Patient Preferences Regarding Benefit and Risk into Regulatory Assessments of New Medical Technology (http://mdic.org/pcbr)
Thank You