Use of Patient-Reported Outcomes in Device Development: FDA Division of Cardiovascular Devices Perspective

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PRO: FDA’s Definition

• A 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. The outcome can be measured in absolute terms (e.g., severity of a symptom, sign, or state of a disease) or as a change from a previous measure.

• In clinical trials, a PRO instrument can be used to measure the effect of a medical intervention on one or more concepts (i.e., the thing being measured, such as a symptom or group of symptoms, effects on a particular function or group of functions, or a group of symptoms or functions shown to measure the severity of a health condition).

PRO Guidance 2009
Where Patient Perspectives Inform Device Development and Evaluation

Patient-Informed Needs

Patient-Centered Outcomes

Patient Preference
Benefit-Risk Information

Patient-Informed
Clinical Trial Design,
Patient Reported Outcomes

Communicating
Benefit-Risk Information
to Patients

What PROs Tells us and Potential Uses

Experience of the Patient

- Functional Limitations
- Impact on Daily Activities
- Impact on Emotional Well-being
- Impact on Psychological Health
- Impact on Social Function

Potential Uses by the Physician

- Determine Baseline Status
- Clinical Trial Endpoints
- Monitor Therapy Effectiveness
- Assess Change in Status
- Prognosis Predictor

Good PROs Require Scientific Development

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<tr>
<th>Item-level evaluation</th>
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<tr>
<td>• Response category performance</td>
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<td>• Reliability and Validity</td>
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<th>Determination of scoring</th>
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<td>• Consistency</td>
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<td>• Handling of missing data</td>
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<th>Scale-level evaluation</th>
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<th>Interpretation of scores and change</th>
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<td>• Clinically important differences</td>
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Various Types of PRO Validity & Reliability

**Validity** (of the use of PRO score)

- **Content Validity**: extent to which PRO measures appropriate content
- **Criterion Validity**: extent to which PRO agrees with outside standard
- **Construct Validity**: extent to which the evidence demonstrates that the PRO measures the intended construct

**Reliability**

- **Internal Consistency**: extent to which PRO measures consistent responses across items
- **Reproducibility**: extent to which PRO measures consistent responses across time
Treatment Goals: Survival, Free of Hospitalization, and Quality of Life

- Live longer: Mortality, readmission, EF, etc.
- Feel better: Symptoms, function, well-being
- PROs inform us on
  - Clinical trials: evaluate treatment benefit
  - Regulatory decisions: support labeling claim
  - Clinical practices: guide treatment decisions
  - Quality of care: measure patient-centered values for payment decisions

Hunter NL, O’Callaghan KM, Califf RM. JAMA 2015;314(23):2499-2500

PROs: Clinical Measures’ Critical Complement

- PROs & clinical outcomes complement each other
- PROs are not replacing hard clinical science and biomarkers
- Together they complete the picture of treatment impact on patients (e.g., symptoms, functioning, quality of life)
PROs: Critical Complement to Clinical Data

- Reflect important matters to patients e.g., symptoms, functioning, health-related QOL
- Inform the FDA of the effectiveness of treatment from the perspective of patients

<table>
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<th>PRO</th>
<th>Values to Patients</th>
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<tr>
<td>Symptoms</td>
<td>Relieves freq., severity, or burden of symptoms</td>
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<tr>
<td>Functional Performance</td>
<td>Improves physical, participation (work or family), social functioning</td>
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<tr>
<td>Psych. well-being</td>
<td>Experience less anxiety or depression</td>
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<td>HRQL</td>
<td>Better quality of life</td>
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2 Examples of PROs in Cardiology*

<table>
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<tr>
<th>PRO</th>
<th>Recall Period</th>
<th>Domains (# items)</th>
<th>Symptoms (S) and Impacts (I)</th>
<th>Scoring</th>
</tr>
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</table>
| KCCQ      | 2 wks         | Physical (6), Symptoms (7), Change (1), Self-efficacy (2), Social (1), QoL (7) | (S) Shortness of breath, fatigue, ankle swelling  
(I) Physical limitation, self-efficacy, social interference, QoL | 23 items  
5, 6, or 7-point Likert scale  
Overall and domain scores  
(0–100) higher is better |
| MLHFQ     | 4 wks         | Physical (8), Emotional (5) | (S) Ankle/leg swelling, shortness of breath, fatigue, poor memory or concentration, depression  
(I) Physical activity, sleep, sexual activity, financial difficulty, leisure activity, eating | 21 items  
6-point Likert scale  
Overall and domain scores  
(0–105) lower is better |

*Psotka et al., J Am Coll Cardiol HF. 2016; 4(10): 791-804
† Kansas City Cardiomyopathy Questionnaire
‡ Minnesota Living with Heart Failure Questionnaire
Common Challenges w/PROs for Regulatory Use

• How to interpret “clinically meaningful” change in a PRO measure
• How to distinguish suitable PRO instruments from others
• How to overcome challenges of certain study designs (unblinded, single arm, small N)
• How to decrease missing data
• Better understand PROs (e.g., roles, validity)
• Inconsistent policy for including PROs in labeling

Meaningful to Include PROs in Study

Clinical Impact
• Assess condition changes
• Decrease toxic patient experiences
• Improve clinical care

Regulatory Impact
• Include patient perspective
• Provide complete picture of patient health
Clinical and Regulatory Path Schematics: Phased Approach

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<tr>
<th>Sample Size</th>
<th>Analysis Timing</th>
<th>Clinical Evidence</th>
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<tr>
<td>Phase 1: N_randomized</td>
<td>Subjects (N%) complete six months of follow-up (Enrollment continues)</td>
<td>Safety evaluation</td>
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<tr>
<td>Phase 2: N_randomized</td>
<td>(N% from Phase 1 + additional new subjects)</td>
<td>Three Buckets: Relevant Biomarker, Exercise, and QOL endpoints</td>
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<tr>
<td></td>
<td></td>
<td>Sufficient mortality and mortality data collected on all subjects (N%)</td>
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KCCQ Inform Patient Management

- Freedom from CV Mortality/hospitalization n=1,516 outpatients
- Scores grouped in ranges of 25 points
- Graded relationship with lower scores associated with worse outcomes

Conclusions

• PRO information can be useful for device evaluation
• Challenges should be recognized with use and interpretation
• Further research and experience in this area is needed
PROs Inform PMAs Decisions

- Walking Impairment Questionnaire (WIQ)
- Seattle Angina Questionnaire (SAQ)
- Peripheral Artery Questionnaire (PAQ)
- Atrial Fibrillation effect on Quality-of-Life Questionnaire (AFEQT)
- Aberdeen Varicose Vein Questionnaire (AVVQ)
- Kansas City Cardiomyopathy Questionnaire (KCCQ)

Heidenreich et al. JACC 2006;47(4):752-56
Other Utility of PROs in Heart Failure*

• PROs can be more reproducible than left ventricular ejection fraction or valve gradients assessments
• Helpful clinical interpretation:
  – 5-pt Δ in KCCQ† ~ 10% Δ in fully adj. mortality / hosp. risk
  – MLHFQ‡ ~ NYHA classes I, II, III
• Can help patient decision making to improve their QoL without necessarily longevity benefit, e.g. diuretic adjustments

*Kelkar, et al., J Am Coll Cardiol HF. 2016; 4(3): 165-75
† Kansas City Cardiomyopathy Questionnaire
‡ Minnesota Living with Heart Failure Questionnaire

PROs Are Not All Created Equal

• Some biomarkers are better than others.
• Example: STS score is better than general clinical impression of frailty to accurately predict the risk of mortality or major morbidity.
• Similarly, some PROs can be better than others in various ways for capturing certain concepts.
  – Measure the concept that the PRO was designed to capture
  – Measure the concept more reliably or precisely

Symptom is to PRO as general clinical impression of frailty is to STS risk score.
“FDA recognizes that patient tolerance for risk and a patient-centric assessment of risk may reveal reasonable patients who are willing to tolerate a very high level of risk to achieve a probable benefit, especially if that benefit results in an improvement in quality of life.”