

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

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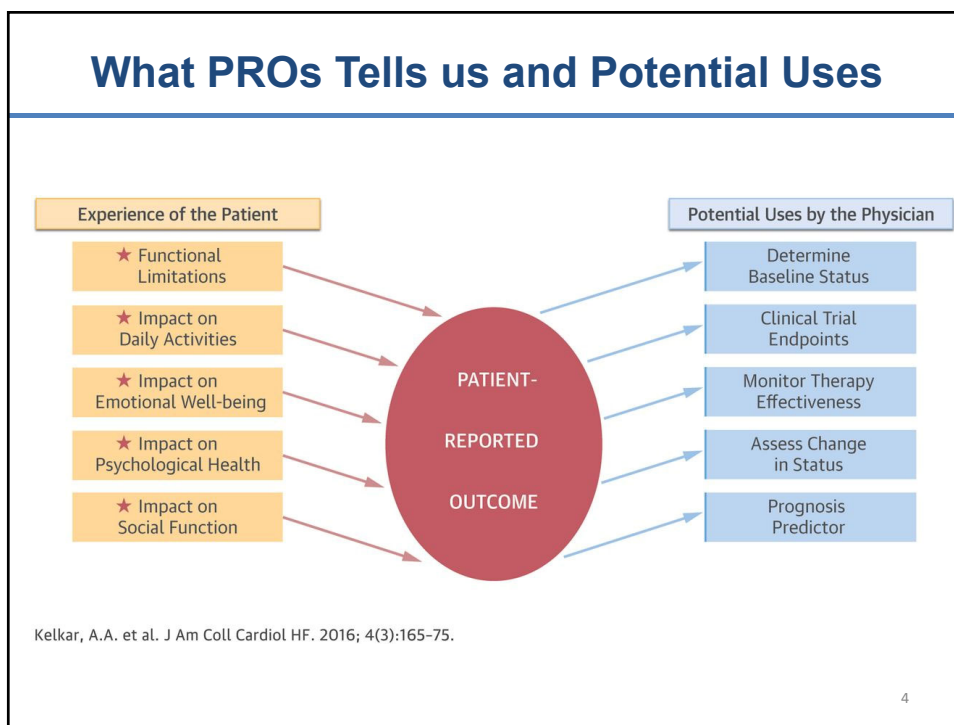
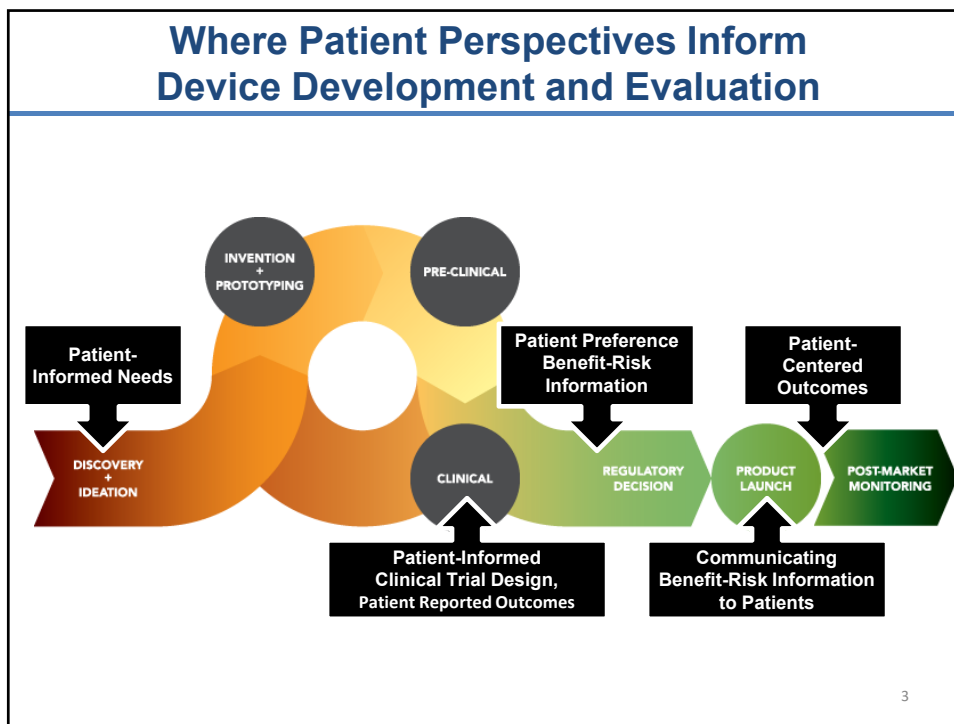
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## PRO: FDA's Definition

- 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

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## Good PROs Require Scientific Development

### Item-level evaluation

- Response category performance
- Reliability and Validity

### Determination of scoring

- Consistency
- Handling of missing data

### Scale-level evaluation

- Reliability and Validity
- Responsiveness

### Interpretation of scores and change

- Clinically important differences
- Responsiveness

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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

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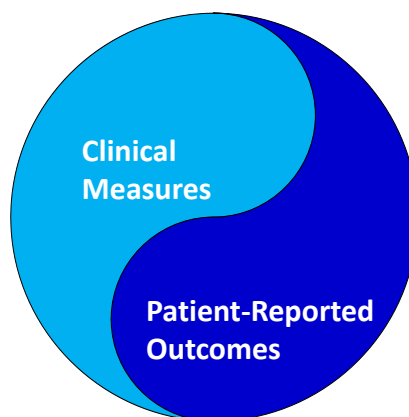
## Treatment Goals: Survival, Free of Hospitalization, and Quality of Life

- 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  
Psozka MA, et al. JACC 2016;4(10)794-804*

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## 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)

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## 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

PRO	Values to Patients
Symptoms	Relieves freq., severity, or burden of symptoms
Functional Performance	Improves physical, participation (work or family), social functioning
Psych. well-being	Experience less anxiety or depression
HRQL	Better quality of life

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## 2 Examples of PROs in Cardiology\*

PRO	Recall Period	Domains (# items)	Symptoms (S) and Impacts (I)	Scoring
KCCQ <sup>†</sup>	2 wks	<ul style="list-style-type: none"> <li>• Physical (6)</li> <li>• Symptoms (7)</li> <li>• Change (1)</li> <li>• Self-efficacy (2)</li> <li>• Social (1)</li> <li>• QoL (7)</li> </ul>	<ul style="list-style-type: none"> <li>• (S) Shortness of breath, fatigue, ankle swelling</li> <li>• (I) Physical limitation, self-efficacy, social interference, QoL</li> </ul>	<ul style="list-style-type: none"> <li>• 23 items</li> <li>• 5, 6, or 7-point Likert scale</li> <li>• Overall and domain scores</li> <li>• (0–100) higher is better</li> </ul>
MLHFQ <sup>‡</sup>	4 wks	<ul style="list-style-type: none"> <li>• Physical (8)</li> <li>• Emotional (5)</li> </ul>	<ul style="list-style-type: none"> <li>• (S) Ankle/leg swelling, shortness of breath, fatigue, poor memory or concentration, depression</li> <li>• (I) Physical activity, sleep, sexual activity, financial difficulty, leisure activity, eating</li> </ul>	<ul style="list-style-type: none"> <li>• 21 items</li> <li>• 6-point Likert scale</li> <li>• Overall and domain scores</li> <li>• (0–105) lower is better</li> </ul>

\*Psotka et al. , J Am Coll Cardiol HF. 2016; 4(10): 791-804

<sup>†</sup> Kansas City Cardiomyopathy Questionnaire

<sup>‡</sup> Minnesota Living with Heart Failure Questionnaire

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## Common Challenges w/PROs for Regulatory Use

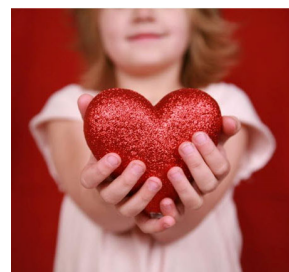
- How to interpret “clinically meaningful” change in a PRO measure
- How to distinguish suitable PRO instruments from others
- How to overcome challenges of certain study designs (unblinded, single arm, small N)
- How to decrease missing data
- Better understand PROs (e.g., roles, validity)
- Inconsistent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

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## Meaningful to Include PROs in Study

### Clinical Impact

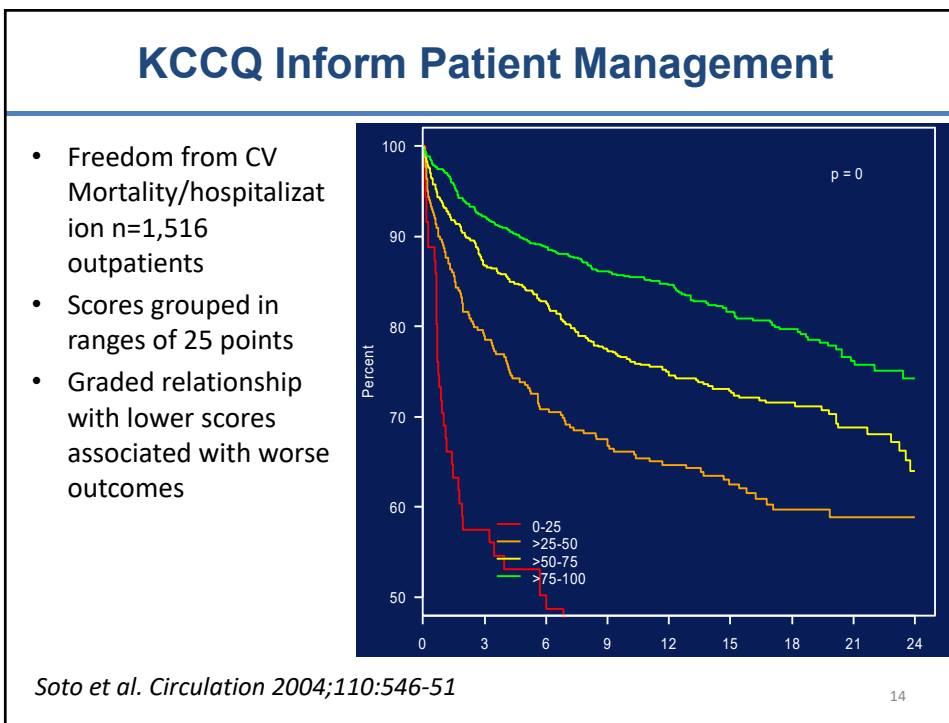
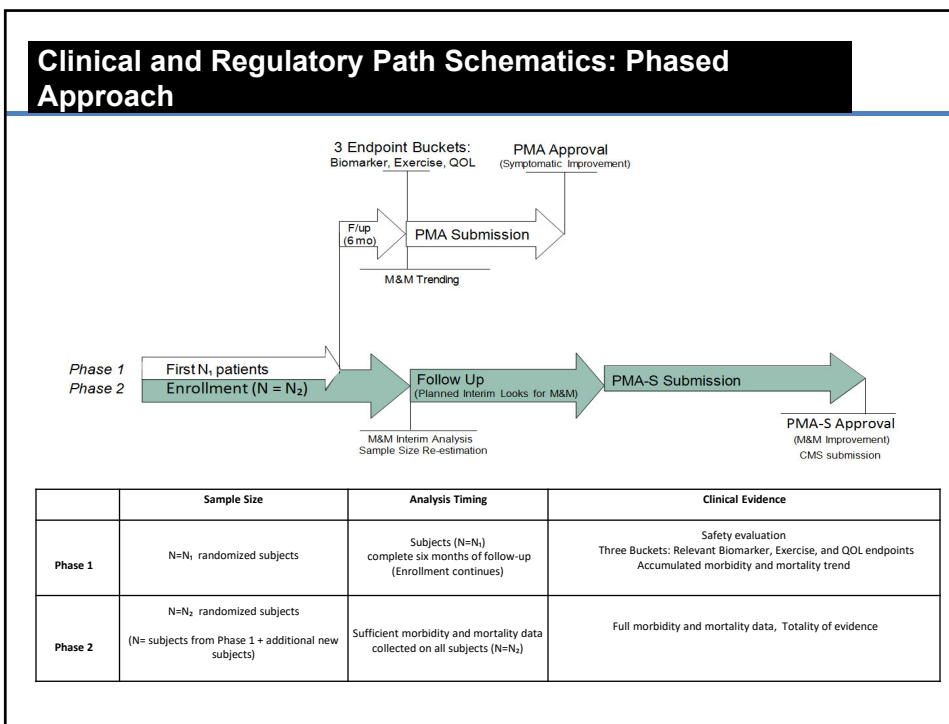
- Assess condition changes
- Decrease toxic patient experiences
- Improve clinical care



### Regulatory Impact

- Include patient perspective
- Provide complete picture of patient health

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## Development of Joint Models for QOL and Survival Data

### Basic Concepts and Methods for Joint Models of Longitudinal and Survival Data

*Joseph G. Ibrahim, Haitao Chu, and Liddy M. Chen*

#### A B S T R A C T

Joint models for longitudinal and survival data are particularly relevant to many cancer clinical trials

Statistics  
in Medicine

#### Featured Article

Received 27 January 2014, Accepted 19 February 2014 Published online 14 March 2014 in Wiley Online Library  
(wileyonlinelibrary.com) DOI: 10.1002/sim.6141

### Joint modeling of survival and longitudinal non-survival data: current methods and issues. Report of the DIA Bayesian joint modeling working group

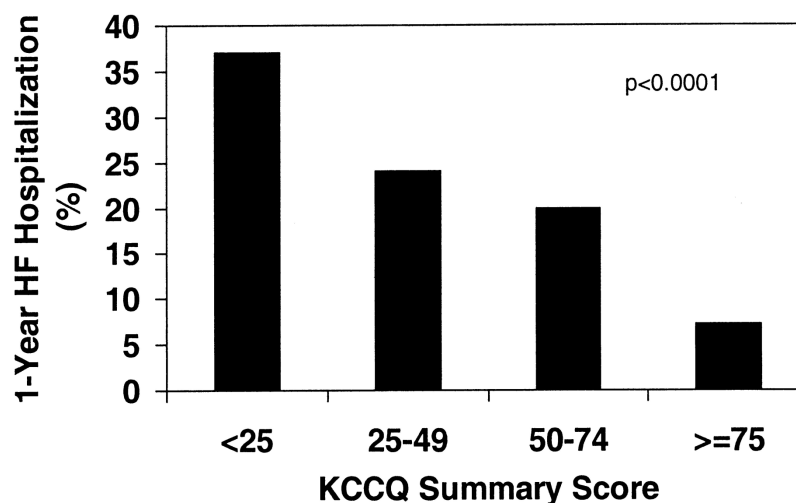
A. Lawrence Gould,<sup>a,\*†</sup> Mark Ernest Boye,<sup>b</sup>  
Michael J. Crowther,<sup>c</sup> Joseph G. Ibrahim,<sup>d</sup> George Quartey,<sup>e</sup>  
Sandrine Micallef<sup>f</sup> and Frederic Y. Bois<sup>g,h</sup>

## 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



## KCCQ Inform Patient Management (cont.)



Heidenreich et al. JACC 2006;47(4):752-56

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## 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)

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## 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  $\Delta$  in KCCQ<sup>†</sup> ~ 10%  $\Delta$  in fully adj. mortality / hosp. risk
  - MLHFQ<sup>‡</sup> ~ 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

<sup>†</sup> Kansas City Cardiomyopathy Questionnaire

<sup>‡</sup> Minnesota Living with Heart Failure Questionnaire

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## 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.

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## CDRH Benefit-Risk Guidance

“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.”