HealthMeasures in the Regulatory Setting: The FDA Perspective

Michelle Campbell, PhD
Reviewer and Scientific Coordinator
Clinical Outcome Assessments Staff
Office of New Drugs
Center for Drug Evaluation and Research
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Disclaimer

The views expressed in this presentation are those of the speaker, and do not necessarily represent an official FDA position

Outline

- Patient Focused Drug Development Initiative
- Clinical Outcome Assessments (COAs) as measures of clinical benefit
- Regulatory Considerations for use of COAs to support clinical trial endpoints
- COA Qualification
- HealthMeasures in the Regulatory Setting
- How HealthMeasures Researchers can inform the FDA

A New Era of Patient Empowerment

Dr. Janet Woodcock:

- "It turns out that what is really bothering the patient and what is really bothering the doctor can be radically different things….patients are true experts in their disease".
- "It's clear you have to start with an understanding of the impact of the disease on the people who have it, and what they value most in terms of alleviation before you set up a measurement and go forward with truly patient-focused drug development."

PDUFA V Clinical Outcome Assessments Public Workshop, April 1, 2015

It takes a village

- While patients are experts in their disease, they are not necessarily experts in clinical trials or in endpoint measure development

It takes a village: patient focused drug development cannot be done by any one group in isolation!

FDA's Patient-Focused Drug Development Initiative

- Patients are uniquely positioned to inform understanding of the therapeutic context for drug development and evaluation
  - There is a need for more systematic ways of gathering patient perspective on their condition and treatment options
  - Current mechanisms for FDA to obtain patient input often limited to discussions related to specific applications under review

- Patient-Focused Drug Development (PFDD) is part of FDA commitments under PDUFA V*
  - FDA is convening 24 meetings on specific disease areas in FY 2013-17
  - Meetings can help advance a systematic approach to gathering input

*The fifth authorization of the Prescription Drug User Fee Act, enacted in 2012

PFDD meetings for Fiscal Years 2013-2017

Fiscal Year 2013	Fiscal Year 2014	Fiscal Year 2015	Fiscal Years 2016-2017
• Chronic fatigue syndrome/ myalgic encephalomyelitis • HIV • Lung cancer • Narcolepsy	• Sickle cell disease • Fibromyalgia • Pulmonary arterial hypertension • Inborn errors of metabolism • Hemophilia A, B, and other heritable bleeding disorders • Idiopathic pulmonary fibrosis	• Female sexual dysfunction • Breast cancer • Chagas disease • Functional gastrointestinal disorders • Parkinson's disease and Huntington's disease • Alpha-1 antitrypsin deficiency	• Non-tuberculous mycobacterial lung infections • Psoriasis • Neuropathic pain associated with peripheral neuropathy • Patients who have received an organ transplant • Sarcopenia • Autism- • Alopecia areata • Hereditary angioedema

http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm347317.htm

Externally-Led PFDD Meetings

- There is external interest in expanded efforts to gather patient input in support of drug development and evaluation
- Meetings conducted by external stakeholders provide an opportunity to expand the benefits of PFDD
  - Meetings should target disease areas where there is an identified need for patient input on topics related to drug development
  - FDA's PFDD meetings can serve as a model
- Possible mechanisms the patient group could explore:
  - Public meeting (conducted within Metro D.C. area)
  - Web-only meeting
  - Small internal meeting at FDA, with patients
- For more information, please visit: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm453856.htm

FDA Key PFDD Learnings and Next Steps

- Patients with chronic serious disease are experts on what it is like to live with their condition. Their "chief complaints" may not be factored into drug development and data collection plans
  - Each PFDD meeting results in a report that faithfully captures patient input
- FDA plans to engage wider community of patients, researchers and drug developers to discuss methodologically sound approaches that:
  - Bridge from initial PFDD meetings to more systematic collection of patients' input
  - Generate meaningful input on patients' experiences and perspectives to inform drug development and B-R assessment
- FDA plans to provide regulatory guidance
  - On pragmatic and methodologically sound strategies, pathways, and methods to gather and use patient input

21st Century Cures Act of 2016

Section 3002: PFDD Guidance

Publish Guidance for Industry addressing:

- Collection of accurate and representative patient experience data
- Collection of data on patients' burden of disease, burden of treatment, and benefits/risks in disease management
- Identification and development of methods to measure impacts (e.g., burden of disease/treatment) to patients
- Collection and analysis of COAs for purposes of regulatory decision-making

Conduct public workshop on:

- COAs and better ways to incorporate COAs into endpoints

Bridging from patient input to patient-focused clinical trial endpoints

Clinical Benefit: How do we define it?

- A positive clinically meaningful effect of an intervention, i.e., a positive effect on how an individual feels, functions, or survives.
  - How long a patient lives
  - How a patient feels or functions in daily life
- Can be demonstrated as either:
  - A comparative advantage in treatment of the disease or condition; OR
  - A comparative reduction in treatment-related toxicity
- Clinical benefit is described in labeling in terms of the outcome of interest measured

Types of Outcome Assessments

- Clinical outcome assessments (COAs)
  - Patient reported outcomes (PROs)
  - Clinician-reported outcomes (ClinROs)
  - Observer reported outcomes (ObsROs)
  - Performance outcomes (PerfOs)

- Biomarkers

- ***Patient-reported outcome (PRO)*** —

A measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else.

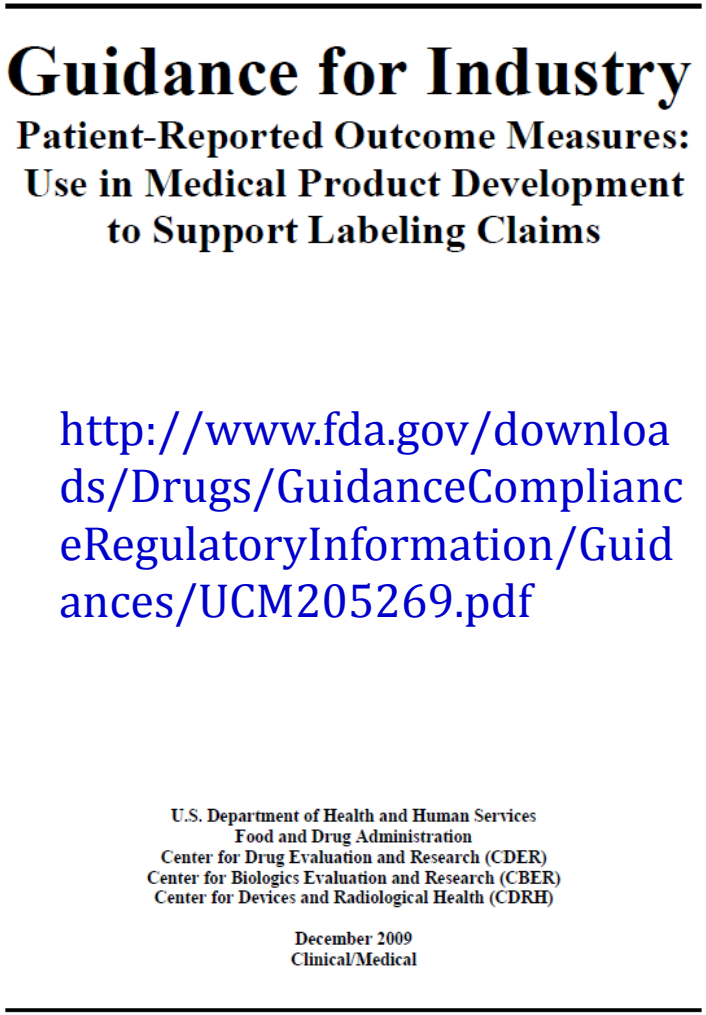
  - Examples: pain intensity, seizure episodes, asthma symptoms, rescue medication use, health-related quality of life

FDA Review of Clinical Outcome Assessments

Does the instrument measure the outcome of interest?

- Well-defined and reliable (21CFR 314.126)
- Appropriate for the target population
- Appropriate for the target indication
- Adequate measurement properties
  - E.g., content validity: PRO development relies on patient input to support content validity

Good Measurement Principles



- Defines how the Agency interprets "well-defined and reliable" (21 CFR 314.126) for PRO measures intended to provide evidence of treatment benefit

- All COAs can benefit from the good measurement principles described in the PRO Guidance (i.e., valid, reliable, sensitive to change)

- Provides optimal approach to PRO development

- **But, flexibility and judgment are needed to meet practical demands!**

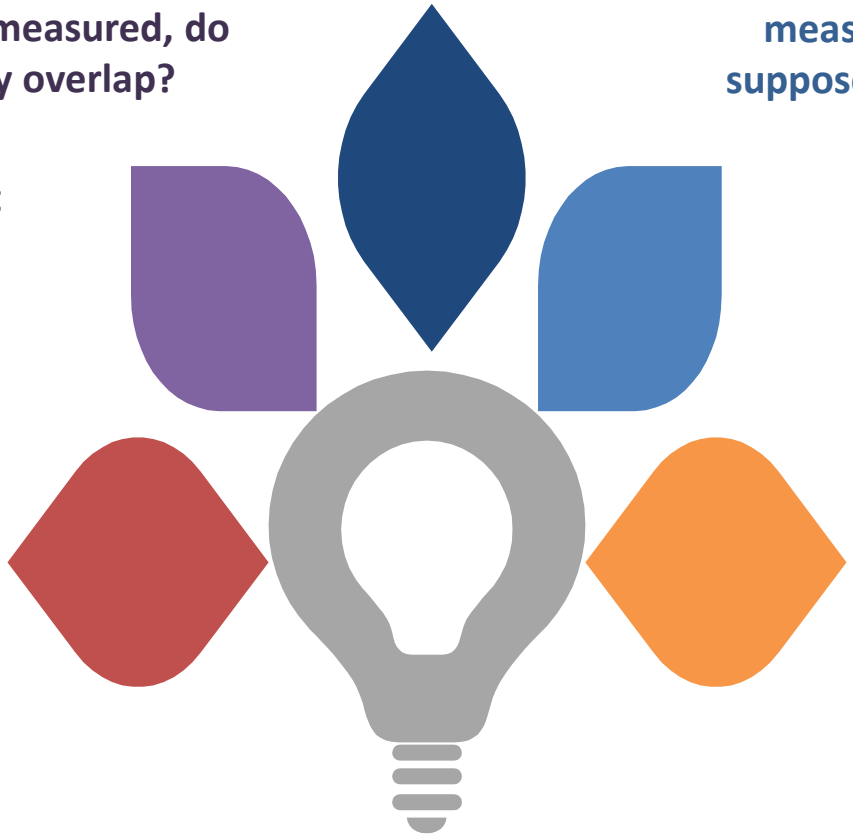
Good Measurement Principles

If there are multiple concepts/domains being measured, do they overlap?

Is the instrument reliable?

Does the instrument measure what it is supposed to measure?

Does the instrument measure what is important to the patient?



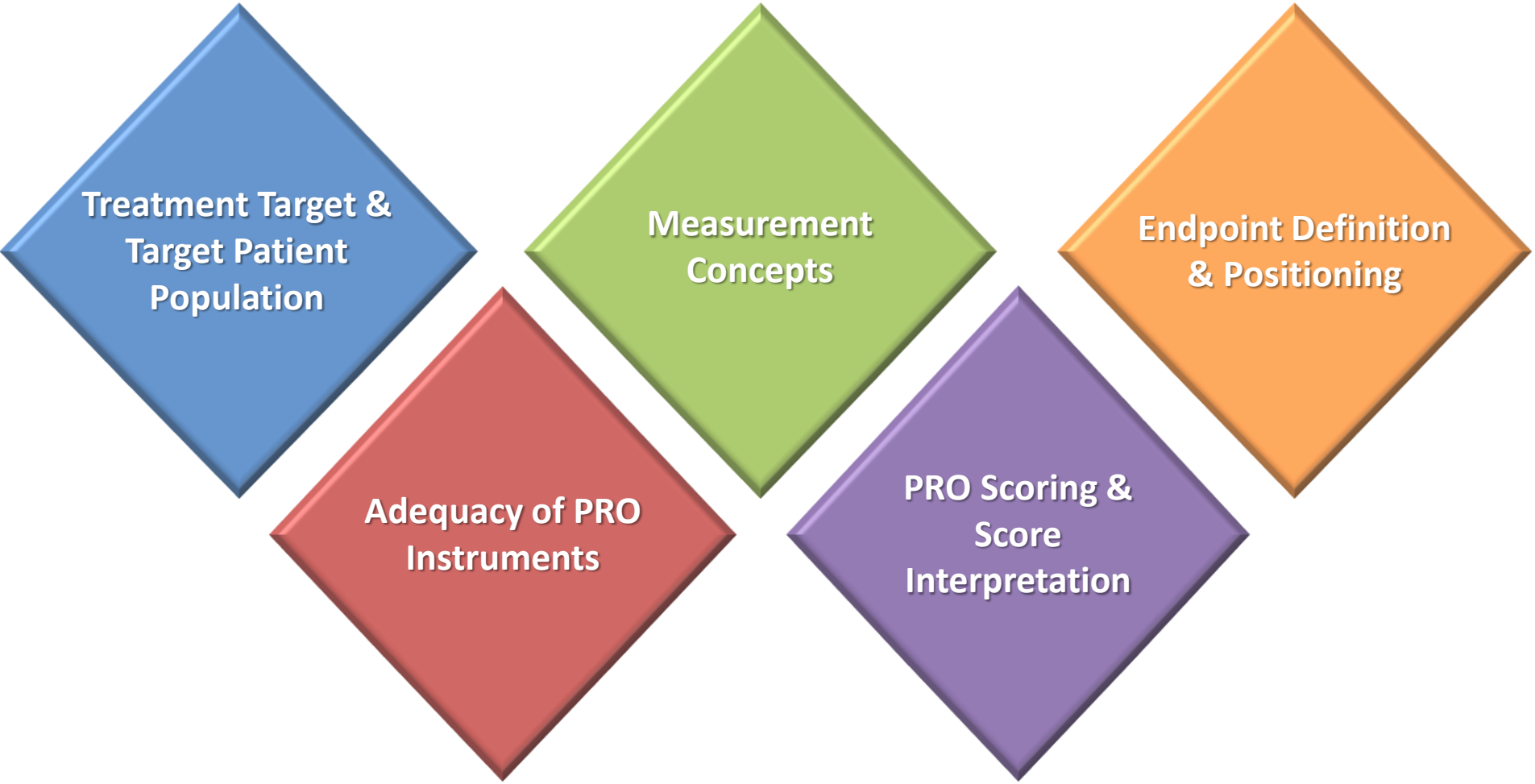
Is the instrument sensitive to detect change over time?

Is the instrument appropriate for use in the study population?

Did a subset of questions drive the result?

What does a score improvement of X-points mean?

Key Considerations When Evaluating a PRO Measurement Strategy



Key Characteristics to Be Evaluated

- Content Validity
- Psychometric Properties
  - Reliability
    - Test-retest or intra-rater reliability
    - Internal consistency reliability
    - Inter-rater reliability (*if appropriate*)
  - Validity
    - Construct Validity (known-groups validity; discriminant and convergent validity)
    - Ability to detect change
- Interpretation of Clinically Meaningful Change

Interpretation of Clinically Meaningful Change

- Statistical significance alone is not sufficient; changes have to reflect a positive clinically meaningful effect of an intervention (i.e., clinical benefit - a positive effect on how an individual feels, functions, or survives)

- To establish clinical benefit we consider two questions:
  1. Does the assessment measure or reflect something of significance to patients?
  2. Is the magnitude of change at the individual level sufficiently large enough to affect how patients feel or function in daily life?

Ways FDA can work with stakeholders in selecting or developing COAs

Pathways for FDA Clinical Outcome Assessment Review & Advice

1 IND/NDA/BLA Pathway

Within an individual drug development program

Investigational New Drug (IND) submissions to FDA

Potential to result in *labeling* claims

2 DDT COA Qualification Pathway

Outside of an individual drug development program

Development of novel COAs for use in multiple drug development programs addressing unmet measurement needs

Potential to result in *qualification* of COA

Voluntary Program

3 Critical Path Innovation Meetings Pathway

Outside of an individual drug development program

Potential for *general CDER advice* on specific methodology or technology (e.g., PRO) in its early stages of development

Meetings are informal, non-binding discussions

CDER Qualification of Clinical Outcome Assessments

- DDT Qualification Statement: COA qualification is a conclusion that within the stated context of use (COU), the results of measurement can be relied upon to represent a specific concept (COI) with a specific interpretation when used in drug development and regulatory decision-making

- CDER qualification is currently reserved for those COAs that are ultimately intended to support primary or secondary endpoints in clinical trials

- Qualified instruments shall be made available publically available

21st Century Cures Act

- Signed into law: December 13, 2016
- Adds new section 507 to the Food, Drug, and Cosmetic Act (FD&C Act) concerning the qualification of DDTs
  - Subtitle B—Advancing New Drug Therapies
  - Sec. 3011. Qualification of drug development tools
- Legislation establishes new processes for qualification of DDTs (biomarkers and clinical outcome assessments)

https://www.congress.gov/bill/114th-congress/house-bill/34/text

Key provisions of 21st Century Cures

- Process
- Transparency

Process:
Three Submission Milestones

- Letter of Intent
- Qualification Plan
- Qualification Package

Transparency

Bi-annually the Agency will post publically:

- Agency response letter to qualification submitters
- Information on what a qualification submitter sent in for review
  - Type of DDT
  - Context of Use
  - Concept of Interest
  - Summary of what was in the submission provided by the submitter

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Leveraging PROMIS® for unmet public health needs

Disease Approach/Domain Approach

PROMIS® In Qualification

Disease	Measure	Population	Submitter
Rheumatoid Arthritis	Fatigue	Adult	PRO Consortium
Multiple Sclerosis	Fatigue and Physical Function	Adult	PRO Consortium
ME/CFS/SEID	Fatigue	Adult	San Keller, AIR
Oncology and Hematology	Physical Function	Adult	Dave Cella, Northwestern
Sarcopenia	Physical Function	Adult	Dave Cella, Northwestern
Crohn's Disease	Fatigue and Pain Interference	Pediatrics	PEPR Consortium
Chronic Kidney Disease	Fatigue	Pediatrics	PEPR Consortium

How Can HealthMeasures Research Inform the FDA

- Examining what is meaningful change
- For pediatrics, can any of the parent item banks be leveraged as an observable reported outcome?
- Rare Diseases
- May need limited qualitative work in specific diseases to support a short form

Closing Thoughts

- The FDA encourages the development and implementation of patient-focused clinical outcome assessments (COAs) in clinical trials to support drug approvals and labeling claims
  - Early patient input is critical in the road to patient-focused outcome measurement
- The identification of tools is just one aspect of patient focused drug development
  - The values of patients need to drive the selection of outcome measures as patients are the ultimate end users of this information
- We are continuing to learn best ways to engage patients in drug development
- HealthMeasures may provide an option for potential use in the regulatory setting
- Early communication with the FDA is encouraged

Thank You!

Helpful Links

- FDA's Patient-Reported Outcome (PRO) Guidance for Industry:
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071975.pdf
- DDT Clinical Outcome Assessment Qualification Program webpage:
  - http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm
    - Includes Roadmap diagram
    - Table of current qualification projects (with permission by submitter)
- FDA's DDT Qualification Program Guidance for Industry:
  - http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm230597.pdf


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Back Up Slides

Roadmap to **PATIENT-FOCUSED OUTCOME MEASUREMENT** in Clinical Trials

1 Understanding the Disease or Condition

A. Natural history of the disease or condition
- Onset/Duration/Resolution
- Diagnosis
- Pathophysiology
- Range of manifestations

B. Patient subpopulations
- By severity
- By onset
- By comorbidities
- By phenotype

C. Health care environment
- Treatment alternatives
- Clinical care standards
- Health care system perspective

D. Patient/caregiver perspectives
- Definition of treatment benefit
- Benefit-risk tradeoffs
- Impact of disease

2 Conceptualizing Treatment Benefit

A. Identify concept(s) of interest (COI) for meaningful treatment benefit, i.e., How a patient:
- Survives
- Feels (e.g., symptoms)
- Functions

B. Define context of use (COU) for clinical trial:
- Disease/Condition entry criteria
- Clinical trial design
- Endpoint positioning

C. Select clinical outcome assessment (COA) type:
- Patient-Reported Outcome (PRO)
- Observer-Reported Outcome (ObsRO)
- Clinician-Reported Outcome (ClinRO)
- Performance Outcome (motor, sensory, cognition)

3 Selecting/Developing the Outcome Measure

A. Search for existing COA measuring COI in COU:
- Measure exists
- Measure exists but needs to be modified
- No measure exists
- Measure under development

B. Begin COA development
- Document content validity (qualitative or mixed methods research)
- Evaluate cross-sectional measurement properties (reliability and construct validity)
- Create user manual
- Consider submitting to FDA for COA qualification for use in exploratory studies

C. Complete COA development:
- Document longitudinal measurement properties (construct validity, ability to detect change)
- Document guidelines for interpretation of treatment benefit and relationship to claim
- Update user manual
- Submit to FDA for COA qualification as effectiveness endpoint to support claims

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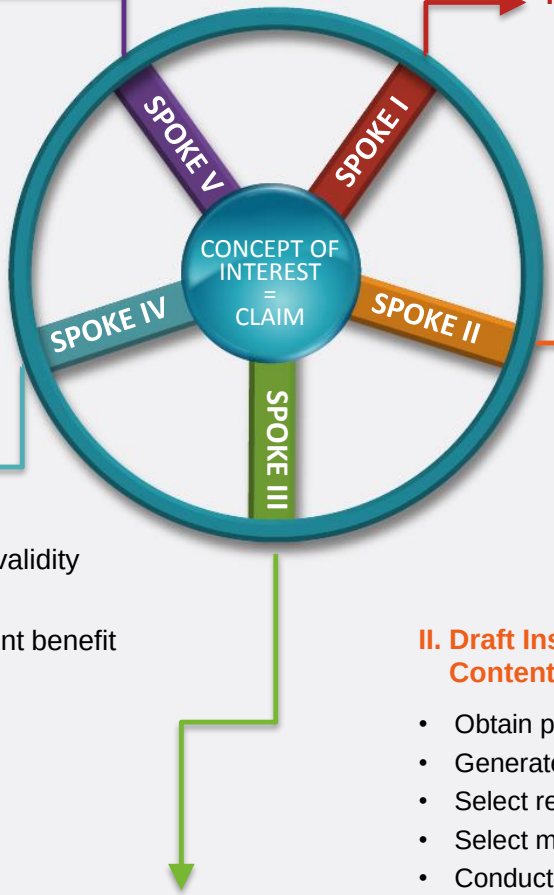
http://www.fda.gov/Drugs

Idiopathic Pulmonary Fibrosis

Natural history **-Rare,** chronic, progressive -Variable progression -Median survival 3 to 5 years	**Treatment benefit goals for which endpoints needed** -Symptoms & signs -Targeted impacts of IPF on patients' lives	**Search for existing PRO measures** -ATAQ-IPF (A Tool to Assess Quality of Life in Idiopathic Pulmonary Fibrosis)
Patient subpopulations -Males > females -5th and 7th decade -Caucasians-predominant -Oxygen use	**Context of use** -Study design and objectives -Subpopulations and stage of disease -Other	**Begin COA development** -ATAQ-IPF modification underway for clinical trial use -Qualitative research and quantitative research in the target patient population with IPF
Health care environment -Unmet therapeutic needs **Patient/caregiver input** -Survival -Disease progression -Symptoms and impact on life	**Select Clinical Outcome Assessment Type** -PRO -ClinRO -ObsRO -Perfo	**Complete COA Development** -Longitudinal evaluation of ability to detect change -Guidelines for interpretation of clinically meaningful change (e.g., responder definition)

Qualification of **CLINICAL OUTCOME ASSESSMENTS** (COAs)



V. Modify Instrument

- Identify a new COU
- Change wording of items, response options, recall period, or mode/method of administration/data collection
- Translate and culturally adapt
- Evaluate modifications using spokes I – IV
- Document all changes

I. Identify Context of Use (COU) and Concept of Interest (COI)

- Outline hypothesized concepts and potential claims
- Determine intended population
- Determine intended application/characteristics (type of scores, mode and frequency of administration)
- Perform literature/expert review
- Develop hypothesized conceptual framework
- Position COA within a preliminary endpoint model
- Document COU and COI

IV. Longitudinal Evaluation of Measurement Properties/ Interpretation Methods

- Assess ability to detect change and construct validity
- Identify responder definition(s)
- Provide guidelines for interpretation of treatment benefit and relationship to claim
- Document all results
- Update user manual

II. Draft Instrument and Evaluate Content Validity

- Obtain patient or other reporter input
- Generate new items
- Select recall period, response options and format
- Select mode/method of administration/data collection
- Conduct cognitive interviewing
- Pilot test draft instrument
- Finalize instrument content, format and scoring rule
- Document content validity

III. Cross-sectional Evaluation of Other Measurement Properties

- Assess score reliability (test-retest or inter-rater) and construct validity
- Establish administration procedures & training materials
- Document measure development
- Prepare user manual

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Updated on February 27, 2017