Session III: Patient-Reported Outcome (PRO) Instruments as Drug Development Tools

Co-Chairs

Stephen Joel Coons, PhD ■ C-Path

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Creating Consensus Science: New Tools and Tactics for Next-Gen Drug Development

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"Measuring Treatment Benefit: Clinical Trial Outcome Assessments in the Evaluation of Medical Products"

Risa Hayes, PhD

Co-Director, PRO Consortium
Lead Scientist for Patient-Reported Outcomes
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"Road Less Traveled: the Pharmaceutical Perspective of the PRO Consortium"

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"Clinical Trial Outcome Assessments (COAs) in the Evaluation of Medical Products in Pediatrics"

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Vice Director, ePRO Consortium
Executive Director ePRO, Oxford Outcomes (ICON)

"ePRO Consortium"

PRO Consortium: Filling Measurement Gaps for PRO Endpoints to Support Labeling Claims

Stephen Joel Coons, PhD

Executive Director, PRO Consortium

Critical Path Institute ■ Tucson, Arizona

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PRO Endpoints in Clinical Trials: A Brief Introduction

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Clinical trial endpoints for assessing treatment benefit include

- Survival
- Biomarkers (e.g., CD4 count, HbA1c)
- Clinical Outcome Assessments
  - Clinician-Reported Outcomes (ClinROs)
  - Observer-Reported Outcomes (ObsROs)
  - **Patient-Reported Outcomes (PROs)**

PRO Endpoints in Clinical Trials

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ClinRO measures and biomarkers account for the majority of efficacy endpoints for FDA-approved products

But…

- For new molecular entities (NMEs) approved by the FDA from 1997 through 2002, PRO endpoints were included in 30% (64/215) of product labels reviewed (Willke et al. 2004)

- Data regarding NMEs and biologic license applications approved between January 2006 and December 2010 show that 24.1% (28/116) of the products had PRO endpoints in their labeling (Mordin et al. 2011)

PRO Endpoints in Clinical Trials

(Willke et al. 2004)

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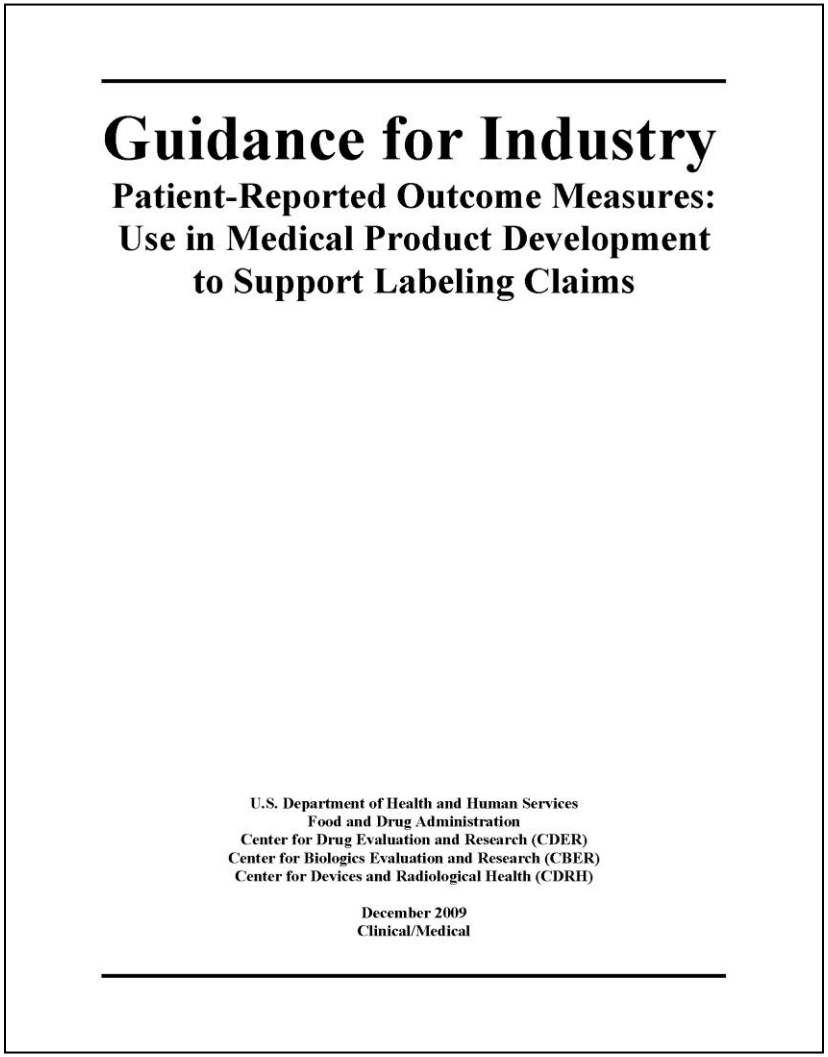
Examples

- Pain (e.g., severity, frequency, time to relief)
- Seizure frequency
- Urination and incontinence episodes
- Itching (i.e., ocular)
- Dry mouth symptoms
- Stool frequency and consistency
- Sexual function
- Time to flu symptom relief
- Nausea and/or vomiting

FDA PRO Guidance



Guidance for Industry

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

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2009
Clinical/Medical

- Clear acknowledgement of the importance of appropriately and effectively incorporating the patient's voice into the evaluation of medical products
- Draft: February 2006
- Final: December 2009

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM205269.pdf

FDA PRO Guidance

- Describes how the FDA plans to evaluate PRO (and ClinRO and ObsRO) instruments used as efficacy endpoints in clinical trials.

- PRO assessment is "… a measurement of any aspect of a patient's health status that comes directly from the patient (i.e., without the interpretation of the patient's responses by a physician or anyone else)."

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM205269.pdf

FDA Drug Development Tool (DDT) Guidance

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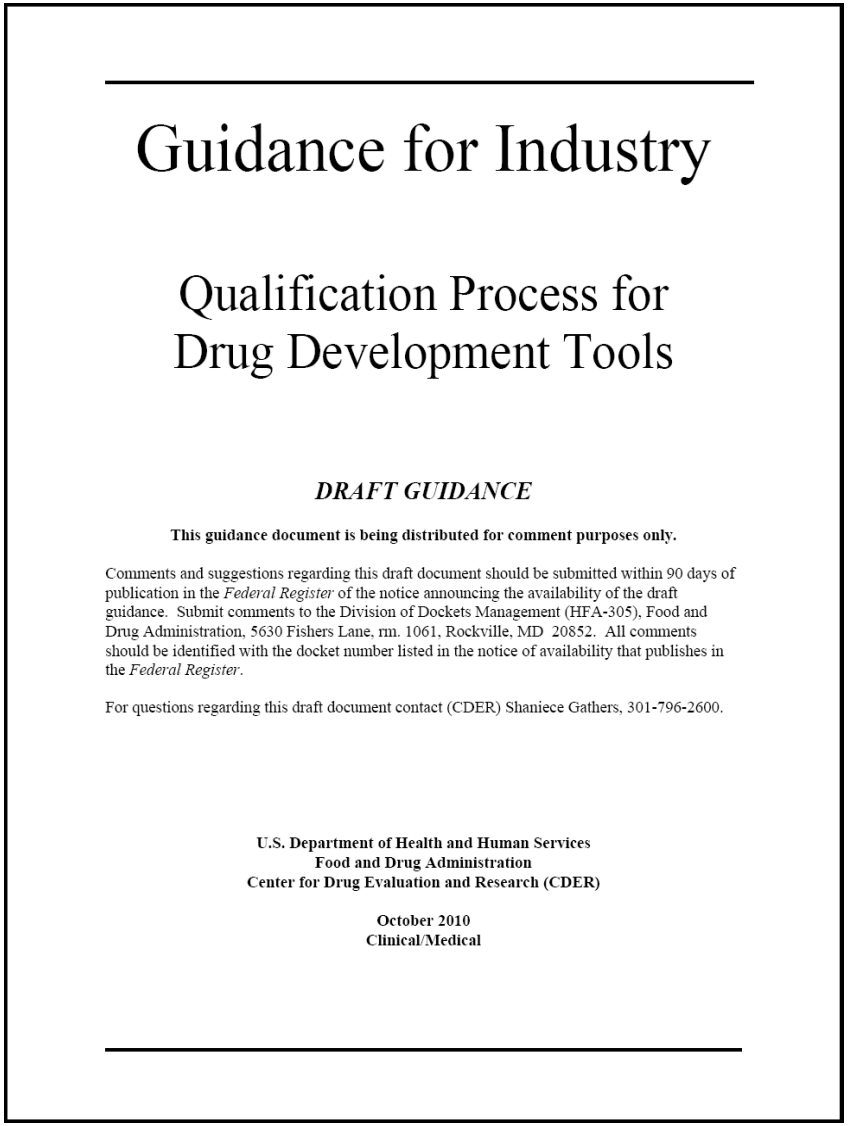

Guidance for Industry

Qualification Process for Drug Development Tools

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Shaniece Gathers, 301-796-2600.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2010
Clinical/Medical

- Draft version currently available (October 2010)
- Final version coming soon; no major changes expected; will clarify of the process
- Describes the DDT qualification process

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf

FDA Drug Development Tool (DDT) Guidance

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"Because of the substantial work needed to achieve qualification, CDER encourages the formation of collaborative groups to undertake these tool-development programs to increase the efficiency of joint efforts and to lessen the resource burden upon any individual person or company working to gain qualification for a tool."

PRO Consortium

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- Formed in 2008 by C-Path, in cooperation with the FDA and the pharmaceutical industry
- The consortium's mission is to develop PRO instruments for use in clinical trials where PRO endpoints are used to support product labeling claims.

Goals

- Enable pre-competitive collaboration that includes FDA input/expertise
- Develop qualified, publicly available PRO instruments
- Avoid development of multiple PRO instruments for the same purpose
- Share costs of developing new PRO instruments
- Facilitate FDA's review of medical products by standardizing PRO endpoints

PRO Consortium

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- **Membership**

  Only available to medical product (pharmaceutical, diagnostic, and device) companies

- **Non-Voting Participants**
  - Representatives of governmental agencies
  - Clinical consultants, patient advocates, academic researchers, and CROs partnering in the development of the PRO instruments

Membership Fees

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Used for

- Meeting and teleconference costs
- Legal/IP expenses
- Data storage and maintenance
- Some C-Path travel expenses

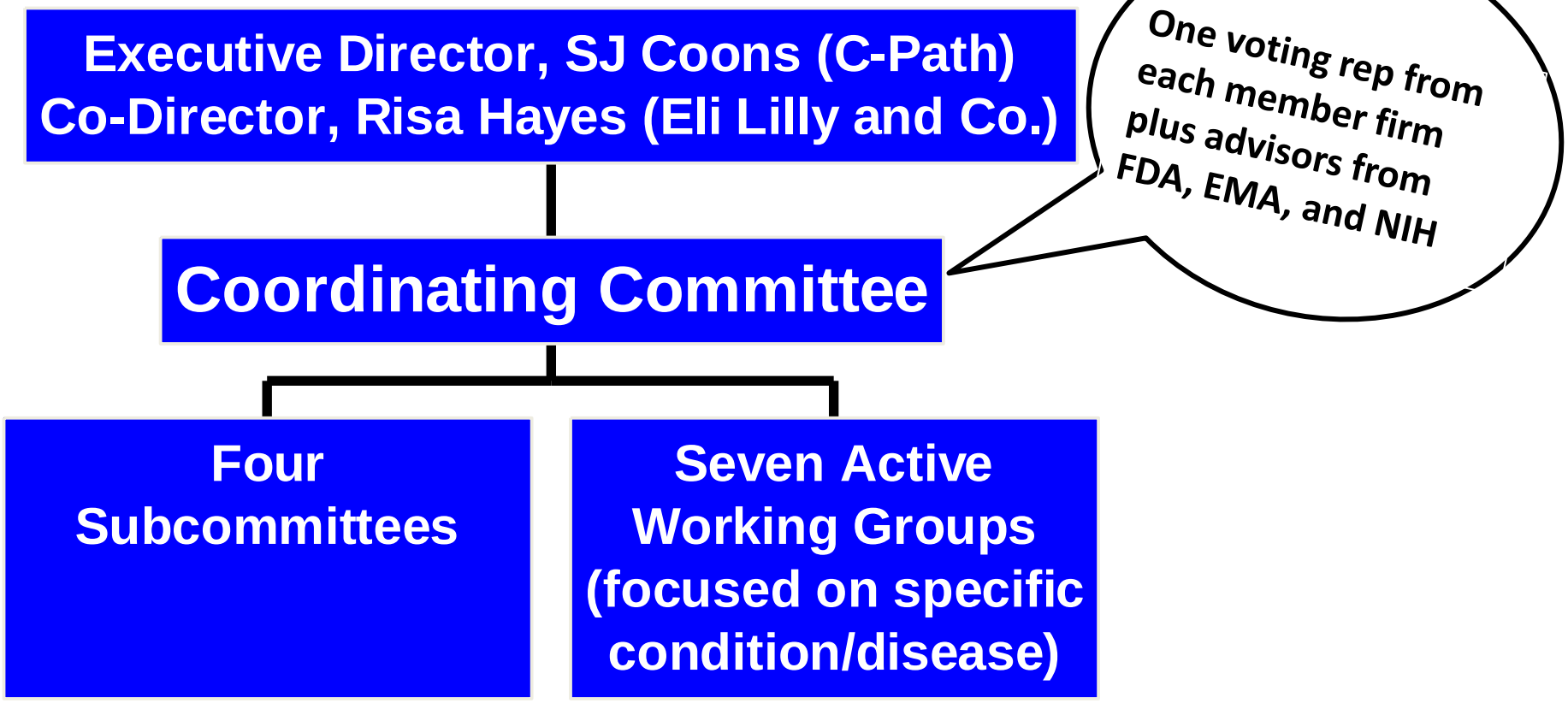
Not used for

- Salaries for C-Path personnel
- C-Path operations/management
- PRO instrument development costs

Members

- Abbott
- Actelion Pharmaceuticals
- Allergan
- Amgen
- Astellas Pharma
- AstraZeneca
- Boehringer Ingelheim
- Bristol-Myers Squibb
- Daiichi Sankyo
- Eisai
- Eli Lilly & Company
- Forest Laboratories
- GlaxoSmithKline
- Ironwood Pharmaceuticals
- Johnson & Johnson
- Merck Sharp & Dohme Corp.
- Novartis
- Novo Nordisk
- Pfizer
- Roche
- sanofi-aventis
- Shire
- Sunovion
- Takeda Pharmaceuticals
- UCB

Governance



Over 150 scientists and/or clinicians participate

Working Groups

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Rheumatoid Arthritis

Functional Dyspepsia

Lung Cancer (NSCLC)

Asthma

Depression

Cognition (mild cognitive impairment)

Irritable Bowel Syndrome

PRO Instrument Qualification

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Has the potential to

- Increase number of accepted PRO measures used to support claims in product labeling
- Enhance comparability/consistency of endpoints across clinical trial
- Improve efficiency for sponsors in endpoint selection
- Improve product labeling

Summary

- PRO measures are often the best—or even the only—means to capture direct evidence of treatment benefit in clinical trials.
- The development and qualification of standardized measures of key PRO concepts for use in clinical trials is a very worthy goal.
- A process for collaborative, pre-competitive PRO instrument development has been established within the PRO Consortium.

For more information

CRITICAL PATH INSTITUTE

In your folder

- Coons SJ, Kothari S, Monz BU, Burke LB. The Patient-Reported Outcome (PRO) Consortium: filling measurement gaps for PRO endpoints to support labeling claims. *Clinical Pharmacology & Therapeutics* 2011;90:743-748.

- sjcoons@c-path.org

Measuring Treatment Benefit:
Clinical Trial Outcome Assessments in the Evaluation of Medical Products

Critical Path Institute Conference
Silver Spring -- November 30, 2011

Laurie Beth Burke
Director, Study Endpoints and Labeling Development Staff
Office of New Drugs
CDER-FDA

The views expressed are those of the author, and do not necessarily represent an official FDA position

Treatment Benefit

- The impact of treatment on how patients survive, feel, or function in their daily lives
  - Assessed as effectiveness or comparative safety
  - Assessment tools must be well-defined and reliable
- Can be assessed directly (ex: symptoms)
- Can be assessed indirectly (ex: biomarker)
- Described in labeling as a claim using words that represent the concept measured
- Labeling must not be false or misleading.

Types of Clinical Trial Outcome Assessment for Measuring Treatment Benefit

- Clinical Outcome Assessments (COAs)
  - "Reported" assessments (influenced by human choices, judgment, cooperation or motivation)
    - Patient reported outcome assessments (PROs)
    - Clinician reported outcome assessments (ClinROs)
    - Observer reported outcome assessments (ObsROs)
- Biomarkers (not influenced by humans)
- Survival

FDA Review of COAs

- Two processes for FDA submission and review
  - As part of a drug application (IND/NDA/BLA) review
  - Under the DDT qualification process
- COA
  - Identify the measurement concepts
  - Indentify the context of use
    - Primary or secondary endpoints?
    - Disease definition and trial inclusion criteria
    - Trial design and endpoint model
    - Other

Qualification

For COAs, FDA qualification represents a conclusion that within the stated context of use, the results of assessment can be relied upon to measure a specific concept and have a specific interpretation and application in drug development and regulatory decision-making and labeling

DDT COA Qualification Program

- A <u>novel and voluntary</u> submission process for drug development tools (DDTs), intended for potential use, over time, in multiple drug development programs
- Goal: **Publicly available DDTs!**
  - Publication in the Federal Register
  - Publication in the FDA DDT website
- Builds on developing public-private partnerships between FDA and consortia representing medical product industry, instrument developers, NIH, and academia

COA Qualification Process

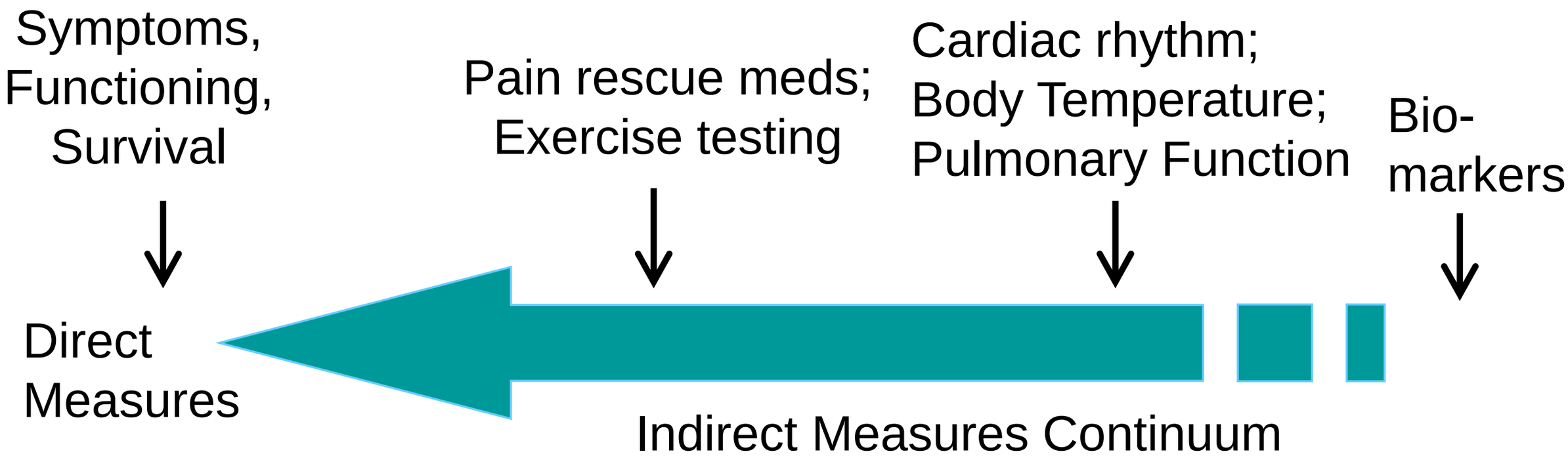
Target context of use and assessment concept(s) Ø Methods & Results Sharing Ø Dossier Submission; FDA Review Ø DDT Publicly Available

Planning Phase

FDA Consultation & Advice | FDA Review | Statement of Qualification

FDA review and comment on qualitative and quantitative draft protocols and instrument

All Indirect Measures Are Not Created Equal in Terms of Outcome Replacement Value



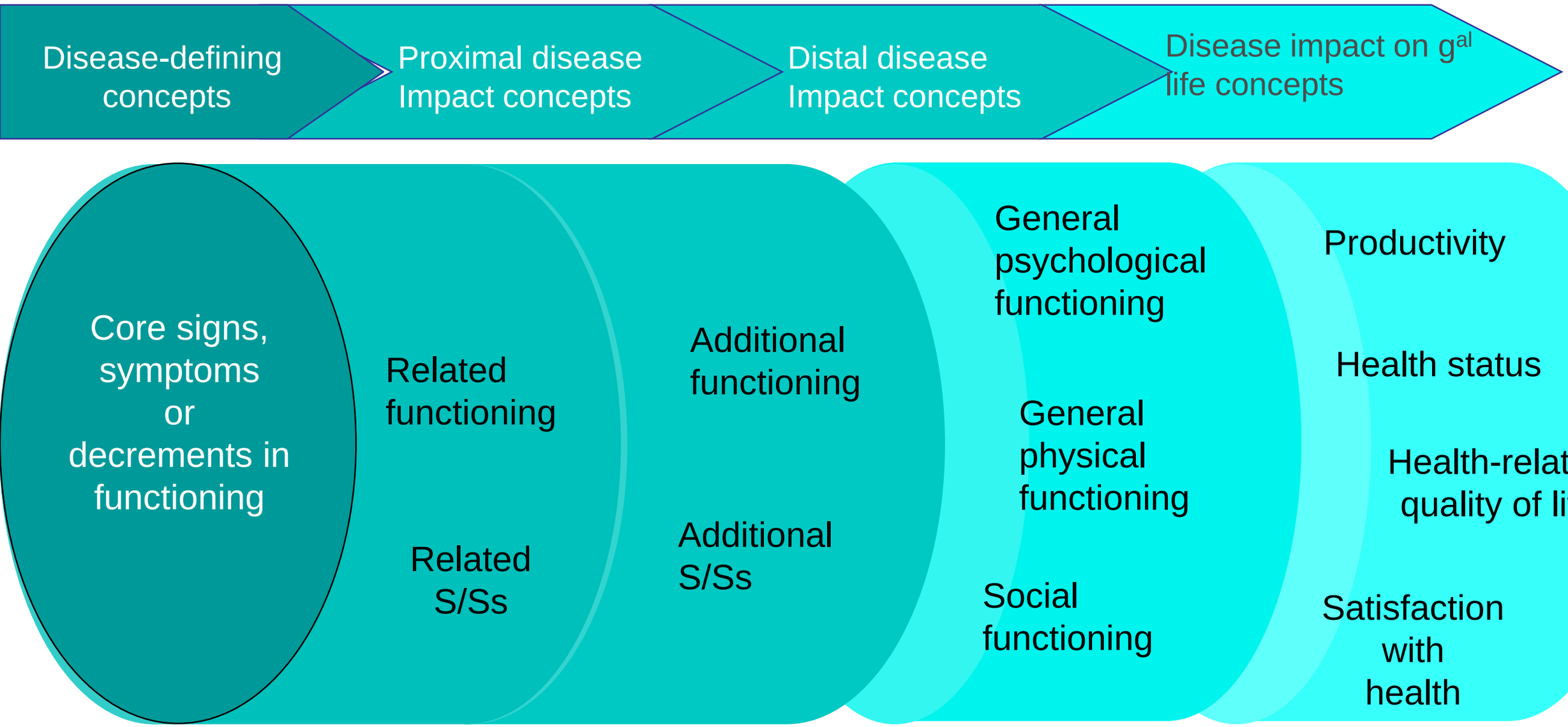
Indirect assessment needs empiric justification for replacement value and relationship to how patients survive, feel or function

U.S. Food and Drug Administration
Protecting and Promoting Public Health

www.fda.gov

Direct Treatment Benefit: What To Measure?

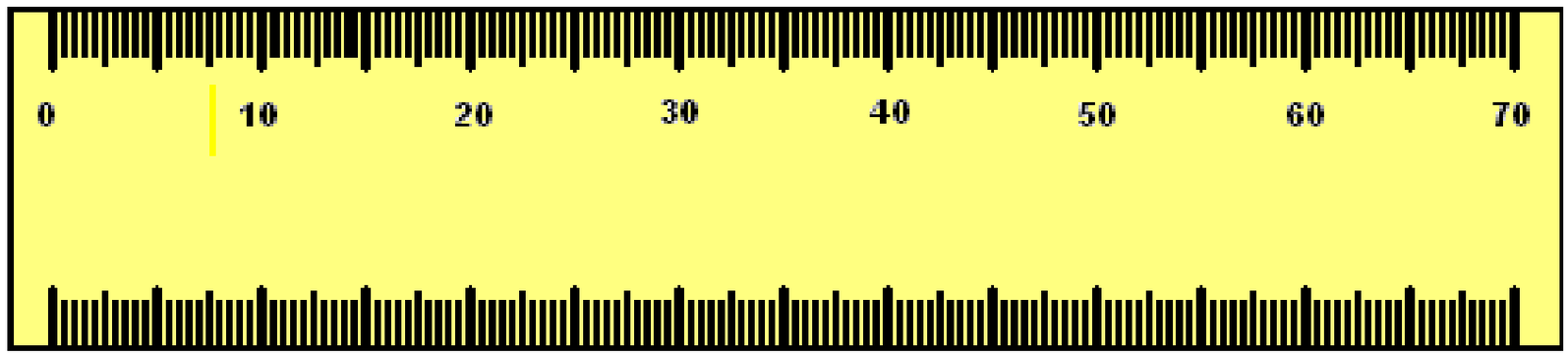
All is important, but interpretation of trial results depends on knowing how treatment impacts the core disease-defining concepts first.



Scale Development Must Address Two Major Uncertainties

What is the concept (definition of the variable) ?

How is it best articulated with “words” ?



Hobart J, COA workshop, Oct 19 2011

Establishing Content Validity: New COA Development or Review of Existing COA

- Begins after confirmation that the concept and the context of use are appropriate
- Empiric evidence that the instrument measures the targeted concept in the context of use
  - If existing instrument is used for a new context of use, additional content validity evidence may need to be developed
- Content validity must be established before other evidence of construct validity, reliability or sensitivity to change can be interpreted
  - Problem: For older measures, content validity documentation is often unavailable

Evolving Methods to Establish Content Validity

- Literature review
- Expert opinion
- Qualitative Research: Critical
  - Input from target responder population to document understandability and comprehensiveness
    - PRO: target population of patients
    - ObsRO: target population of respondents
    - ClinRO: target population of clinicians
- Quantitative Analyses (Rasch, IRT)
  - Recommended for efficiency in instrument development

Iterative Approach to Document Content Validity

- Rasch/IRT graphical displays can
  - Illustrate whether the measurement ruler for a given concept in a given context of use has been created successfully
  - Evaluate the degree of overlap between the response options and uniqueness of information provided by response options
- The order and importance of items needs to agree with qualitative research and clinical expectations
- Does not eliminate the need for high quality cognitive debriefing of the final instrument in the relevant respondent population.

In Closing…

- Focus on content validity for COA development is meant to drive development of better information for patients and to increase innovation and efficiency in drug development.
- Good measurement science deserves the same level of support and rigorous standards development as any other area of science.
- Patients who are contemplating the use of a new treatment need to know its possible impact on how they will feel and function in their daily lives.

In press….

- Patrick DL, Burke LB, Gwaltney CJ, Kline Leidy N, Martin ML, Molsen E, Ring L. Content Validity—Establishing and Reporting the Evidence in Newly Developed Patient-Reported Outcomes (PRO) Instruments for Medical Product Evaluation: ISPOR PROGood Research Practices Task Force Report: Part 1—Eliciting Concepts for a New PRO Instrument. Available on ISPOR website and targeted for December 2011 issue of Value in Health.
- Patrick DL, Burke LB, Gwaltney CJ, Kline Leidy N, Martin ML, Molsen E, Ring L.Content Validity—Establishing and Reporting the Evidence in Newly Developed Patient-Reported Outcomes (PRO) Instruments for Medical Product Evaluation: ISPOR PROGood Research Practices Task Force Report: Part II—Assessing Respondent Understanding. Availabale on ISPOR website and targeted for December 2011 issues of Value in Health.
- Magasi S, Ryan G, Revicki D, Lenderking W, Hays RD, Brod M, Snyder C, Boers M, Cella D. Content Validity of Patient-Reported Measures: Perspective from a PROMIS Meeting . Article in Press in Qual Life Res.

Road Less Traveled: the Pharmaceutical Perspective of the PRO Consortium

Risa Hayes, PhD
Creating Consensus Science
November 30, 2011

PRO Instrument Development

Two roads diverged in a yellow wood,

Individual company process?

DDT Qualification process?

Road Not Taken by Robert Frost

PRO Development Resources: Monetary

Literature review	$ 50,000 - $ 150,000
Expert consulting/panel	$ 25,000 - $ 100,000
Qualitative study	$150,000 - $ 300,000
Items/Cognitive interviewing	$150,000 - $ 200,000
Quantitative study	$100,000 - $ 900,000
Document development	$100,000 - $ 200,000
Dossier development	$150,000 - $ 300,000
	$725,000 - $2,150,000

PRO Consortium:

Costs (monetary) of PRO development is divided equally among working group members.

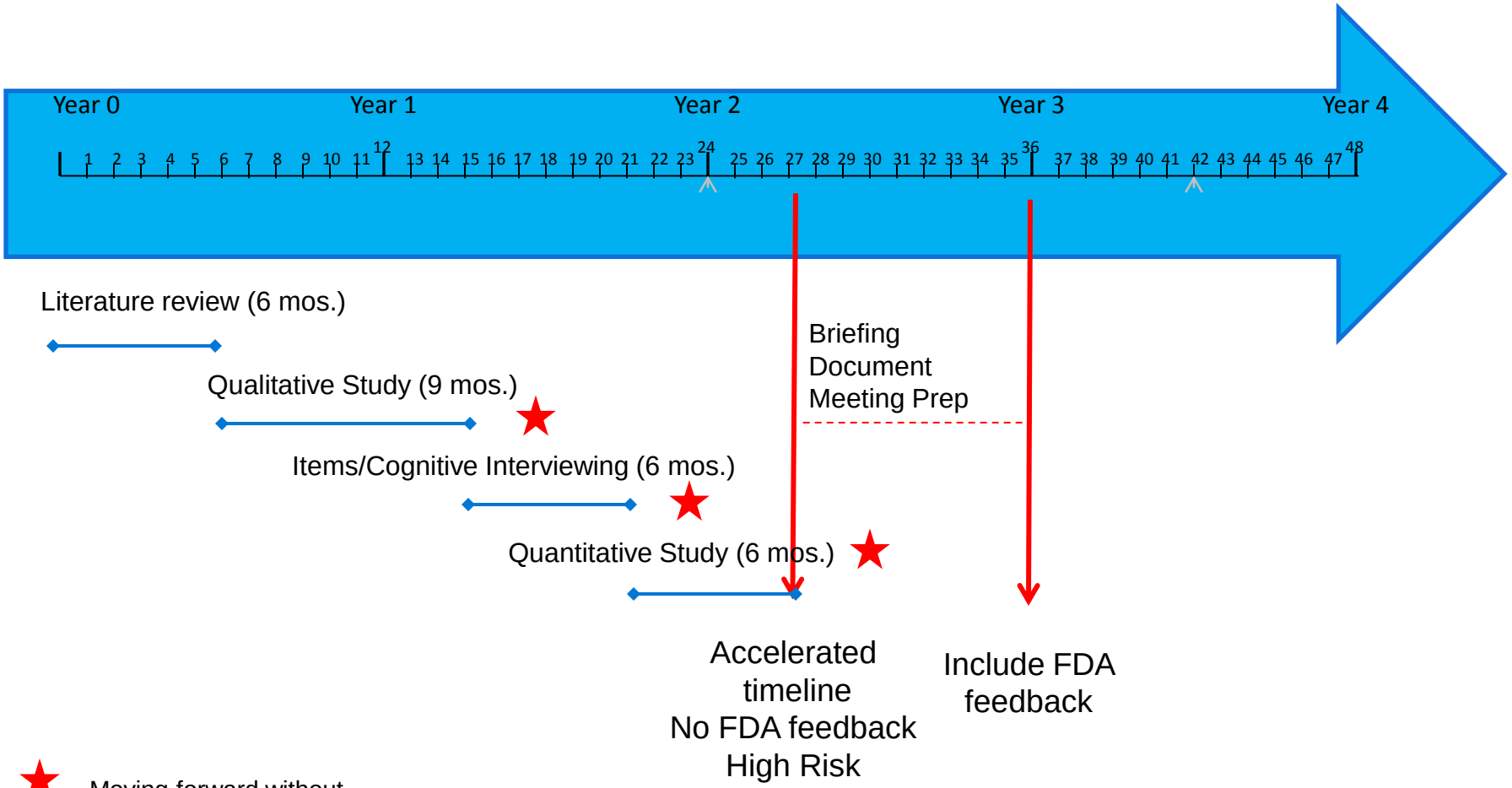
PRO Development Resources: Human

- Medical
- Regulatory
- Health Outcomes
- Statistics
- Project Management
- Medical Writing
- Marketing

PRO Consortium:

Costs (human) of PRO development is divided among working group members.

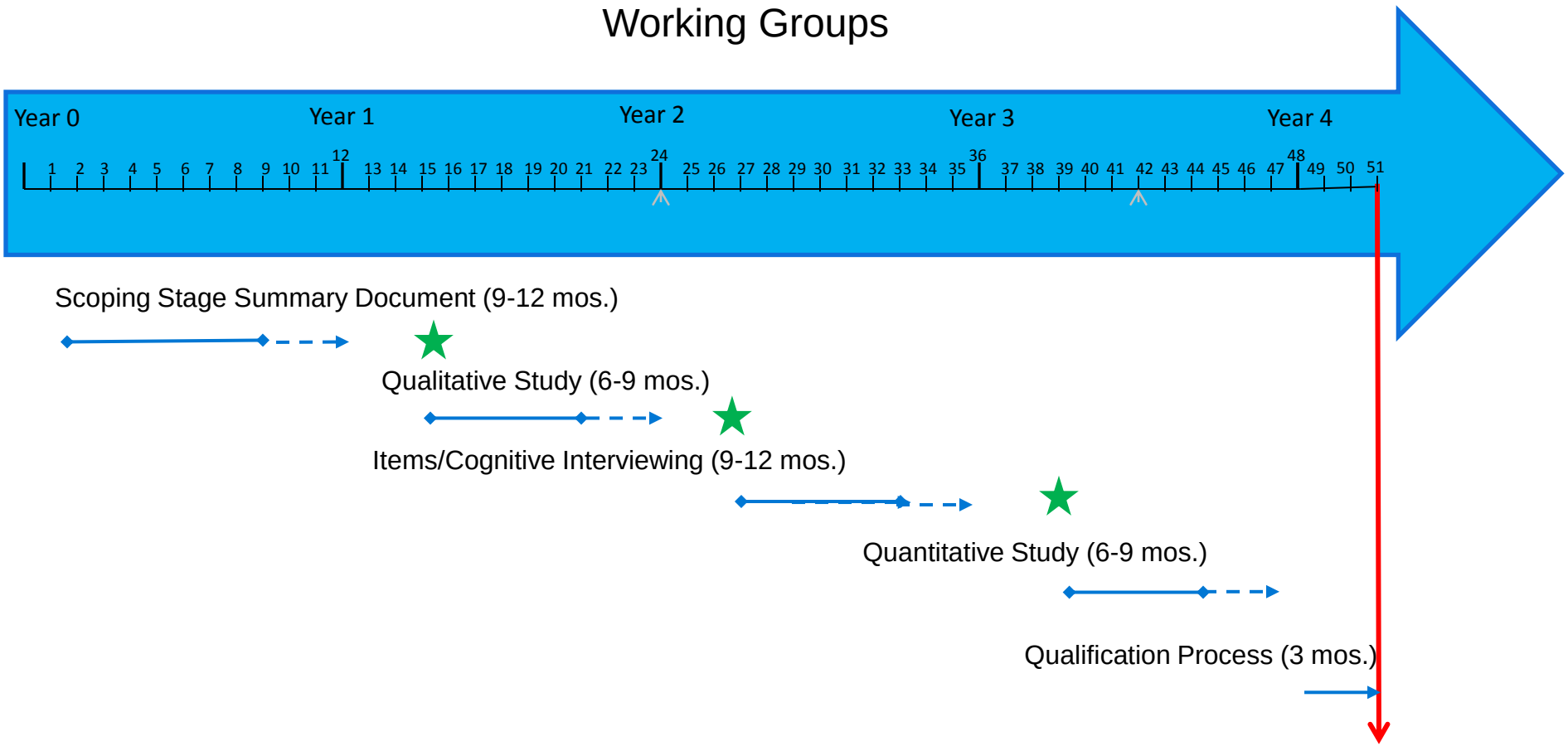
PRO Development Timeline: Hypothetical Individual Company Timeline



★ Moving forward without feedback at one or all of these points is moving forward "at risk."

Will PRO instrument be acceptable to support labeling?

PRO Development Timeline: Examples for DDT Qualification



Summary

I shall be telling this with a sigh
Somewhere ages and ages hence:
Two roads diverged in a wood, and I—
I took the one less traveled by,
And that has made all the difference.

Road Not Taken by Robert Frost

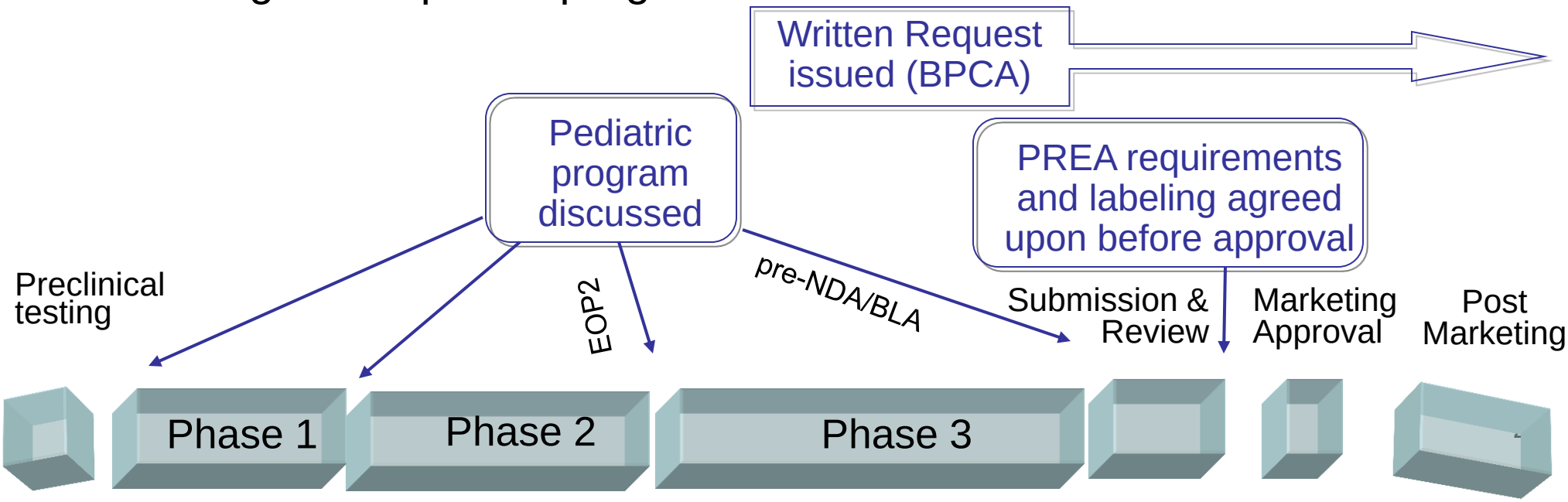
Clinical Trial Outcome Assessments (COAs) in the Evaluation of Medical Products in Pediatrics

Elektra Johanna Papadopoulos
Medical Officer for Study Endpoints and Labeling (SEALD)
Study Endpoints Team
Office of New Drugs
CDER-FDA

The views expressed are those of the author, and do not necessarily represent an official FDA position

Pediatric Planning in Drug Development

- PREA requires a pediatric assessment (data to support dosing, efficacy and safety in the appropriate age group) at the time of NDA/BLA submission unless the requirement is waived, deferred or inapplicable
- Adequate endpoint measures should be selected/developed early in the drug development program



Challenges with COAs in Pediatrics

- Disease manifestations
  - Are the signs and symptoms in children similar to those of adults?
  - What are the expected treatment benefits in each age group?
- Rapidly changing and variable child development
  - Can patients report for themselves?
  - Are patients willing to discuss and report their symptoms?

Endpoint Selection

Step 1: Define disease population

Step 2: Define context of use

Step 3: Select concept(s) of measurement that will define treatment benefit

Step 4: Select or develop well-defined and reliable outcome assessments to measure each concept for the proposed context of use

Observable

No Clinical Judgment

Self-report?

No → **ObsRO**

Yes → **PRO**

Clinical Judgment → **ClinRO**

Non-Observable → **PRO**

Physiologic or lab findings that can be measured without human assessment → **Biomarker**

Principles of Clinical Outcome Assessment in Pediatrics

- Self-report of symptoms and impacts provides ***direct*** evidence of treatment benefit and should be used when possible

- Verifiable observation of signs and behaviors provides ***indirect*** evidence of treatment benefit;
  - Use ***verifiable*** report of observable concepts when self-report not possible

Verifiable Observation

- A sign or impact must be detectable by a sense or senses:
  - Seen (*vision*)
  - Heard (*auditory*)
  - Smelled (*olfactory*)
  - Felt (*touch*)

Cut-Off Age for Self-Report?

- No established guidelines; affected by concreteness of reported concept
  - Age 7 years: Often cited as bottom of age range
  - Ages 7 to 11 years: Mixed validity & reliability results such that combination of self- and observer-report may be best
  - Age 11+ years: Generally acceptable psychometrically
- Consideration of age alone is generally inadequate; consideration of inter-individual variability in comprehension & willingness/motivation to respond is also needed

Adapted from Todd Edwards, Donald Patrick, COA workshop, Oct 19 2011

Translating Patient-Experienced Concepts to Clinician and Observer Assessments

- Observers (clinicians and non-clinician observers) introduce an additional element of uncertainty into measurement
- Validity (the degree to which intermediaries' observations reflect concept of interest and its variability) cannot be assumed
  - For instance, observable signs of distress in infants with acute otitis media are generally non-specific to the disease of interest
- Reliability of measurement also cannot be assumed

Adapted from Nathaniel Katz, COA Workshop, Oct 19 2011

Validity of Assessment

- Content validity in context of use is paramount
  - OBsROs and ClinROs: Qualitative research with responders with appropriate knowledge of the target patient population is indispensable
  - PROs: Qualitative research with targeted patient population is needed to ensure developmental appropriateness of measurement
  - Similar principles for instrument development apply for ClinROs and OBsROs as for PROs

Select or Develop COA Carefully

- Consider outcome measures that are well-defined and limited in scope
  - Concept of measurement: “disease-defining symptoms” vs. “health-related quality of life”
  - Short recall period
  - Simple recall task (worst symptoms vs. weekly average)
- Differentiate between observable vs. non-observable concepts
  - “Pain” vs. “fussy/crying/withdrawn/sleepy”
- Different concerns in children from a similar diagnosis in adults
  - Modification from adult scales needs to take into account specific phase of children’s development and disease-related concerns
- Application of a tool across contexts of use often requires additional evidence to document content validity (e.g., concept elicitation or cognitive interviews)

Planning for Pediatric Measurement

- Start planning early
  - Consider a collaborative approach under the DDT qualification process
- Establish the operational disease definition
- Define the concept of measurement based on an understanding of the disease expression in the target patient population
- Consider the context of use
- Establish an age appropriate measurement strategy (different modules are often needed)
- Develop or select the instruments and document content validity
- Pilot test the instruments (e.g., in phase 2 or observational studies)

Summary

- Well-defined and reliable COAs for documenting treatment benefit in children are urgently needed in many therapeutic areas
- Early planning for pediatric assessment in the drug development process is critical to meet challenges associated with outcome measurement in children
- The DDT qualification process provides a framework for collaboration in COA development to meet unmet measurement needs

Acknowledgements

SEALD, OND, CDER

- CAPT Laurie Burke
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- Dr. Rosemary Addy

ePRO Consortium

Willie Muehlhausen

Vice Director, ePRO Consortium
Executive Director ePRO, Oxford Outcomes (ICON)

Agenda

- Who is involved?
- What are we trying to achieve?
- Who benefits?
- Where are we today?
- Vision 2020

Who is involved?

- Currently 6 ePRO vendors
  (Almac, CRF, ERT, ICON, invivodata, PHT)
- Handheld, IVRS, Web (IWRS), Tablet, digital Pen

- Coordinating Committee
- Subcommittee Instrument Migration

What are we trying to achieve?

- Shorten setup times
- Reduce cost
- Add value to the (e)PRO development process
- Reduce ambiguities, find answers to open questions

Standardisation

How will we achieve this?

Existing instruments:

- Determine the “validation status“ of each instrument
  - What work has been done to show equivalence?
  - What has been published?
  - What can we publish and where can we publish?
- Preparing a presentation for a wider audience
- Prioritising instruments with PRO Consortium

How will we achieve this?

New instruments:

- Develop recommendations about user interface
- Define migration guidelines
- Establish certification process
- Support instrument development projects
  - PRO Consortium
  - Other instrument developers

What are the benefits?

Developers:

- Standardised representation independant of vendor platform
- Wider distribution via many vendors

Pharma:

- Complete “package“ will be delivered
- Translations will only be done/paid for once
- Assurance that quality will be maintained

Vendor

- Easier access and less resources needed for setup
- Market as such will grow faster via a faster adoption

Where are we in the process?

- Common understanding of what is needed and are prioritising tasks
- List of most common instruments among us vendors
- Contacted several instrument developers and organisations to work with them through our process
- Developed Guidelines around Migration and Development of ePRO (early drafts)

Vision 2020

- Established accepted processes and best practices
- Clearinghouse for ePRO instruments
- Publicly available database with
  - Instruments
  - Supporting documentation
  - Available translations
- Shorter Setup times