Novel Endpoints: A Regulatory Perspective

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Elektra J. Papadopoulos, MD, MPH
Division of Clinical Outcome Assessment
Office of New Drugs
Center for Drug Evaluation and Research, FDA

Disclaimer

- Views expressed in this presentation are those of the speaker and do not necessarily represent an official FDA position.

Overview

- Background and terminology
- Evidentiary Framework
- Examples

Patient-Focused Outcomes

"Those outcomes important to patients' survival, function, or feelings as identified or affirmed by patients themselves, or judged to be in patients' best interest by providers and caregivers when patients cannot report for themselves."

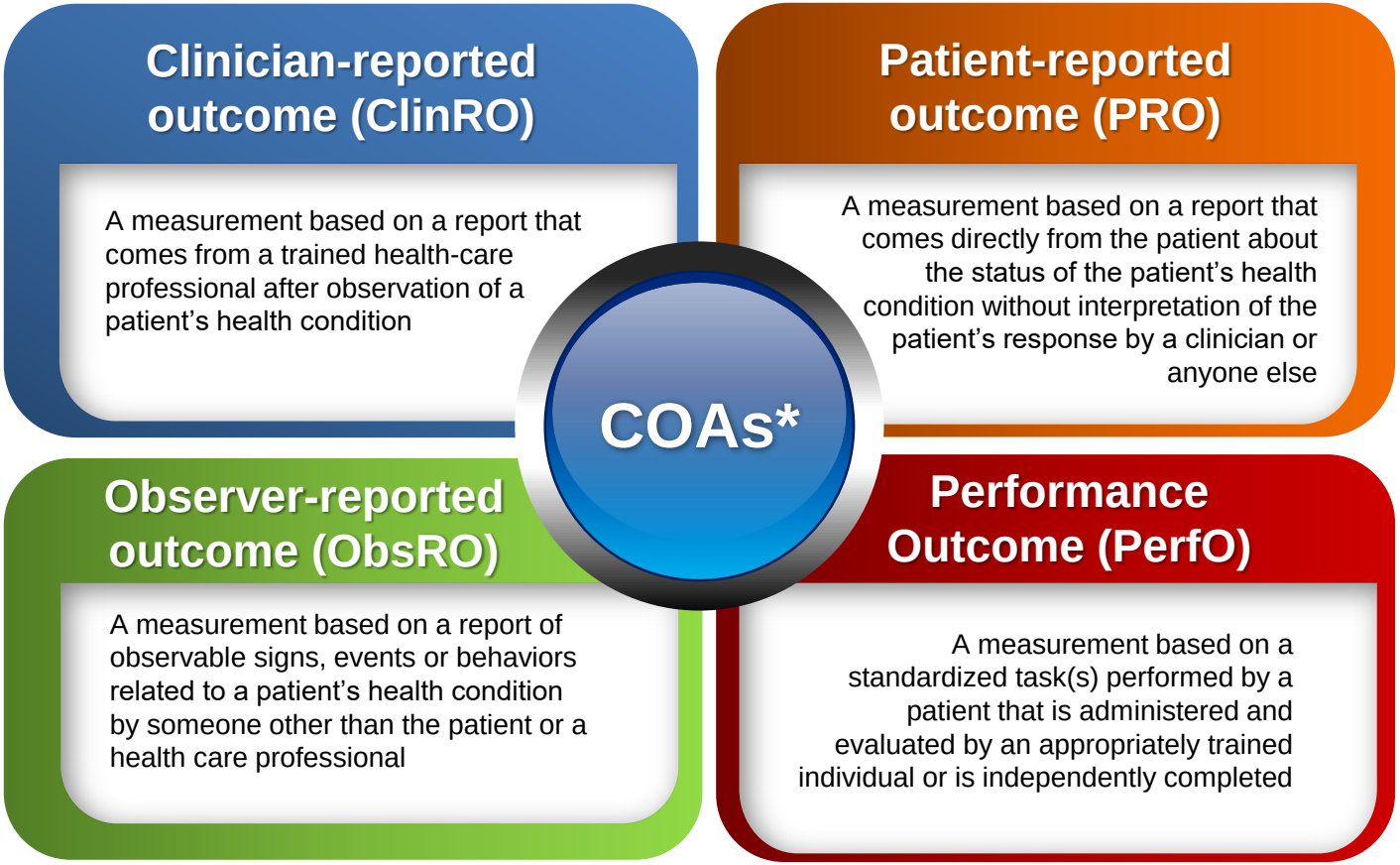
Donald L. Patrick, Ph.D., MSPH
May 20, 2013

Clinical Benefit

- 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

- **Clinical outcome:** An outcome that describes or reflects how an individual feels, functions or survives
  - Assessed using clinical outcome assessments (COAs)

Clinical Outcome Assessments



***Digital health technology tools (DHHTs)--including activity monitors and sleep monitors--can also be used to collect clinical outcomes.**

Digital health technology tools*

- Electronic technology tool, its score(s), and the interpretation of its scores that are intended for use in clinical investigations
- DHTTs can capture data:
  - Passively (e.g., through accelerometers, cardiac rhythm monitors) or
  - Actively e.g., through patient responses or tasks

*Dashiell-Aje E, Kovas S, Sacks L, 2019

Why Digital Health Technology Tools?

- We're interested in using existing or emerging technologies to help us:
  - measure traditional efficacy endpoints more accurately or reliably or
  - measure meaningful endpoints that were not previously feasible or easy to assess

Some potential impacts of endpoints collected via remote data capture

- Enhancement of endpoints that matter to patients in daily life (e.g., information of patients' experiences between clinic visits)
- Reduced participation burden/fewer barriers to clinical trial participation (e.g., travel)
- Larger, more inclusive, and more generalizable trials (including the possibility of decentralized clinical trials)

Adapted from: Clinical Trials Transformation Initiative's Mobile Clinical Trials – Novel Endpoints Project

FDA's Comprehensive Effort to Advance New Innovations: Initiatives to Modernize for Innovation

August 29, 2018

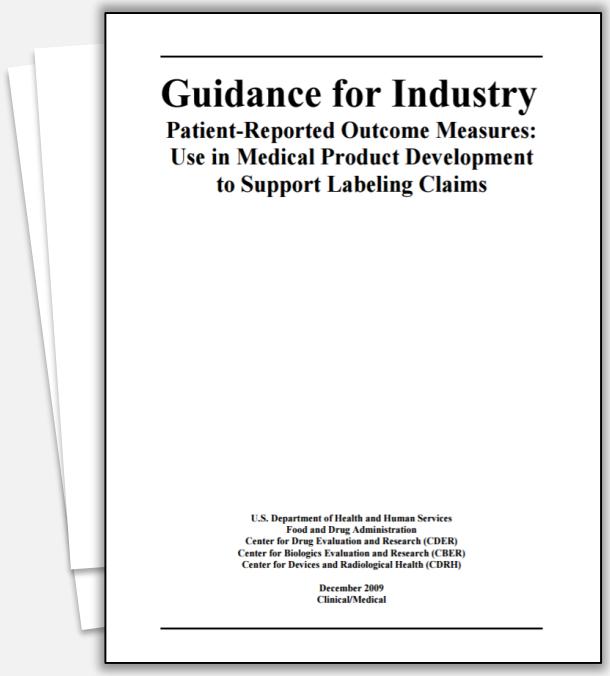
By: Scott Gottlieb, M.D.

- *"Electronic capture of PRO data (ePRO) is also becoming standard, providing a rich pipeline of structured clinical data.*
- *...mobile wearable technologies can complement traditional PRO surveys by generating objective, continuous activity and physiologic data.*
- *Obtaining reliable wearable device data on activity level, coupled with direct patient report on their ability to carry out important day to day activities, can provide information on physical function that is directly relevant and important…."*

https://www.fda.gov/NewsEvents/Newsroom/FDAVoices/ucm619119.htm

Evidentiary framework

FDA PRO Guidance (2009)



- Defines ***good measurement principles*** to consider for "***well-defined and reliable***" (21 CFR 314.126) PRO measures intended to provide evidence of clinical benefit
  - Content validity
  - Reliability
  - Construct validity
  - Ability to detect change (interpretation of change)
- All clinical outcome assessments can benefit from the good measurement principles described within the guidance

Highlights of 21st Century Cures and PDUFA VI

- 21st Century Cures and PDUFA VI increasingly places FDA as an *active participant* in drug development, broadening our traditional regulatory role

- Requires expanded efforts to enhance drug development including but not limited to:
  - Patient-focused drug development: collect / analyze patient experience, to use in designing drug development programs (endpoints), and in regulatory decision making (endpoints and risk/benefit considerations)
  - Drug development tools—biomarkers and COAs

Patient-Focused Drug Development Guidance Series Overview

- Guidance 1: Identifying research questions and developing a sampling strategy to collect representative patient input; operationalizing data collection, management and analysis *(draft June 2018)*
- Guidance 2: Methods to elicit detailed, unbiased, and comprehensive input from patients, patient groups, and caregivers *(draft September 2019)*
- Guidance 3: Using patient input to develop or identify appropriate COAs for use in clinical trials
- Guidance 4: Developing COA-related clinical trial endpoints based upon patient input; interpreting those endpoints

Fit-for-purpose

- For medical product development tools, fit-for-purpose is a conclusion that the level of validation associated with a tool is sufficient to support its context of use

*BEST (Biomarkers, EndpointS, and other Tools) Resource
https://www.ncbi.nlm.nih.gov/books/NBK338448/

What makes a COA "fit-for-purpose" for medical product development?

- Appropriate for its intended use e.g.,
  - Study design
  - Patient population
- Validly and reliably measure a concept that is
  - Clinically relevant
  - Important to patients and able to be impacted with treatment
- Can be communicated in labeling in a way that is accurate, interpretable, and not misleading (i.e., well-defined)*

* If the COA is appropriately applied in medical product development

Digital health technology tools: Regulatory considerations for clinical outcome assessment

- Evidentiary considerations--broadly similar to other types of outcome measures
  - Is the assessment is ***well-defined*** and ***reliable****?*
  - Does the endpoint score represents something meaningful to patients?
  - How much within-patient change in score/variable makes a difference in patients' lives?
- For continuous monitoring, defining meaningful endpoints can be challenging given the potential for large amounts of data
- Feasibility and usability

Key DHTT Design, Implementation, and Analysis Considerations

Instrumentation and Instrument Validation

- Device model and manufacturer
- Documentation of instrument validation

Data Collection

- Data collection environment
- Duration of data collection period
- Days of the week for monitoring

Variable Selection and Endpoint Definition

- Concept to be assessed
- Clear definitions of selected variables
- Well-defined, reliable, and clinically meaningful endpoint(s)

Data Processing, Scoring, and Analysis

- Data file preparation and transfer
- Decisions regarding time interval setting (daily diary, episodic event occurrence)
- Scoring criteria
- Missing data rules
- Clinically meaningful within-patient change

Examples

FDA's DDT Qualification Program: DHHTs using activity monitors

- Letter of intent stage
  - Congestive heart failure (2019)-
  - Duchenne Muscular Dystrophy
  - Multiple sclerosis
  - Musculoskeletal pain in patients with knee osteoarthritis
  - Sarcopenia in patients following surgical treatment of hip fracture
- Note: Many of these disease areas have multiple tools in the COA QP including patient-reported outcome assessments and other COA types

https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/clinical-outcome-assessments-coa-qualification-submissions

Activity monitors- Common review considerations

- Patient and expert input to identify the relevant and important physical activity parameter(s) (e.g., step count, walking speed)
- Accuracy and precision of the device to capture the chosen physical activity parameter
- How data will be aggregated, processed, and analyzed
  - Includes scoring criteria (e.g., algorithms and handling missing data)
- Guidelines for how to interpret within-patient change; What is meaningful?; What normative data exists or could be developed to aid interpretation?
- Instructions/training for patients and investigators; Includes how to ensure the data are attributable to the patient
- How to capture and address non-compliance with wearing the device and loss/malfunction of the device
- Others

FDA's DDT Qualification Program: Duchenne Video Assessment

- Duchenne muscular dystrophy:
  - Video captured by parents/caregivers in the home
  - Assesses patients' "quality of movement" at home to evaluate disease progression due to muscular weakness
  - Movements captured in videos scored by expert clinicians (novel clinician-reported outcome scale)

https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/clinical-outcome-assessments-coa-qualification-submissions

Some pathways for FDA engagement: Clinical Outcome Assessments in CDER

1

IND/NDA/BLA Pathway

Within an individual drug development program

Investigational New Drug (IND) submissions to FDA

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

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 instrument)

Meetings are **informal, non-binding** discussions

Closing thoughts

- Science and technology is rapidly evolving with opportunities and challenges in the use of novel endpoints
- Multidisciplinary, collaborative approach needed to ensure evidence is patient-centered and ultimately fit for regulatory decision-making
  - Includes incorporating patient/caregiver perspectives
- Seek regulatory guidance early
  - Precompetitive collaboration encouraged

For more information

- **Clinical Outcome Assessment Qualification Program Webpage:**
  - http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm
- **Critical Path Innovation Meetings (CPIM):**
  - http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm395888.htm
- **BEST (Biomarkers, EndpointS, and other Tools) Resource** https://www.ncbi.nlm.nih.gov/books/NBK338448/
- **CDER: Patient-focused drug development webpage:**
  - https://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm579400.htm

Thank you!