Assessing Patient Functioning in Drug Development Using Performance Outcome Assessments (PerfOs): Evidentiary, Methodological and Operational Considerations

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Disclaimer

- The views and opinions expressed in the following slides are those of the individual presenters and should not be attributed to their respective organizations/companies or the U.S. Food and Drug Administration

Objectives

1) Provide an overview of Performance Outcome Assessments (PerfOs)
2) Discuss evidentiary considerations for Perfo measures
3) Discuss practical considerations for implementing PerfO measures in clinical trials

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Participants

- ***Moderator: Elektra J. Papadopoulos, MD, MPH-*** Associate Director Clinical Outcome Assessments Staff, OND, CDER, FDA
- ***Heather R. Adams, PhD-*** Pediatric neuropsychologist; Associate Professor, Department of Neurology, University of Rochester School of Medicine and Dentistry, Rochester, NY
- ***Daniel C. Chung, D.O.-*** Ophthalmology Lead for Clinical Research and Development at Spark Therapeutics
- ***Daniel S. Rooks, PhD, FACSM-*** Director of Musculoskeletal Translational Medicine and Head of the Neuromuscular group at Novartis Institutes for BioMedical Research

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Workshop Outline

- Overview and key learnings from expert workshop— E Papadopoulos
- Practical considerations: Neurocognitive functioning and pediatrics — H Adams
- Practical considerations: Physical performance — D Rooks
- Case Study: Multi-luminance Mobility Test (MLMT) — D Chung
- Panel Discussion and Q & A

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Types of Outcome Assessments

- **Clinical Outcome Assessments (COAs)–** assess how an individual feels, functions, or survives
  - Patient-Reported Outcome (PRO)
  - Clinician-Reported Outcome (ClinRO)
  - Observer-Reported Outcome (ObsRO)
  - **Performance Outcome (PerfO) assessments**
  - Other (e.g., mobile technology-based activity monitoring)

- **Surrogate**
  - Often a biomarker* that is intended as a substitute for how a patient feels, functions, or survives

** Biomarker: A physiologic, pathologic, or anatomic characteristic that is objectively measured and evaluated as an indicator of some normal or abnormal biologic function, process or response to a therapeutic intervention*

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Background

- Dec 6-7, 2016: Duke-Margolis Center for Health Policy convened an expert workshop on PerfOs
  - Key learnings:
    - A new working definition of PerfO is needed
    - A large and diverse stakeholder group may have input in the development of PerfO measures
    - Considerations for evaluating measurement properties are largely similar whether evaluating physical or cognitive function
    - Many challenges remain: Use in heterogeneous populations, interpreting meaningful within-patient change
- May 8, 2018: A paper summarizing the discussion from the workshop as well as additional input from a working group of experts was published (Richardson, E et al)

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Performance Outcome Assessment*

- A measurement based on a standardized task performed by a patient that is administered and evaluated by an appropriately trained individual or is independently completed
  - Physical (e.g., timed 25 foot walk test)
  - Cognitive (e.g., word recall test)
  - Perceptual/sensory function (e.g., visual acuity test)

Important: PerfOs rely on the patient's effort, cooperation and motivation.

* https://www.ncbi.nlm.nih.gov/books/NBK338448/def-item/performance-outcome/

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Why use PerfO measures?

- Different types of outcome assessments are often used in various combinations providing complementary information
- PRO measures are used to assess symptoms (e.g., pain, fatigue) and provide important insight into patient functioning in daily life
- PerfO measures may overcome some limitations of PRO measures, such as
  - Recall error
  - Differences in the activities patients perform in their daily lives
    - A given PRO item may not be applicable across all patients (e.g., stair climbing)
  - Differences in patients' perceived abilities from their actual abilities

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Who can provide input in the PerfO measure development process?

- Range of stakeholders is wide and includes:
  - Patients, caregivers, clinical trial sponsors, healthcare providers, payers, disease experts/researchers, regulators, advocacy groups, measurement specialists, among others
  - The appropriate stakeholders to engage depends on the stage of development of the measure, the disease area and intended use of the measure

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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
- 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

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Content validity for PerfO measures

- **Content validity-** Evidence that demonstrates that the tasks and domains of a measure are both appropriate and comprehensive with regard to the concept (construct), target population, and intended use
- Considerations for a PerfO measure include:
  - Is the concept relevant and important to daily functioning?
  - Are the PerfO measure's tasks clearly connected to and reflective of the concept?
  - Do the testing conditions reflect demands of patients' day-to-day activities?
  - What does the score represent?

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Other key considerations

- Standardization
- Assessment burden/feasibility
- Ceiling and floor effect
- Practice effect
- Use in multinational trials
- Special populations
- Interpretation of clinically meaningful change

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Interpretation of Clinically Meaningful Change

- 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?
- Interpretation of magnitude of change can be challenging, particularly for PerfOs
  - There may be variability among patients in what they consider meaningful
  - Many of the tests are sensitive and can detect very small changes in functioning
  - Some tests lack obvious relationship to daily functioning (e.g., some neurocognitive tests)
- Interpretation methods: Anchor-based, distribution-based, and others

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Resources

- FDA Clinical Outcome Assessments Staff Website: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm349031.htm#Endpoints
- PRO Guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf
- DDT COA Qualification Website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm
- Richardson, E, Burnell, J, Adams, HR. et al. Developing and Implementing Performance Outcome Assessments: Evidentiary, Methodologic, and Operational Considerations. Ther Innov Regul Sci. Prepublished May 8, 2018, DOI: 10.1177/2168479018772569

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