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Performance Outcome Assessment Emerging Good Practices Task Force: Final Recommendations

Presented by the ISPOR Performance Outcome Assessment Emerging Good Practices Task Force

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Moderator:

- **Stephen Joel Coons, PhD (*Task Force Co-Chair)***
  Senior Vice President, Critical Path Institute, USA

Speakers:

- **Christopher James Edgar, PhD, MSc (*Task Force Co-Chair)***
  Chief Science Officer, Cogstate Ltd, UK
- **Elektra Papadopoulos, MD, MPH**
  Director, Patient Experience Data & Strategy in Immunology and Oncology, AbbVie, USA
- **Michelle Campbell, PhD**
  Senior Clinical Analyst for Stakeholder Engagement and Clinical Outcomes, Office of Neuroscience, FDA, USA

Outline

Introduction to Performance Outcome (PerfO) Assessments and the PerfO Assessment Task Force | Stephen Joel Coons

1. In which contexts might PerfO assessments be the optimal approach to measurement? | What issues should be considered when identifying and developing appropriate tasks? | Chris J Edgar
2. Patient Centricity in PerfO assessment | Elektra Papadopoulos
3. Challenges when evaluating fitness-for-purpose of PerfO assessments | Michelle Campbell
4. Questions & Answers

Definition: Performance Outcome (PerfO) Assessment

A type of clinical outcome assessment. A measurement based on standardized task(s) actively undertaken by a patient according to a set of instructions. A PerfO assessment may be administered by an appropriately trained individual or completed by the patient independently. Examples of PerfO assessments include:

- Measures of gait speed (e.g., timed 25-foot walk test using a stopwatch or using sensors on ankles)
- Measures of memory (e.g., word recall test)

Source: FDA-NIH Biomarkers, EndpointS, and other Tools (BEST) Resource Glossary

Task Force Goal

To enhance the appropriate use and usefulness of PerfO assessments in the evaluation of clinical benefit in medical product development by providing consensus-driven good practice recommendations regarding:

- The development, selection, and modification of PerfO assessments, including the evaluation and documentation of validity, reliability, usability, and interpretability (Report 1 to be discussed today); and

- The scientific and operational issues associated with appropriate and effective PerfO assessment implementation in clinical trials (Report 2).

Task Force Scope

The task force reports will address PerfO assessments of physical function (e.g., mobility), cognitive function (e.g., working memory) or cognition-dependent function (e.g., instrumental activities of daily living), and sensory function (e.g., low contrast visual acuity).

Please Note

Although our forum title indicates we will be addressing final task force recommendations, there are two disclosures we need to make.

- A decision was made to wait to finalize our recommendations after the release of draft Guidance 3 (Selecting, Developing or Modifying Fit-for-Purpose Clinical Outcome Assessments) in FDA's patient-focused drug development guidance series aimed at "Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making."
- Report 2 has yet to be written

Task Force Report 1 Content Outline - 1

- Introduction
  - The role and types of clinical outcome assessments (COAs) in clinical trials
  - The definition and role of performance outcome (PerfO) assessments
- Identifying the concept of interest (COI) for measurement
- Determining if a PerfO assessment is the optimal COA type to measure the COI
- Deciding to use or modify an existing PerfO assessment or develop a new one
- PerfO assessment development
  - Develop initial conceptual framework
  - Identify relevant tasks
  - Qualitative assessment to confirm content validity

Task Force Report 1 Content Outline - 2

- Pilot evaluation
  - Pilot evaluation design
  - Interpreting pilot evaluation results
- Refine conceptual framework and finalize scoring procedure/algorithm
- Evaluation of other measurement properties
  - Construct and ecological validity
  - Reliability
  - Ability to detect change and meaningful within patient change
- Conclusions

PerfO Assessment Task Force Leadership Group - 1

- **Heather R. Adams, PhD**, Pediatric Neuropsychologist, Associate Professor, University of Rochester, USA
- **Rachel Ballinger, PhD, BSc,** Principal, Patient Centred Outcomes, ICON, UK
- **Elizabeth (Nicki) Bush, MHS (*Task Force Co-Chair),*** Global Head, Patient-Focused Outcomes Center of Expertise, Eli Lilly and Company, USA
- **Bill Byrom, PhD**, Vice President of Product Strategy & Innovation, Signant Health, UK
- **Wen-Hung Chen, PhD**, Director, Patient-Centered Outcomes, GSK, USA
- **Helen Doll, DPhil**, Senior Principal, Clinical Outcomes Solutions, UK

PerfO Assessment Task Force Leadership Group - 2

- **Sonya Eremenco, MA**, Executive Director, PRO Consortium, Critical Path Institute, USA
- **Richard S.E. Keefe, PhD**, CEO, VeraSci and Professor, Psychiatry and Behavioral Sciences, Duke University, USA
- **Fiona McDougall, PhD**, Associate Director, Genentech, USA
- **Bray Patrick-Lake, MFS**, Director, Strategic Partnerships, Evidation, USA
- **Ashley F. Slagle, PhD,** Principal, Scientific and Regulatory Consulting, Aspen Consulting, LLC, USA

SECTION

1

In which contexts might PerfO assessments be the optimal approach to measurement?

What issues should be considered when identifying and developing appropriate tasks?

Chris Edgar, PhD
Chief Science Officer, Cogstate Ltd, UK

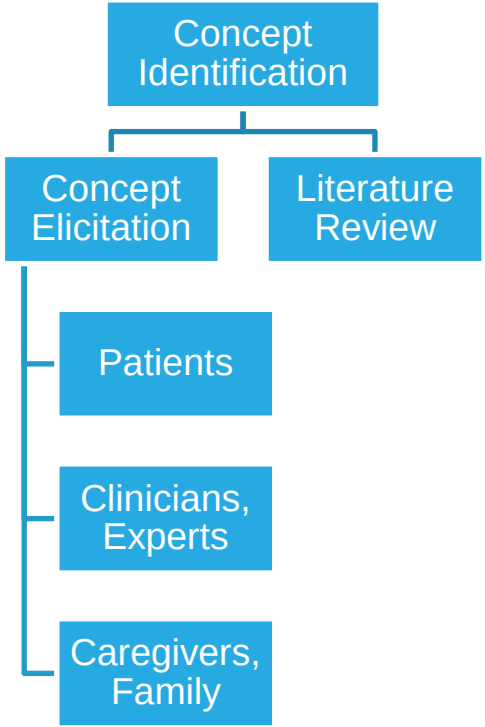
Role of PerfO assessments

- A PerfO assessment should be used when the optimal means of capturing the clinical benefit of therapeutic interventions is through the completion of defined/standardized tasks that reflect or are the foundational building blocks for day-to-day activities that are important and meaningful in patients' lives.

- Primary relevant impairment types: cognitive, mobility and sensory

- "Establishing a well-understood relationship of the measurement with the patient's usual life is central to the conclusion that the observed effect is actually a treatment benefit." (Walton et al., 2015)

In which contexts might PerfO assessments be the optimal approach to measurement?



What to measure?

- Meaningful aspect(s) of health
- Concept(s) of interest of measurement

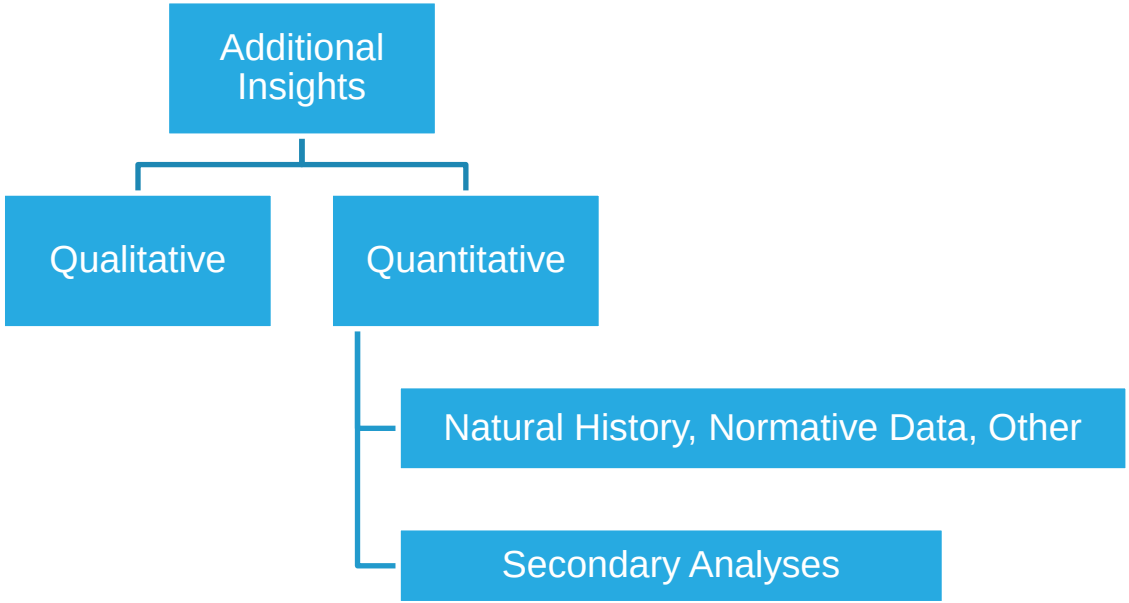
PerfO assessments may be the optimal means 1) Patient population

1	Cognitive impairment, including loss of insight and memory impairment, or language difficulties on the part of the patient
2	Paediatric populations: age and/or developmentally-appropriate measures unavailable

PerfO assessments may be the optimal means
2) Potential limitations with other COA types

1	Concept(s) of interest not best reported by the patient (e.g., memory impairment)
2	Difficulty observing concept(s) of interest without prompting task performance (e.g., tremor in movement disorders not evident at rest, but posture, movement, or task dependent)
3	Issues with recall periods (e.g., COI(s) infrequently, rarely performed and/or assessment of current state needed)
4	Patient biased in reporting/rating leading to under or over-estimation (e.g., bias due to negative affect or loss of insight)
5	Observer biased in reporting/rating leading to under or over-estimation (e.g., bias due to psychosocial factors/relationship with patient)

What issues should be considered when identifying and developing appropriate tasks?



How to measure?

- Concept confirmation
- Conceptual frameworks
- Abstract tasks

Qualitative Data Insights Supporting Task Identification or Development

- Relative importance of tasks and functions/Concept confirmation
- Emergence of problems in specific situations or at certain times (e.g., high stress environments)
- Impacts across a range of activities (e.g., self-care, work, social, leisure)
- Use of aids and adaptations (lists and notes, assistive devices, support, etc.)
- Normal or 'idealized' performance as a target for clinical benefit, but beyond a patient's current ability or conceptualization
- Prior/premorbid level of function
- Embarrassment, stigma, or fear regarding admission of problems (e.g., loss of driving license) that may hinder concept elicitation or self-report

Direct Vs Indirect Tasks

Realism Spectrum	Very High	High	Moderate	Low
Intended degree of realism	Task is a real-world activity and is performed in the usual environment	Task intended to represent a real-world activity	Contextual association to real-world activity	Task is abstract
Development of task/item content	Concept elicitation critical to informing task/item content	Concept elicitation critical to informing task/item content	Concept elicitation partly informs task/item content	Concept elicitation indirectly informs task/item content
Example PerfO assessment	Kitchen assessment tool(s): *Performance of kitchen tasks within a naturalistic setting*	University of California Performance-based Skills Assessment: *Performance of activity vignettes, e.g., planning a day out, within a clinical assessment setting*	International Shopping List Test: *Ability to recall/remember grocery items from a preset list*	Symbol Digit Modalities Test: *Speeded coding of abstract symbols to numbers within a fixed time-period to assess processing speed*

PerfO Assessments may be optimal means
3) Nature of the concept(s) of interest for measurement

1	Concept(s) of interest not universally representative/substantial heterogeneity of lived experience (e.g., influenced by culture, gender role, age)
2	Concept(s) of interest distal to disease or condition (e.g., influenced by environment, age, behaviours, psychosocial factors)
3	Concept(s) of interest not feasible or difficult to measure in context of clinical trial (e.g., actual performance of certain ADLs)
4	Patient no longer performs the actual COI(s), or performs them rarely or differently to before (e.g., uses assistive devices, wishes to avoid causing certain symptoms, needs recovery time)

Potential Challenges

- Relatively underrepresented COA type
  - Approx. 7% COA compendium Vs 42% ClinRO assessments
  - Approx. 13% COA qualification program submissions Vs 59% PRO assessments
- Preponderance of motor function assessments
  - Approx. 75% of COA compendium PerfO assessments
- Difficulties with development and validation
  - 10 COA qualification program: 2 LOI not accepted; 2 qual. plan rejected
- Cognition may be uniquely challenging
  - 3 PerfO assessments in COA compendium
  - 2 COA qualification program submissions
  - Co-primary requirement to establish clinical benefit in AD and CIAS

In Summary

- PerfO assessment development and validation follows the same foundational good practice as for other COA types
  - Concept elicitation is central to understanding what to measure
- To identify or develop tasks to support PerfO assessments, the use of both qualitative and quantitative (task performance) data may be of value e.g.,
  - Motor function assessments
  - Neuropsychological test batteries
  - Sensory function tests
- A relationship between a task or group of tasks and the patient's usual life must still be established in order that the PerfO assessment can evaluate treatment benefit
  - In a unitary validity model, this may be supported using ecological validity evidence

SECTION

2

Patient Centricity in PerfO assessment

Elektra Papadopoulos, MD, MPH
Director, Patient Experience Data & Strategy in Immunology and Oncology, AbbVie, USA

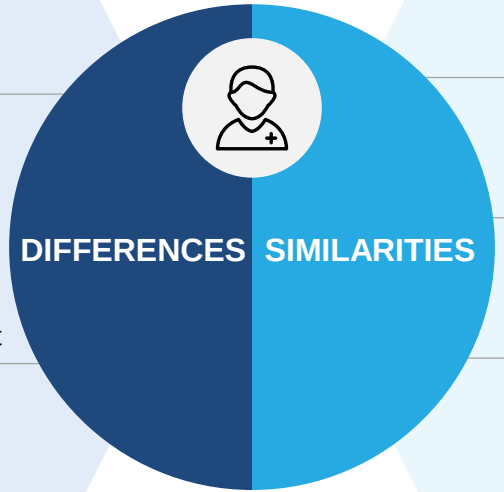
Patient centric measurement: Some differences and similarities among COA types/assessment methods

COA types can provide complementary information→ Richer picture of clinical benefit

PRO measures can provide insight into patients' lived experience
- For example, what they do in daily life and with how much difficulty

PerfO measures:
- Assess what functions patients can do using standardized tasks in a controlled setting
- Reliant on motivation
- May lack information on patient perceived difficulty
- Additional data to link to meaningful clinical benefit i.e., concept of interest for meaningful treatment benefit

Activity monitoring
- Assess movement in daily life; may not assess functioning
- Discretionary activities-> variable



Truly patient-centered measurement includes input from the target patient population

Selection of task(s) for a PerfO measure

Selection of item(s) for a PRO measure

Identification of variable(s) from an activity monitor

Other key considerations e.g.,
- Patient burden
- Usability
- Comprehensibility

US FDA CDER DDT COA Qualification Program: Patient-centricity highlighted

Virtual Reality Functional Capacity Assessment Tool (VRFCAT): cognitive functional capacity in patients with schizophrenia (DDT COA #000107)

> *As you develop your qualification plan, please make sure to describe how the VRFCAT was developed and if patient input was obtained during development*

> *Please clarify if failure to complete a task within 300 seconds had created any stress or frustration for patients in the past, as this could interfere with cognitive performance and ability to detect change.*

Gathering robust patient input

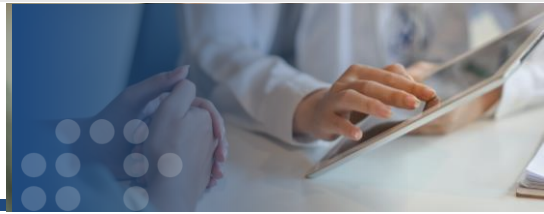
Qualitative methods including patient interviews from representative sample foundational

- Best practices include ISPOR task force papers and FDA guidance

Examples: Many for PRO measures vs. relatively few for PerfO measures and activity monitor-derived endpoints

- Recent development efforts in the precompetitive environment provide examples
  - Critical Path Institute's PRO Consortium: Chronic Heart Failure Working Group
  - Critical Path Institute's: Critical Path for Parkinson's Digital Drug Development (3DT) Initiative

Content validity evidence generation: Case example in Parkinson's Disease (PD)



Critical Path for Parkinson's Digital Drug Development (3DT)

Watch PD is a multicenter, prospective, digital assessment study of disease progression in subjects with early, untreated PD

- Conducted qualitative research in Watch PD participants
- Asked participants questions such as:

Do you understand what the task is asking you to do?

What PD symptoms would be related to what is being done?

Are the tasks similar or relevant to your daily life?

Are they important when assessing PD progression?

Key take-away:
Cognitive debriefing for a PerfO instrument was much like debriefing a PRO measure

Key learnings

Foundational principles of patient-centered measurement common across COA types

Patient/caregiver input and linkage to meaningful health concept is critical

Research in the precompetitive setting provides examples and learnings for all

SECTION

3

Challenges when evaluating fitness-for-purpose of PerfO assessments

Michelle Campbell, PhD
Sr Clinical Analyst for Stakeholder Engagement and Clinical Outcomes, Office of Neuroscience, FDA

Reminder: 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

- Can be demonstrated as either:
  - A comparative advantage in treatment of the disease or condition; OR
  - A comparative reduction in treatment-related toxicity

Clinical Meaningfulness

- When selecting your performance measure, consideration should be taken that the measure represents clinically meaningful concepts.

- Utilize both qualitative and quantitative evidence to inform decision making.

Examples

- May not provide clinically meaningful information
  - Clinician reporting exam changes of decreased vibratory sense, decreased movement against resistance, or decreased reflexes in arms/hands.
    - Changes may suggest a change in the disease status but do not reflect any impact on patient symptoms or daily functioning.

- Does provide clinically meaningful information
  - Numbness in hands that interferes with the ability to button clothes
  - Weakness in hands that interferes with ability to hold spoon and eat
  - Weakness in arms causing difficulty carrying groceries

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*

*A statement that fully and clearly describes the way the medical product development tool is to be used and the medical product development-related purpose of the use.

Fit-for-Purpose Is More Than Content Alone

- Know your population
  - Ex. Understand if patients can follow instructions to complete assessments
- Standardization of Administration of Performance Measures
  - Standardize how measures are to be administered
  - Appropriate training of study staff on administration (includes clear and sufficiently detailed user manual)
  - Pilot test to make sure that patients are able to complete the assessment correctly and safely
- Come Early for Advice

4

Q&A

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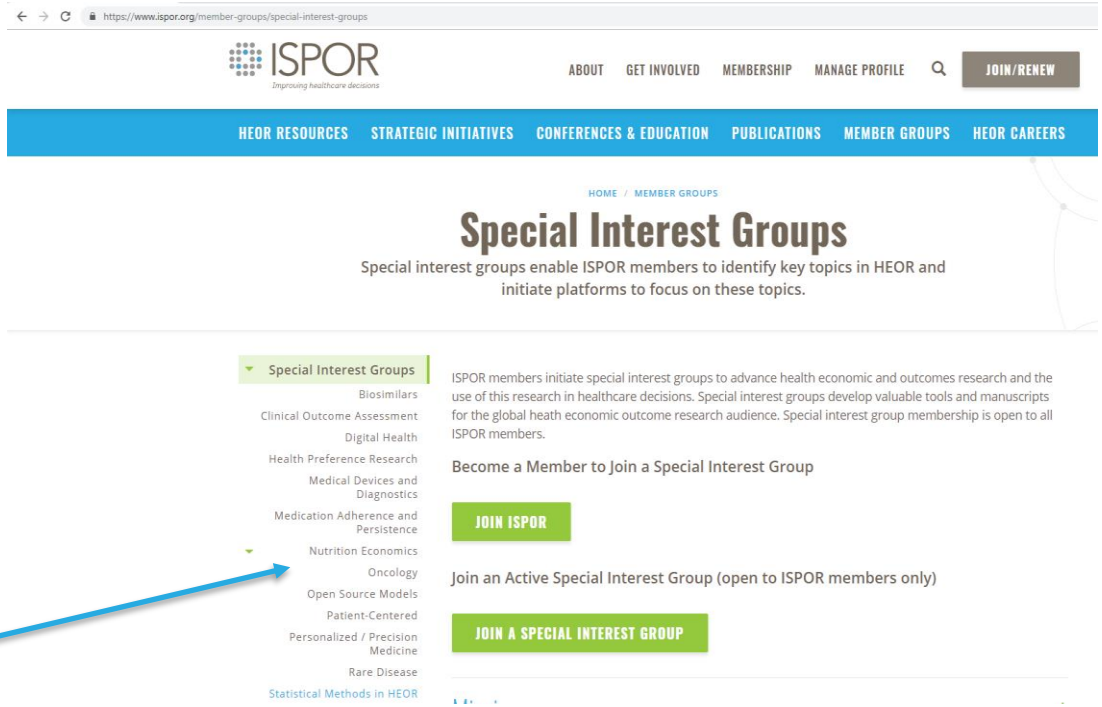


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