ISPOR Clinician-Reported Outcomes Good Measurement Practices Task Force

ClinROs Task Force Leadership Group

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Nearly 20% of ISPOR’s 7,200 members in 100 countries around the world identify PROs as a primary research interest.

ISPOR ClinROs Task Force manuscripts will be #9 and #10 of ISPOR PRO Task Force Report publications since 2009.
Patient Centered & Clinician-Reported Outcomes Methods Task Force Reports

- Clinical Outcomes Assessments: Conceptual Foundation *(in development)*
- Clinician-Reported Outcomes (ClinROs) Good Measurement Practices *(in development)*
- PRO Data Collection Using Mixed Modes in Clinical Trials *(in development)*
- Assessment of PROs in Children and Adolescents *(June /July 2013)*
- ePRO Systems Validation *(June/July 2013)*
- ePRO-Changing Mode of Administration of PRO Instruments from Paper to Electronic
- Content Validity in Existing PRO Instruments & Their Modification
- Content Validity in Newly-developed PRO Instruments Part 1 - Eliciting Concepts for a New PRO Instrument
- Content Validity in Newly-Developed PRO Instruments Part 2 - Assessing Respondent Understanding
- Translation & Linguistic Validation of PRO Instruments

http://www.ispor.org/workpaper/practices_index.asp

Task Force Objective

Develop a Good Research Practices report to:

- Further improve development and use of clinical outcome assessments (COA), including ClinROs in US and European clinical research and practice

- Improve patient outcomes and allow better assessments of benefits and harms through better measures
**Clinical Outcome Assessment**

- A COA is any assessment that depends on a patient's volition or a rater's judgment.
- COAs include: patient-reported outcome (PRO) measures, clinician-reported outcome (ClinRO) measures, observer-reported outcome (ObsRO) measures, and performance outcome measures (PerfO).
- COAs exclude: survival and biomarkers.

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**Background**

- **2009: FDA PRO Guidance**
  - “A PRO instrument, like physician-based instruments, should be shown to measure the concept it is intended to measure, and the FDA will review the evidence that a particular PRO instrument measures the concept claimed.”

- **2010: DDT Qualification Process Guidance**

- **2011: Review and Qualification of Clinical Outcome Assessments; Public Workshop**
Treatment benefit

- Favorable effect on meaningful aspect of how patients feel or function in their lives, or how long patients survive
  - Improved effectiveness
  - Decreased harms

What an Outcome Assessment Is

- Measurement of the effects of an intervention (benefice or harm to a patient) = comparison between test and control group

  "The purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation." 21CFR 314.126
**What an Outcome Assessment is Not**

- It is NOT a:
  - **Diagnostic tool** – used to define disease
  - **Predictor of outcome** – select person likely to experience an outcome independent of intervention
  - **Enrichment strategy** – selecting patients most likely to benefit from intervention for enrollment in trial

**Types of Outcome Assessments**

- **Mortality**
- **PRO** – Patient-Reported Outcome
- **ClinRo** – Clinician-Reported Outcome
- **ObsRO** – Observer-Reported Outcome
- **PerfO** – Performance Outcome
- **Biomarkers**
Choosing Clinical Outcome Assessments

- Observable* concepts
  - Report by trained health professional not needed
    - Self-report feasible and appropriate?
      - Yes
        - ObsRO
        - PRO
  - Report by trained health professional needed
    - PRO
    - ClinRO

- Unobservable concepts (e.g., feelings, sensations)
  - Performance of a task
    - [patient cooperation and motivation required - instructions provided by a health professional - e.g., cognitive testing, 6 min WT]

When is a ClinRO Appropriate?

- When the clinician is in a good position to form the assessment that becomes the measurement on which a study endpoint is based

- For example,
  - Where patients are unable to self-report on their own health status due to mental or physical impairment or age (e.g., neonates)
  - Or where patients cannot comment on a specific sign (e.g., Parkinson’s disease)
Clinician-Reported Outcomes

- Report that comes from a trained health-care professional after observation of patient’s health condition
- Involve a clinical judgment or interpretation of the observable signs, behaviors, or other physical manifestations thought to be related to a disease or condition
- ClinRO measures cannot directly assess symptoms that are known only to the patient (e.g., pain intensity)

Types of ClinROs:

- **Readings** – dichotomous report: fracture on a radiography, absence of presence skin lesions, emetic episodes
- **Ratings** – categorical/scoring report: spleen size, change in skin lesions, severity of schizophrenia (PANSS); improvement in vein appearance
- **Globals** – Clinician Global Impressions (CGI): overall judgment on patient status. Questionable since what is measured and how an assessment is made not clearly defined
“Clinicians” can be various types of trained members of an investigative team
- Physicians
- Nurses, nurse practitioners, physicians assistants
- Clinical research associates
- Etc.

Same concept can be measured using different types of outcome assessments
- Concept = systemic blood pressure
- Blood pressure measured by investigator using sphygmomanometer (blood pressure cuff) and stethoscope = ClinRO (individual skill in listening for pulse)
- Blood pressure measured by automated machine cuff = Biomarker (test performed and analyzed according to specific algorithm)
1) Define the context of use of the measure
2) Define concept of interest
3) Explain relationship of assessment to direct treatment benefit
4) Documentation of content validity
5) Documentation of other measurement properties
6) Interpretation and analysis
7) Implementation in clinical trials

Outline presented “linearly”, but process is iterative.
Learning occurs during development that feeds back to inform measures.
“Wheel and Spokes” in FDA PRO guidance and COA qualification update
Disease definition including, if appropriate
-- Pathogenesis
-- Disease subtype
-- Disease severity
-- History of previous treatment

Targeted subpopulations
-- Patient demographics
-- Culture and language

Clinical trial design and objectives
-- Endpoint model;
-- Endpoint definitions
-- Analysis plan
-- Targeted labeling

Study setting
-- Inpatient vs. outpatient
-- Geographic location
-- Clinical practice variation

--- Good Measurement Principle 1:
Define the Context of Use

--- GMP2:
Define Concept of Interest

- The specific “thing” to be measured, or the measurement goal
- Clarity of what is actually measured is critical before any other evaluation can be made.
- Basis for interpretation and labeling
- The COI can’t be the instrument itself (e.g., CGI).
- COI critical to establish the validity of a ClinRO.
As with PROs, need to understand patient’s perspective on what should be measured.

If patient cannot self-report, obtain information from other sources (e.g., other types of patients who can self-report).

What is needed depends upon context of use.
Empirical evidence from qualitative and quantitative research that measures / reflects the intended purpose

- Similar to PRO guidance principle
- Depending upon the type of ClinROs, both patient and clinician input are necessary to establish the appropriateness and comprehensiveness of the content purported to measure the concept of interest

Understandability of the instructions to implement or perform the measure and to score or interpret the outcomes (clinician)

Understandability of the instructions to perform the assessment (patient)

Comprehensiveness of measure

Integrity of measure in other targeted languages

Integrity of measure across modes of administration
GMP5: Evaluate Other Measurement Properties

- Only done after content validity documented
- Reliability (intra- and inter-rater)
- Ability to detect change
- Similar considerations to PROs

GMP6: Determine Rules for Interpretation

- How much difference makes a difference
- Blinding
- Other issues related to interpretation:
  - Time point for analysis in relation to natural history of disease and treatment effects
  - Minimizing missing data
  - Multiplicity
- Presentation of results – group mean differences, analysis of proportions, time to event, etc.
Rater training on performance and interpretation of measures
- Minimize random error
- Minimize bias

Planning for minimizing losses to follow-up

Measurements within assigned time windows

Methods of administration

Same measurement standards apply to all COAs — PerfO, PRO, OBSRO, and ClinRO

All clinical trials should include patient-centered outcomes that measure survival, function, and/or feelings (directly or indirectly)

Legacy instruments are acceptable only if tested in the context of use with a clear concept of interest and evidence from the target population to whom they apply.
Persons who wish to be on review group please contact Elizabeth Molsen:
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