

Workshop on Health technology Assessment: Roles, Methods and Challenges

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- Advancing personalized medicine and patient-centered care has elevated patients' roles in healthcare decision-making, driving significant recognition of Patient-Reported Outcomes (PRO).
- PRO are now extensively applied in **clinical effectiveness evaluation, market authorization review , medical insurance reimbursement, health technology assessment** (HTA), etc.

- 2009, FDA, <Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims>
- 2021, NMPA, <Technical Guidelines on the Application of Patient-Reported Outcomes in Drug Clinical Development (Trial)>
- 2023, FDA, <Submitting Patient-Reported Outcome Data in Cancer Clinical Trials>

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GUIDANCE DOCUMENT

Submitting Patient-Reported Outcome Data in
Cancer Clinical Trials

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

国家药监局药审中心关于发布《患者报告结局在药物临床研发中应用的指导原则（试行）》的通告
(2021年第62号)

发布日期: 20220104

为鼓励以患者为中心的新药研发理念, 科学合理的运用患者报告结局, 药审中心组织制定了《患者报告结局在药物临床研发中应用的指导原则（试行）》（见附件）。根据《国家药监局综合司关于印发药品技术指导原则发布程序的通知》（药监综药管〔2020〕9号）要求, 经国家药品监督管理局审查同意, 现予发布, 自发布之日起实施。

特此通告。

附件: 患者报告结局在药物临床研发中应用的指导原则（试行）

国家药监局药审中心
2021年12月27日

- Clinical outcomes are cornerstone evidence for evaluating therapeutic benefits and risks of medicinal products.
- PRO, as a key modality, are increasingly used in pharmaceutical registration trials.
- Advancing Patient-Focused Drug Development (PFDD) mandates systematic collection and integration of **patient experience**, **insights**, and **needs** throughout the drug lifecycle.
- Clinical Outcome Assessments (COA), particularly PRO, directly measure patients' lived experiences and are fundamental to patient-centered drug development.

Source: Center for Drug Evaluation, National Medical Products Administration. Technical Guidelines on the Application of Patient-Reported Outcomes in Drug Clinical Development (Trial). <https://www.cde.org.cn/main/news/viewInfoCommon/c2f79c22e8678241b030c71523eb300c>.

Clinical Outcomes Assessment (COA) is an evaluation of patients' feelings, functional status, etc., mainly including:

- Patient-Reported Outcome, PRO
- Clinician-reported Outcome, ClinRO
- Observer-reported Outcome, ObsRO
- Performance outcome, PerfO

Source: U.S. Food & Drug Administration. Patient-focused drug development: incorporating clinical outcome assessments into endpoints for regulatory decision-making.

What is PRO?



- PRO: Any report coming **directly from patients**, without interpretation of the patient's response by clinicians or anyone else.
- PROs are reports coming directly from patients regarding their health condition, functional status, and treatment experience, without interpretation by clinicians or others.
- PROs emphasize direct reporting by patients. When patients lack or lose self-assessment capacity, proxies (guardians or designated representatives) may complete PRO records, but proxy bias must be rigorously evaluated.

Source: U.S. Food and Drug Administration (FDA). (2009). Guidance for Industry. U.S. Department of Health and Human Services. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. <https://www.fda.gov/downloads/drugs/guidances/ucm193282.pdf>.

What is PRO?



- PRO encompass patient-reported information on symptoms, functional status, health-related quality of life (HRQoL), health behaviors, treatment preferences, treatment satisfaction, and physician-patient communication.
 - Health Related Quality of Life · HRQoL
 - Health Preference · HP
 - Health Behavior · HB
 - Symptom Burden · SB
 - Functional Status · FS
 - Patient-Reported Experience · PRE
- PRO data may be collected via qualitative interviews, self-administered scales, or patient daily diaries.

- PROs have become increasingly critical in evaluating health interventions.
- Direct self-reporting by patients on the impact of diseases, symptoms, and treatments represents outcomes that matter most to patient. Changes in PROs are key factors influencing care needs and treatment satisfaction.
 - *“The ultimate goal of health care is to restore or preserve functioning and well-being related to health, that is health-related quality of life.”(Osoba and King, 2005, P 243)*
- For disorders such as pain, functional disability, or mental health conditions, the most relevant outcomes are patients' experiences, which can only be obtained through self-reporting.

Why Use PRO?



- PRO provide insights into patients' subjective experiences of disease and treatment – perspectives often unattainable through objective clinical metrics. These perspectives are equally vital to patients and may significantly influence treatment adherence.
- An optimal treatment regimen must demonstrate:
 - Clinical efficacy (supported by objective endpoints),
 - Cost-effectiveness (validated by health economic analyses), and patient acceptability (reflecting treatment burden and alignment with patient preferences).
- Crucially, clinical endpoints fail to assess patient' lived experiences, functional status, or personal treatment goals.

Example: Why Use PRO?

- Clinical Evidence in COPD Management
 - A patient was diagnosed with Chronic Obstructive Pulmonary Disease (COPD).
- Key findings from a systematic review of COPD therapies:
 - **Tiotropium significantly reduced acute exacerbation rates** compared to Long-Acting Beta Agonists (LABA) (OR 0.86; 95% CI 0.79–0.93).
 - **No statistically significant differences** were observed in Forced Expiratory Volume in 1 second (FEV₁) or symptom scores between tiotropium and LABA groups.
- Do these outcomes reflect patients' subjective experiences with the new treatment? How do such clinical changes translate to improvements in daily functioning?

Example: Why Use PRO?



Need to understand further what these data mean for patients

- Do reduced exacerbations translate to lower hospitalization rates?
Or can symptoms (e.g., cough) be managed at home?
- Does improved FEV₁ directly enhance patients' functional capacity?
- Do symptom scores capture patients' subjective experience or merely "objective" metrics?

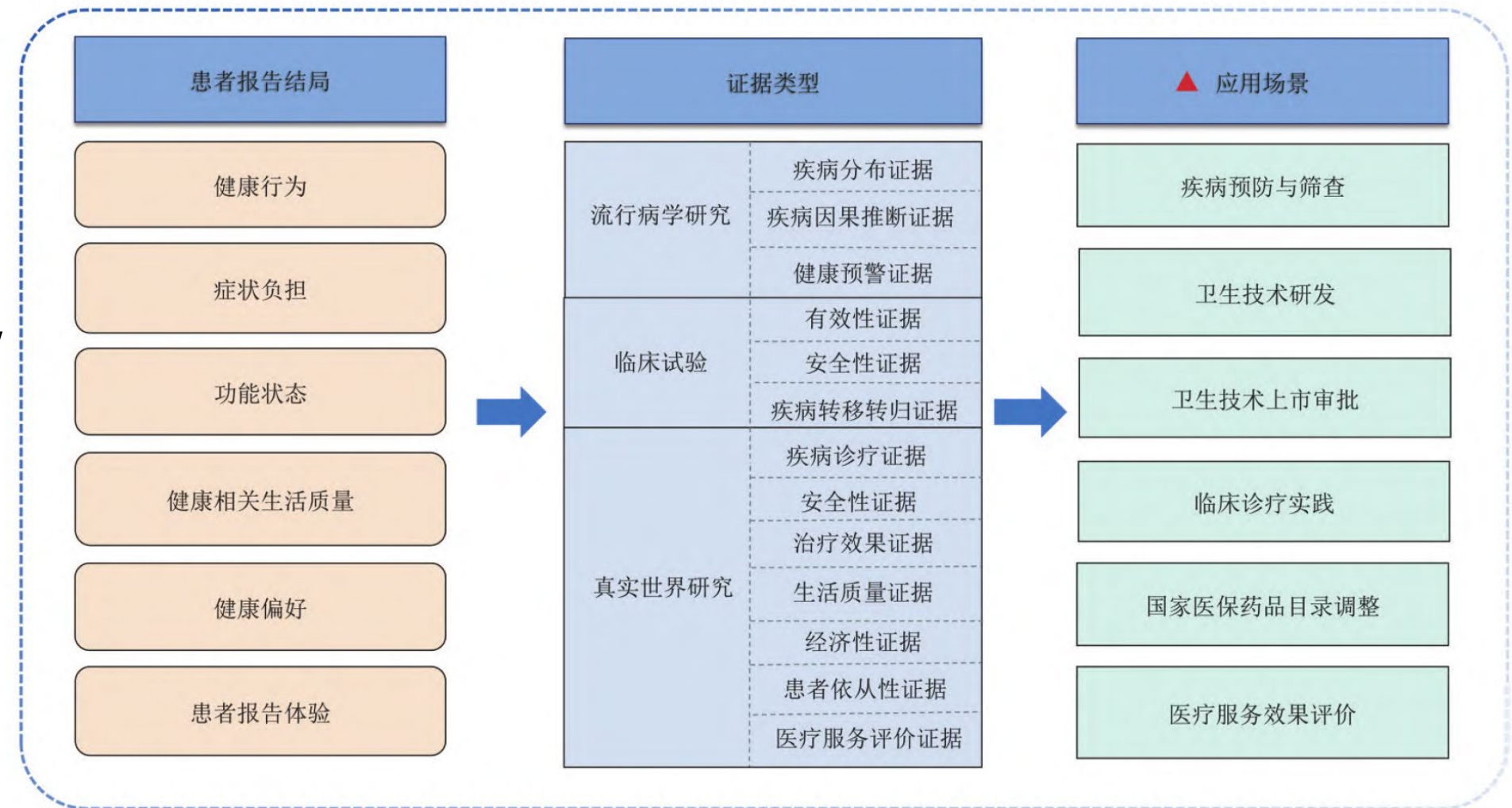
PROs truly reflect patient well-being

- Unlike traditional clinical endpoints, PROs provide unique insights into how treatments impact patient's lived experiences.
- **Subjective variability:** Individuals with identical diagnoses may perceive their symptoms and functional capacity differently due to psychosocial factors (e.g., coping mechanisms, resilience)
- **Adaptive perception:** Patients' adaptation to limitations/disabilities and external factors (e.g., social support) can significantly alter their satisfaction with life despite objective health status
- **Driving patient-centered innovation:** PRO data compel medical technology development to prioritize meaningful patient benefits (e.g., functional improvement over purely biomarker changes)

Application of PRO



- Disease Prevention and Screening
- Health Technology Research & Development (R&D)
- Market Authorization Review for Health Technologies
- Clinical Diagnosis and Treatment Practice
- Medical Insurance Reimbursement
- Healthcare Service Effectiveness Evaluation



How to measure PRO?



- PRO must be carefully defined to capture information important to patients
- The information must be measured as accurately as possible to ensure comparability with other measurements
- Poorly developed PRO concepts will lead to measuring outcomes unimportant to patients, even if measurable accurately
- Poor measurement methods may identify outcomes important to patients but difficult to interpret

- Accurately determining what to measure and the granularity of item wording is critical.
- Ambiguous items may yield ambiguous data of limited utility
 - For example, patients may be asked: "How do you feel on a scale of 1 to 10?" (1 = very poor, 10 = excellent). This is highly imprecise.
- Concrete items targeting emotion affected by functions such as mobility or respiration will provide more detailed and specific information.

- In PRO, a “concept” is the subject of measurement
For example:
 - A single symptom or a group of symptoms
 - The impact on a specific function or group of functions
 - A set of symptoms or functions used to gauge the severity of health status
- Once agreement is reached on the “concept”, patients are asked questions related to it. These questions are termed “items”
- “Items” are inquired to understand the changes of “concept”

Example: Concept and Item in PRO

the MOS item short from health survey, SF-36

- Physical Functioning, PF
- Role- Physical, RP
- Bodily Pain, BP
- Validity, VT
- Social Function, SF
- Role- Emotional, RE
- Mental Health, MH
- General Health, GH

Physical Functioning

- Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports
- Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
- Lifting or carrying groceries
- Climbing several flights of stairs
- Climbing one flight of stairs
- Bending, kneeling, or stooping
- Walking more than a mile
- Walking several blocks
- Walking one block
- Bathing or dressing yourself

- **Generic type**
 - Measures aspects of health status and quality of life common to most patients
- **Disease-specific type**
 - e.g., PRO targeting a specific cancer
- **Symptom-specific type**
 - Applicable to a specific service, such as rehabilitation or mental health services; or a segment of the population, such as the elderly

□ Health-related Quality of Life (HRQoL)

- Physical function
- Psychological function
- Social function
- Role function
- Emotional function
- Well-being
- Vitality
- Health status
-

□ Patient satisfaction

- Evaluation of treatments
- Patient's preference
- Healthcare delivery systems and professionals
- Patient education programs
- Medical devices

□ Physical functioning

Physical limitations and activity restrictions, including:

- Walking
- Mobility
- Sleep
- Self-care
- Sex
- Disability

□ Psychological state

Positive or negative affect and cognitive functioning, including:

- Anger
- Alertness
- Self-esteem
- Sense of well-being
- Distress
- Coping

□ Signs and symptoms

Reports of physical and psychological symptoms or sensations not directly observable, including:

- Energy
- Fatigue
- Nausea
- Irritability

❑ Social functioning

- Limitations in work or school
- Participation in community

❑ Treatment adherence

- Reports or observations of actual use of treatments

□ **Utility: The capacity of a self-perceived entity to satisfy needs or desires**

In health economic evaluations, utility measures the intensity of patient preferences, such as the relative importance of various factors to patients, for example:

- Symptoms
- Pain
- Psychological health

- Methodology of measurement is critically important in PRO research
- Once concepts and items to be measured are identified and listed, deliberate decisions are required on:
 - How questions are delivered to patients?
 - When questions are delivered to patients?
 - How responses are recorded when questions are administered?
 - How data are interpreted?

- PROs are primarily measured through questionnaires or surveys:
 - completed independently by patients
 - completed by patients with researchers present
 - administered by researchers via face-to-face or telephone interviews
- Different methods for collecting PRO information have distinct advantages and disadvantages
- Although the use of trained interviewers can minimize errors and ensure survey completion, trial/treatment resources may not permit this approach

How to Measure PRO?



- Focus on capturing patients' true perceptions and target concepts accurately, not interviewer techniques.
- Example: Morning questionnaires about morning symptoms yield more reliable results than afternoon use.
- Researchers must ensure their tools measure patient-valued concepts reproducibly and understandably.

Key Point 1: Clarifying PRO Purpose

- Individual level: Screening, monitoring clinical progress, advancing patient-centered care
- Population level: Aggregating individual PRO data stratified by variables to evaluate service quality within institutions and benchmark care quality across providers
- Designing PRO interventions considering near-term and long-term data collection goals

Source: The International Society for Quality of Life Research (ISOQOL). *A User's Guide for Implementing Patient-Reported Outcomes Assessment in Clinical Practice*.

Key Point 2: Specifying patient population characteristics, settings, and timing for PRO assessment

- Patients: Targeting specific populations enables focused measurement strategies
 - Outpatients: Better health status, greater autonomy in completion timing
 - Inpatients: Require more assistance (increased resource needs); acute/rehabilitation cases
- Implementation frequency: Ranges from single to frequent administrations; higher frequency demands greater resources (though initial setup costs dominate)
- Outpatient PRO assessment: Conducted during visits or between visits (how to remind included patients)
- Self-administration or proxy completion
- Potential interactions between patients, care settings, and assessment timing
 - Treatment initiation day vs. stabilized treatment phase

Key Point 3: Selecting appropriate PRO measures

- Balance clinician and patient priorities
 - PRO domains include symptom burden, functional limitations, quality of life, health behaviors, and treatment adherence
 - Clinicians may prioritize aspects they can clinically manage; patients may emphasize specific symptoms or quality-of-life concerns for discussion
- Other consider: question format, conceptual focus, psychometric properties, recall period, copyright restrictions, etc.



Key Point 3: Selecting appropriate PRO measures

Element		
Generic versus disease-specific	Generic	Disease-specific
	- May capture more commonly experienced health domains - Allow comparison to normative populations - May not be sensitive to changes in disease-specific health domains over time	- May be more sensitive to specific symptoms experienced by patients - May miss domains affecting the patient but unrelated to the disease being treated
Profile versus preference based	Profile	Preference based
	- Provide multiple scores (and sometimes summary measures) across a broad range of PRO domains - Can be longer to complete	- Provide a single score aggregated across multiple PRO domains for an estimate of burden of disease - May not provide clinically relevant information on specific PRO domains affecting the patient
Single item versus multi-item	Single item	Multi-item
	- Enable assessment of more PRO domains - Less reliable for tracking change	- Provide more precise and content valid measurement - More time consuming for patients to complete
Static versus dynamic	Static	Dynamic
	- Feasible for paper and computer administration - May require longer questionnaires to provide a reliable measure of a patient's health status	- Can yield shorter and equally reliable measures than static forms - Require computer administration - Only available for a limited number of domains

Key Considerations for PRO Data Collection

Key Point 4: Selecting appropriate data collection modes

Mode & setting	Advantages	Disadvantages
In person		
Paper	Have low technology requirements so can be implemented at relatively low cost	May not be appropriate for all patients (e.g., low literacy, visual disabilities) Potentially higher rate of missing data Require personnel to coordinate questionnaire completion, and assist when necessary Require personnel for data entry Relatively expensive May create problems with socially desirable responses
Interview	More personal Enable more in-depth questioning Largely circumvent issues of literacy and/or visual handicap	
Computer	Efficient data collection Immediate scoring and simultaneous data entry into statistical database Enable adaptive testing Facilitate graphic score presentation Possibility of linking with electronic medical record Potential for automated reading and voice response	Require personnel to manage the process Software needed to collect and report the PRO data Involve higher upfront costs to develop/purchase and maintain the PRO system
Outside clinic		
Mail	Low technology requirements Comparatively low cost	Require personnel to manage the mailing and score instruments Potentially high nonresponse rate Difficult to respond promptly if the patient reports serious problems Cannot ensure patients complete questionnaires alone
Telephone	Can be conducted by a live interviewer, which is more personal, or through an automated system Circumvent issues with literacy and physical challenges to completing questionnaires Can be more convenient	Live interviews are resource intensive, requiring both a skilled interviewer and data entry and may create problems with socially desirable responses Automated systems have higher upfront costs to develop/purchase and manage a validated, efficient tool and may be impersonal and off-putting to patients Patients may require training on the automated systems
Internet	Efficient because of immediate scoring and simultaneous data entry Enable adaptive testing Facilitate graphic score presentation Allow real-time feedback of results to clinicians Enable flexible timing and can be more convenient Possibility of linking to electronic medical record	Needs upfront investment to design the data collection system Require personnel to manage data collection over time Must ensure data security and privacy Patients may require training on how to use the system Not all patients have Internet access

Source: The International Society for Quality of Life Research (ISOQOL). *A User's Guide for Implementing Patient-Reported Outcomes Assessment in Clinical Practice*.

Key Point 5: Reporting PRO Results

- Integration into clinical workflows:
 - Non-integration means additional task burden
- PRO report recipients:
 - Clinicians, nurses, patients (methods of provision)
- Timing of PRO result processing:
 - During clinical encounters, pre-visit, or post-visit
- PRO presentation formats:
 - Numerical data, graphical displays, changes in data – clinically significant versus statistically significant

Key Point 6: Interpretation of Results

- Meaning of scores (e.g., higher scores indicating better levels?)
- Clinical significance assessment
- Establishing thresholds for different “severity levels”
- Reviewing PRO scores with patients, to clarify and contextualize issues
- Score comparisons (with general populations or similar patient groups)
- Current measurements versus longitudinal changes

Key Point 7: Responding to PRO Findings

- Prioritize issues identified through PRO results to enhance efficiency
- Clinical practice based on PRO results (if available)
 - In many cases, there are no guidelines; avoid compromising clinicians' professional autonomy
 - Integrate PRO tools with clinician workflows
- Provide feedback to clinicians after acting on PRO-identified issues

Key Point 8: Evaluating PRO Effectiveness

- **Quasi-experimental/quality improvement designs:** observational, survey, simple pre-post, uncontrolled designs
- Traditional experimental designs: randomized controlled trials (RCTs), cluster-randomized trials

Source: The International Society for Quality of Life Research (ISOQOL). *A User's Guide for Implementing Patient-Reported Outcomes Assessment in Clinical Practice*.

- Socially desirable bias: Respondents tend to answer questions in ways they believe are viewed favorably by others
- Recall bias: Systematic error due to inaccurate memory recall by respondents



Thank You !

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