

Research Methodology

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Abstract

Patient-reported outcomes: A new era in clinical research

Now-a-days there is significant discussion about patient-reported outcomes (PRO) in medical world. The following article covers almost all the areas of PRO including-their importance, important concepts for understanding of PRO, significance, ideal properties, types, development and evaluation of PRO instruments. It is useful for physicians, pharmacists and patients for the assessment and improvement of the therapy.

Key words: Patient reported outcomes, clinical research, PRO, quality of life

INTRODUCTION

'Patient' can be considered as the centre for any healthcare system. Now-a-days there is growing realization for the patient-centered healthcare system.^[1] The outcomes of a clinical intervention obtained by the patient i.e. patient-reported outcomes (PROs) are seemed to be of more importance in future than any other outcomes like clinical, physiological or caregiver-reported. As per studies, enhanced treatment adherence and outcomes can be obtained by giving attention to patient feedback on healthcare outcomes and patient behavior change.^[2]

As per US-FDA, a PRO is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else.^[3]

IMPORTANCE OF PRO

Though medical technology allows to measure physical, physiological or biochemical data of the patient; it is not able to give all the data about the treatment or the disease. Some data can be obtained only from the patient. Such data includes the things as mentioned in [Table 1].^[4]

In short, patient can tell many things like thoughts, complaints, opinions that technology or any observer can't and which is actually more valuable. As discussed earlier PRO are the measurements come directly from the patient. Further to add, in some diseases survival is not the ultimate goal of the treatment but quality of life also plays an essential role in the treatment. E.g. Cancer chemotherapy.^[5] Therefore, PROs are gaining the importance in clinical world.

PRO AND OTHER TYPES OF OUTCOMES

The outcomes are broadly classified into- clinical (e.g. cure, survival), humanistic (e.g. role performance, emotional status) and economical (e.g. expenses, saving).^[6] In clinical scenario the outcomes can be clinician reported (e.g. performance

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Table 1: Data can only be obtained from the patient

- Various symptoms
 - Symptoms not obvious to observers
e.g. fatigue, headache
 - Psychological symptoms
e.g. depression, anxiety
 - Symptoms in absence of observer
e.g. sleep disturbances
- Frequency of symptoms
e.g. Does the headache occur daily or weekly or monthly?
- Severity of symptoms
e.g. Headache is severe or moderate or mild?
- Nature and severity of disability of the patient
e.g. How severe is the breathlessness?
- The impact if disease or condition on daily life of the patient
e.g. Does rheumatoid arthritis interferes with the activities of daily living of the patient? If yes, how much is the impact?
- Perception or feeling of the patient towards the disease or the treatment given
e.g. Is the patient satisfied with the treatment given?

of the patient), caregiver reported (e.g. functional status), physiologic (e.g. tumor size by using MRI) or patient reported (e.g. symptoms). If the patient is observed for the outcomes by clinician, researcher or caregiver then the outcomes become observer reported outcomes (OROs).^[4] If the patient is revealing in the written questionnaire that he/she is experiencing morning stiffness is PRO but if the clinician is asking to describe about the morning stiffness i.e. severity and nature is considered to be ORO.

Proxy reported outcome is a measurement based on the report by someone other than the patient reporting as if he or she is the patient. It is different from a PRO or ORO.^[3]

DIFFERENCE BETWEEN SYMPTOMS AND HEALTH RELATED QUALITY OF LIFE

Although symptoms of the patient and health related quality of life (HRQOL) hear to be similar, they are the two different concepts. Symptom is a one-dimensional property while HRQOL is multidimensional. Symptoms are often main objective of treatment, mirror clinician-patient discourse and vary dynamically with time but in case of HRQOL all the above things are rarely. Symptoms are directly related to disease and treatment effect while there is indirect relation of them with HRQOL. In case of PRO concepts symptoms are often considered for behavioral objective measure but seldom for HRQOL. Complexity of the concepts is complex in HRQOL and simple in case of symptoms.^[7]

IMPORTANT CONCEPTS

Prior to know about PRO one should be familiar with the following concepts:

PRO instrument

A PRO instrument (i.e., a questionnaire plus the information and documentation that support its use) is a means to capture PRO data used to measure treatment benefit or risk in medical product clinical trials.^[3]

PRO concept

It is nothing but the thing or event being measured. It can be called as the specific goal of the instrument.^[3]
e.g. symptom or group of symptoms

PRO domain

A subconcept represented by a score of an instrument that measures a larger concept comprised of multiple domains.^[3]
e.g. depression

PRO item

An individual question, statement, or task (and its standardized response options) that is evaluated by the patient to address a particular concept.^[3]
e.g. Are you feeling depressed?

Conceptual framework

The conceptual framework explicitly defines the concepts measured by the instrument in a diagram that presents a description of the relationships between items, domain (sub-concepts) and concepts measured and the scores produced by a PRO instrument [Figure 1].^[3]

Endpoint

The measurement that will be statistically compared among treatment groups to assess the effect of treatment and that corresponds with the clinical trial's objectives, design, and data analysis.^[3]

End point model

A diagram of the hierarchy of relationships among all endpoints, both PRO and non-PRO, that corresponds to the clinical trial's objectives, design, and data analysis plan [Figure 2].^[3]

Conceptual equivalence

It is the equivalence in relevance and meaning of the concepts being measured in different languages and /or cultures.^[8]

Health Related Quality of Life

In simple words HRQOL can be defined as personal health status of the individual.^[9] Actually, it is a multi-domain concept which represents the patient's general perception of the effect of illness and treatment on various aspects of life such as physical, psychological, and social.^[3] Some other aspects also can be predicted to affect HRQOL like-economical, disease symptoms, adverse drug reactions, patient-education, disease-treatment given to the patient [Figure 3].

IDEAL PROPERTIES OF PRO INSTRUMENT

As per the literature,^[3,9] following ideal properties can be extracted-

- It should be specific to the concept being measured.
- It should be based on *end-point model*.
- It should have conceptual equivalence.
- It should be based on the conceptual framework.
- It should contain optimum number of items.
- It should have easy and specific measurement properties i.e. use of the scales which is easiest for the intended population to understand.
- It should have proper evidences for the conceptual framework.
- It should maintain the confidentiality of the patient.
- It should be reproducible.

SIGNIFICANCE OF PRO INSTRUMENTS

By using PRO, various types of outcomes can be measured such as physical functions, symptoms, global judgments of health, psychological well-being, social well-being, cognitive functioning, role activities, personal constructs, satisfaction with care,^[10] health related quality of life (HRQOL),^[11] adherence to medical regimens^[12] and clinical trial outcomes.^[10]

PROs may be helpful in determination of the eligibility of the patient for certain clinical trials. E.g. Inclusion criterion for the trial is female patients with hot flashes. PROs can be used for confirmation of the measures. E.g. patients

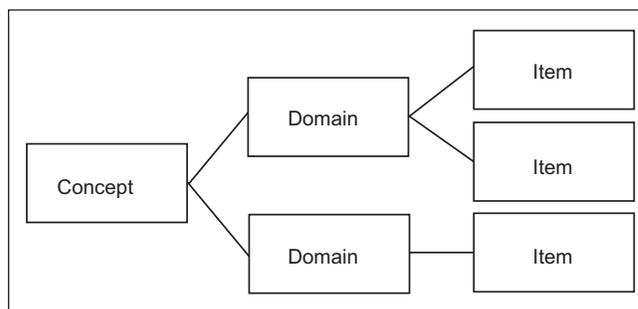


Figure 1: Conceptual framework in PRO instrument

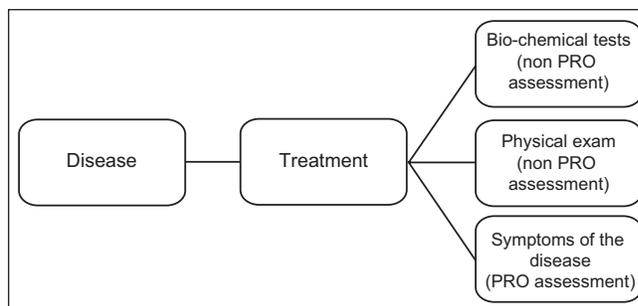


Figure 2: End-point model

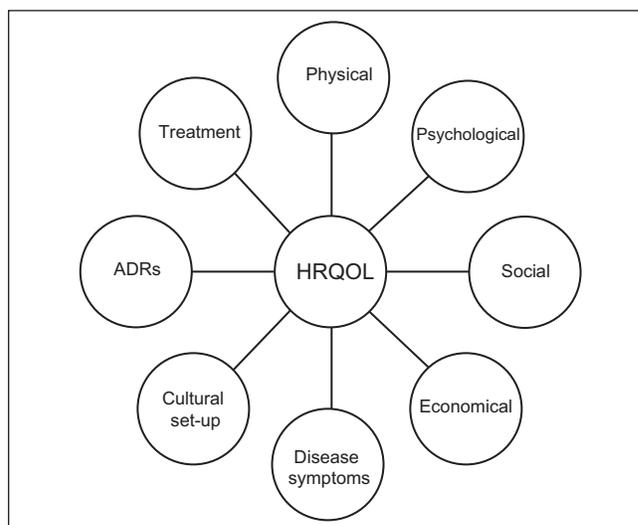


Figure 3: Factors affecting health related quality of life

with morning stiffness are most likely to be suffered from rheumatoid disease. PROs can help to interpret other measures and also help to eliminate other possibilities. E.g. If the patient has breathlessness and the patient is a smoker then COPD can be expected rather than anemia. PROs are useful in determination of patient compliance or reasons for non-compliance. E.g. Are the side effects so severe? PROs may be used as study endpoint. E.g. Efficacy of analgesic drug by determining pain levels.^[4]

In diseases like cancer it is important to determine the quality of life of the patient as patients with progression of cancer frequently experience multiple symptoms, economical

burden, home management problems and lack of emotional well-being, all of which can adversely affect quality of life.^[13] PROs are helpful in the determination of quality of life in cancer patients. Role of QOL/PROs in cancer care can be considered in the following conditions like^[14]

- Determination of negative effects of the adjuvant therapy
- Identification of the needs for the supportive care
- Comparison of two standard therapies having similar survival outcomes
- Identification of negative effects of the therapy when survival time is long
- To find out whether a new therapy is preferable to standard therapy
- To determine whether a therapeutic regimen is better than supportive care only, when survival time is short
- Targeting problems and making the communication easier in clinical practice

As PRO instruments are based upon the scores obtained by the patient without any interpretation; it gives a clear picture about the patient condition. PROs are useful for the patients, patient-family members and loved ones, healthcare providers, payers, regulatory authorities, technological assessors and researchers. PROs are beneficial for the patients as he/she asks for and experience the treatment. It is useful for patient family members and loved ones as they desire the best for the patient and themselves. The PRO data is also useful for healthcare providers and payers as they make a decision with patients on prescribing of treatments/therapy and pay for the treatment respectively. Information obtained from PRO can also be used by regulatory authorities (e.g. FDA) and technology assessors [e.g. National institute for health and clinical excellence (NICE)]. PRO studies make the consequences of the studies accessible through various publications like formulary submission dossiers, direct to consumer advertisements, journals and continuing medical educations (CME).^[9,15,16]

Conclusively, PROs are unique indicators of impact of disease on the patient, helpful in empowerment of the patients, necessary for determination of efficacy of the treatment, by communication helpful in creating a rapport between patient and healthcare providers, useful in the interpretation of clinical outcomes and treatment decision making.^[9]

TYPES OF PRO INSTRUMENTS

Broadly, PRO instruments can be classified as per the measurement of the interested concept as^[10,17]

- Generic (anticipated to detain a very wide variety of aspects of health status and the outcomes of illness

and hence to be applicable to a wide range of patient groups) e.g. Psychological General Well-Being Index (PGWBI)

- Disease specific e.g. Rheumatoid Arthritis Quality of Life questionnaire (RAQoL)
 - Dimension specific e.g. Physical Activity Index (PAI)
 - Region/site specific e.g. Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR)
 - Individualized (instruments in which the respondent is allowed to select issues, concerns or domains of personal concern that are not predetermined by the investigator's list of questionnaire items) e.g. Schedule for the Evaluation of Individual Quality of Life (SEIQoL)
 - Utility measures (considered as generic type but with one particular form of numerical evaluation of healthiness) e.g. Utility measure for major, unipolar depression (McSad)
 - Summary items e.g. questions (regarding limiting enduring illness) in General Household Survey
- All types of PROs have their own advantages and disadvantages.

DEVELOPMENT OF PRO INSTRUMENT

As per US-FDA,^[5] [Figure 4] there are five steps for the development of a PRO instrument. First, there will be theorization of a conceptual network. It may include outlining of potential claims and hypothesized concepts, determination of intended population and application i.e. scores, mode and frequency of administration, performance of expert/literature review, development of the framework, assignment of PROs in preliminary endpoint model and documentation of the preliminary instrument.

The second step may include finding of the patient inputs, making of new items, assortment of recall period, response options and format, selection of mode of administration and data collection, conduction of patient cognitive discussion, pilot testing of the outlined instrument and documentation of content validity.

Third step may include the following-confirmation, assessment and finalization of the instrument, documentation of measurement progress. In assessment of the score reliability, construct validity and ability to detect change will be done.

Fourth step may contain- preparation of protocol and SAP (statistical analysis plan), compilation and analysis of data, assessment of treatment response (by means of responder definition and cumulative distribution),

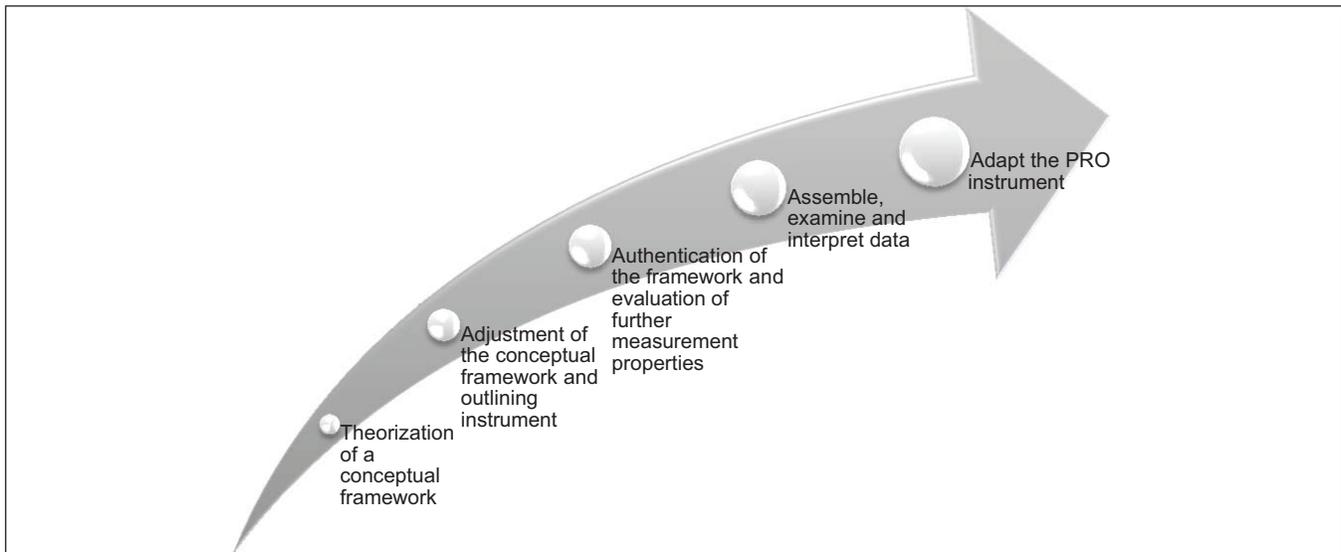


Figure 4: Development of PRO instrument

Table 2: Types of response scales

| Type of scale | Example |
|---------------------------|---|
| Likert scale | I feel that my leisure activities are affected after this illness. <input type="radio"/> Strongly agree <input type="radio"/> Agree <input type="radio"/> Undecided <input type="radio"/> Disagree <input type="radio"/> Strongly disagree |
| Visual Analog Scale (VAS) | To what extent do you feel that you have financial difficulties for the treatment of your disease? 0 ----- 10 |
| Categorized/anchored VAS | What is the severity of your pain? 0 2 4 6 8 10 |
| Pictorial scale | Circle the face that represents how do you feel about the treatment X?  |
| Rating scale | How many episodes have you had since last 7 days? <input type="checkbox"/> >10 <input type="checkbox"/> 7-10 <input type="checkbox"/> 5-7 <input type="checkbox"/> 2-5 <input type="checkbox"/> <2 |
| Checklist | Do you have lump in your breast? <input type="checkbox"/> Yes <input type="checkbox"/> No |

documentation of interpretation of treatment advantage (in relation to claim).

Fifth and last step in the development of the instrument is modification of the instrument which include- altering of phrasing of items, population response options and mode of administration, translation and culturally adaptation of the instrument, evaluation and documentation of the changes.

ADMINISTRATION OF PRO INSTRUMENT AND DATA COLLECTION

Data collection by using a PRO instrument can be done in three ways^[3] as by interview, self administration or combination of both. Live interviews may happen in person or by means of communication medium. Every method has its own positive and negative aspects.^[4]

RESPONSE SCALES

It is a set of answer choices that fall into an order e.g. from highest to lowest. A scale may be composed of pictures, numbers or categories.^[4] Following types of response scales or options may be used in a PRO instrument.^[3] The response scales are mentioned with example in the [Table 2].

Recording of events is also one of the methods to determine the response that can be included by the patient. E.g. diary maintained by the patient for the episodes of urination in night.

EVALUATION OF PRO

For the evaluation of a PRO instrument following things may be checked^[3]

- Validity
Content validity

- Construct validity
- Criterion validity
- Reliability
 - Test-retest or intra-interviewer reliability
 - Internal consistency
 - Inter-interviewer variability
- Ability to detect change

Validity

It is the degree to which evidence and theory support the interpretations of test scores entailed by the proposed uses of tests.^[18] Validity is not the property of the instrument i.e. PRO instrument but of instrument scores and their interpretations.^[18,19] Therefore, validity must be established for all proposed interpretation.

Content validity

It is the extent to which the instrument measures the concept of interest.^[3] Content validity of the instrument can be performed qualitatively as well as quantitatively.^[20] According to US-FDA(1), following attributes can be checked- item generation, data collection method and instrument administration mode, recall period, response options, instrument format instruction and training, patient cognition, scoring items and domains, respondent and administrator burden. The instrument should have proper evidence in the literature linking between concept being measured by the instrument and targeted claims.^[3,20] Quantitative analysis of the items is also desirable and helpful.^[20] E.g. evaluation of how well items deal with complete continuum of patient experiences. Item response theory (IRT) and Rasch analysis can be used to evaluate item information curves and what fraction of the response continuum items address.^[21,22]

IRT is a powerful tool for the evaluation of the questionnaire (PRO instrument) both at item and scale levels and tailors use of the same to the patients.^[23] Some important methodological considerations for IRT modeling are^[24]

- Should IRT methods be used by the researcher for the questionnaire?
- Which IRT model should be used?
- What sample size is needed for IRT analysis?

Rasch model is the only IRT model in which a person is characterized totally by the total score across the questions/items. Further to add, it is the simplest of such models having least number of the parameters for the person and only one constraint for each category of an item. It may be used to verify the degree to which scoring and summing is justifiable in the collected data and how well the information fit in the model.^[25]

Construct validity

It is defined as evidence that relationships among concepts, domains and items conform to *a priori* hypotheses concerning logical relationships that should exist with other measures or characteristics of patients and patient groups.^[3] It includes convergent, divergent and known groups' validity. In construct validity, measures of constructs theoretically should be related to each other and should in fact observe to be related to each other. In the similar way, in discriminant validity, one should be able to discriminate between dissimilar constructs.^[26] In known groups' validity, evidence for the thing that the instrument can differentiate between clinically distinct groups is checked.^[3]

Criterion validity

It is nothing but the extent to which the scores of a PRO instrument are related to a known *gold standard* measure of the same concept.^[3]

Here, the performance of the operationalization is checked against some criterion. In content validity, the criteria are the construct definition itself i.e. it is the direct judgment while in criterion validity, often there is a prediction about how the operationalization will perform based on the theory of construct. It may be of two types as "predictive" and "concurrent". In the former one there is assessment of the ability to predict something in the real world which is present theoretically. For instance, if there is measurement of slowness of movement in Parkinson's disease, we could give our measure to the respective patients and see if there is a high correlation between the scores and the degree of slowness. The presence of high correlation makes available an evidence for "predictive validity". In concurrent validity, there is assessment of the ability of the item to distinguish between the groups in real world as mentioned theoretically. E.g. in the assessment of breathlessness, the item should be able to distinguish between asthma and COPD.^[26]

Practically, it is difficult to determine the criterion validity as there is no gold standard for most PROs.^[3]

Reliability

It is the ability of a PRO instrument to yield reproducible and consistent estimates of true treatment effect.^[3] It is a necessary (but not adequate) component of validity.^[27,28] To establish the reliability of the scores before using the PRO-instrument in practice, it is necessary that there should be sufficient accrual of evidence.^[29] It can be predicted by three ways as 1) test-retest reliability- it is a measure of the ability of a psychologic testing instrument to yield the same result for a single Patient at 2 different test periods, which are closely spaced so that any variation detected reflects reliability of the instrument rather than changes

in the Patient's status.^[30] It may be considered as intra-interviewer reliability for interviewer administered PROs. This type of reliability is checked by intra-class correlation coefficient (ICC).^[31] As per the generic definition ICC is the ratio of true variance i.e. the variability between the targets and observed variance i.e. the total variance-true variance plus other variance. Time period between test and retest is an important factor here. 2) Internal consistency-The consistency of the results delivered in a test, ensuring that the various items measuring the different constructs deliver consistent scores.^[31] Internal consistency is determined with Cronbach's alpha. Cronbach's alpha is coefficient of reliability.^[32] It is defined as^[33]

$$\alpha = \frac{K}{K-1} \left(1 - \frac{\sum_{i=1}^K \sigma_{Y_i}^2}{\sigma_X^2} \right)$$

Where, K = the number of items

σ_X^2 = the variance of the observed total test scores

$\sigma_{Y_i}^2$ = the variance of component i for the current sample of persons

The α value theoretically ranges from 0 to 1. The value of ≥ 0.7 is considered to be optimum. Item-total correlation is yet another test that may be considered for internal consistency. It is the measure of the association between an item and the total score from the set of the items within the scale.^[34] It can be measured by using Pearson correlation coefficient. If the value of the Pearson correlation coefficient is high then stronger is the relationship between the items. 3) Inter-interviewer reliability – It determines the changes in the results when the instrument is administered by two or more interviewers. It is generally measured by Pearson's 'r' value.

Ability to detect the change

It is considered to be an important part in the evaluation of PRO instrument. The instrument should be able to detect the changes in the expected outcomes. For instance if there is an instrument which is determining the quality of life of breast cancer patient, then it should be able to predict the quality of life after the treatment. The quality of life score should be able to predict the improvement/stability in condition/worsening. Ability of the instrument to detect the changes may be affected by the various factors as per the type and concept to be determined.^[3]

ELECTRONIC PRO

Here the outcomes of the patients are collected by using electronic methods like electronic diaries, computers, telephones etc. The use of Electronic PRO (e-PRO) are found to be beneficial than paper based PRO.^[35] e-PROs

avoid data entry errors, give immediate access to data, enable to trigger alerts/notifications, reduce the missing information as compared to paper-based PRO, increase patient's willingness to report sensitive information. Further to add, data obtained from e-PRO gives real-time tracking of survey compliance. Some important barriers in use of e-PRO are- increased expense, limited time for patient-training and infrastructure study site. There may be some cultural resistance for the administration of electronic instrument.^[36]

The use of e-PRO was found to successful in various recent clinical trials.^[37,38]

SUMMARY

- Important concepts to be known - PRO, Concept, Domain, Item, End-point model, Conceptual framework, Conceptual equivalence, HRQOL
- Ideal properties of PRO instrument - Concept specific, End-point model, Based on conceptual framework, Optimum number of items, Reproducibility, Easy accessibility of scales by patients, Availability of proper evidence, Conceptual equivalence, Maintenance of confidentiality.
- Types of PRO instruments - Generic, Disease specific, Dimension specific, Region specific, individualized, Utility measures, Survey items
- Development of PRO instrument- (Steps)
 - Theorization of a conceptual framework;
 - Adjustment of the conceptual framework and outlining instrument;
 - Authentication of the framework and evaluation of further measurement properties;
 - Assemble, examine and interpret data;
 - Adapt the PRO instrument
- Types of response scales - Likert scale, visual analog scale (VAS), Anchored VAS, Pictorial scale, Rating scale, Checklist
- Evaluation of PRO instrument-
 - Validity - Content, Construct, Criterion;
 - Reliability - Test-retest reliability, internal consistency, inter-interviewer reliability
 - Ability to detect change

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