

# From 'Being Alive' to 'Living': why does PRO data matter?

Nimisha Joshi (Nimisha.Joshi@Adelphivalues.com)  
Rachel Thackray (Rachel.Thackray@Adelphivalues.com)



Adelphi  
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## INTRODUCTION

The healthcare industry has moved towards a value-based care system where the assessment of quality of life (QOL) of a patient is important and assessing QOL from the patient's perspective has increased priority.<sup>1</sup> Assessment of QOL is being conducted in many long-term therapies including oncology where it can be equally as important as being disease free. Can we perform QOL assessments by applying medical technology and answer questions such as:

1. How much is the pain?
2. How are you feeling?
3. How well can you perform daily activities?

The above questions can only be answered by the patient themselves. A Patient Reported Outcome (PRO) is a questionnaire filled by the patient on the key aspects of their health status such as symptoms, functioning, health related quality of life (HRQoL) and symptom burden. A PRO is a type of Clinical Outcome Assessment (COA). Other types of COAs include Observer Reported Outcome (ObsRO) completed by the carer of the patient such as a parent; Clinician-Reported Outcome (ClinRO) completed by a medical personnel and Performance Outcome (PerFO) evaluated and completed by trained personnel or completed by the patient independently.<sup>2,3</sup> A PRO can be generic, addressing the general health of a population, or be specific to a therapy area. They can be further classified based on their purpose or the key questions they intend to answer and have been described in Figure 1 below.

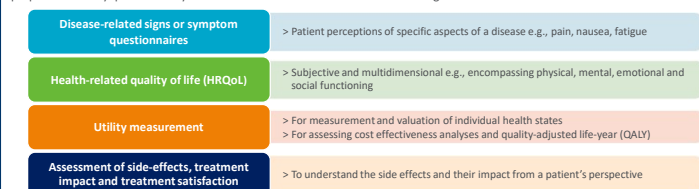


Figure 1: Types of PRO

## HOW IS A PRO DEVELOPED?

- > PROs are developed by the psychometricians and biostatisticians who work with a consortium of clinicians from healthcare institutions and experts from within the pharmaceutical companies.
- > The first step in PRO development is establishing the concept of interests, i.e., 'what is going to be measured by the questionnaire?' for example pain intensity. This requires reviewing existing literature and questionnaires and collecting information on key concepts by conducting open ended interviews with the patients. This collated information is used to develop a draft questionnaire that is revised further based on the feedback from the patients.<sup>7</sup>
- > The modified draft is psychometrically validated, and an appropriate scale is selected to measure the response of the patient. Further research is conducted on the concepts of validity and reliability.<sup>8</sup> Three aspects that are taken into consideration are as follows:
  - ✓ Content validity - 'Is the questionnaire measuring the concept it was designed for?'
  - ✓ Reliability - 'are we measuring the concept correctly?'
  - ✓ Is the score being interpreted appropriately by the investigating team?
- > Questions included in a PRO are qualitative in nature and they are assessed on a scale that assigns a value to each of the responses. The scale can be linear or may contain multiple options to capture the response efficiently. The questions may be adapted so that they are specific to the therapy area in question. A few examples of validated PROs are: EORTC QLQ-C30, FACT-G and EuroQol EQ-5D-5L. Patient's responses are collected on different types of scales as shown in Figure 3.

## WHY IS PRO DATA IMPORTANT?

- > PRO analysis is being applied in therapeutic areas including oncology, renal, immunotherapy, anti-inflammatory, neurology, gastrointestinal and respiratory amongst others.
- > As PRO data is not subject to clinical interpretation it provides vital information on the impact of a medical condition and its therapy from the patient's perspective.<sup>4</sup>
- > In recent years there has been an influx of combination and targeted therapies that produce a variety of side effects and assessment of many of these is dependent on the direct response of the patient.<sup>5</sup> Figure 2 illustrates the key questions that a PRO analysis can help answer.
- > PRO data can assist the clinicians and service providers in making informed decisions on the best cost-effective therapy to improve a patient's experience. It can also provide crucial information to design better clinical trials, to select suitable trial endpoints, and help in regulatory reviews including benefit-risk assessments.<sup>6</sup>

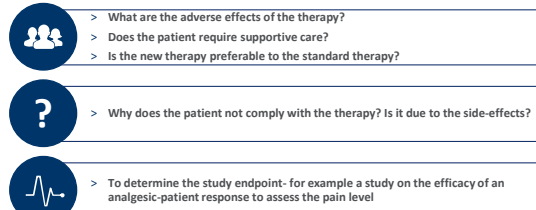


Figure 2: Important questions that PRO data can help answer

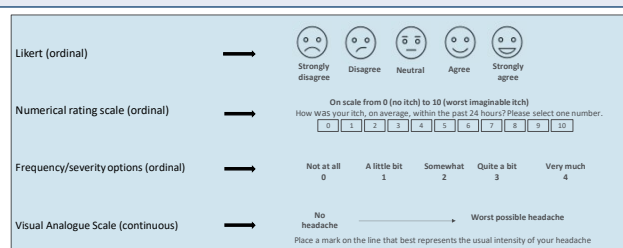


Figure 3: Types of Response scales

## WHAT DOES A PROGRAMMER NEED TO KNOW ABOUT PRO DATA?

### A. PRO items and the concept of domain scores

- > Questions within a PRO are called items and a patient responds to these questions by selecting a score associated with each response option. Related items are grouped together into groups called domains. Summation of all the domain scores is called the total score. Scores are usually derived at the item, domain, and total score level. These scores are recorded at the patient level and are often repeated across multiple visits from baseline onwards, depending on the study requirements.
- > The number of items in a PRO may vary depending on what the PRO is assessing. A PRO may have just one item such as Patient Global Impression of Severity (PGI-S) where the patient answers how they feel at a certain time-point or can be multi-item like Functional Assessment of Cancer Therapy - General (FACT-G) that is used in oncology. FACT-G is a multi-item and multidomain PRO in design and has 27-items designed to assess the HRQoL in cancer patients. The 27 items in FACT-G are grouped into 4 specific domains: Physical, social, emotional, and functional well-being and are shown in Figure 4.

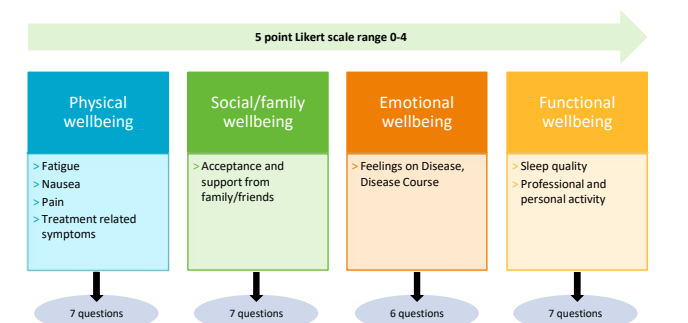


Figure 4: FACT-G is a PRO instrument used in oncology and comprises of 27 questions (items) which are grouped into 4 domains as illustrated above

### B. PRO data analysis: the output types

- > PRO data is used to create a variety of output types, some of them are therapy area specific. However, commonly created output types across all PRO analyses include:
  - > Completion rate tables that determine how many patients complete the PRO questionnaire at baseline and at subsequent time points for HRQoL compliance. This is usually analysed at the item level, and it assesses the completeness of the data.
  - > Descriptive PRO summaries that cover mean, median, variance of PRO data and change from baseline.
  - > Comparison between randomised treatment groups for the study duration.
  - > Sensitivity analyses that involves investigating the robustness of primary analysis of the PRO endpoint in order to confirm if the sensitivity analyses support the main results within a study.
  - > Figure outputs including line graphs, box plots, scatter plots and specialised outputs such as Receiver Operating Characteristic (ROC) curve.

### C. The concept of 'missing data'

As the study progresses patients may drop out due to reaching a pre-determined event (such as progression) or due to death, which creates the challenge of missing data at some timepoints. Graphical representation of missing data for example, plots where patients are described according to their last recorded assessment, helps in decision making to select the appropriate statistical methods for analysis and data interpretation.

### D. The direction of a scale and score interpretation

Programmers of PRO data are not only expected to be aware of the terminology and the PRO types as described in the statistical analysis plan but also need to be aware of the direction of the scale associated with each item, which may differ between items within the same PRO questionnaire.

Figure 5 shows two items from FACT-G questionnaire, GP2 and GS1. If the patient responds 'Not at all' to the question 'I have nausea', it is scored as 0 and is the most positive response for this question and shows increased wellness. However, if the patient responds 'Not at all' to the question 'I feel close to my family', it is also scored as 0 on the questionnaire but this time it is the most negative response and shows the lowest level of wellness for that question. When analysing the data, the programmer needs to take this into account to ensure the direction of the scores is the same for all items. In the case of FACT-G, the score of 0 for 'I have nausea' is treated as: 4 - 0 = 4 and the score of 0 for 'I feel close to my family' is treated as: 0 - 0 = 0. This is applied across all the items that require reverse scores to align the direction of responses across all items in the questionnaire.

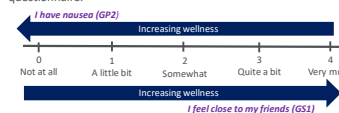
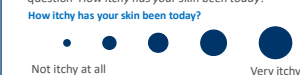


Figure 5: Direction of scale and score interpretation

## ADAPTING A PRO TO DIFFERENT POPULATION TYPES

- > PRO questionnaires are dynamic methods to help assess the quality of life of a patient and often the challenge lies in optimising the questions and responses to cater to different patient populations.
- > Adelphi Values PCO actively works in the development and validation of PRO instruments for niche patient populations. This may be adapting a validated questionnaire for a specific disease type or adapting it for children whose responses are more challenging to capture as they may not be able to read or measure the difference between options in the questionnaire and may find it difficult to select the appropriate response.
- > For instance, in an eczema trial in children, to measure the degree of itch, the response could be depicted as an increase in the size of a circle from 'Not itchy at all' to 'Very itchy' for the question 'How itchy has your skin been today?'



## CONCLUSION

- > Applications of PROs are likely to continue to expand in the future, with them becoming more commonly part of the initial design of clinical trials for the development of new drugs.<sup>11</sup>
- > The increased use of PROs in clinical trials means clinical trial programmers should be aware of the nuances of PRO data.
- > PROs assist with the process of identifying unmet needs of patients, providing greater autonomy to the patient.

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## DATA COLLECTION METHOD FOR PRO ANALYSIS

Like all clinical trials data, PRO data has historically been collected largely on paper-based forms, filled by the patient. However, in recent years these forms have been rapidly replaced by e-PROs and smart wearable devices.<sup>9</sup> e-PROs may be developed as apps that can be downloaded to the patient's phone or tablet or a loan tablet that may be provided to the patient. Wearables based on sensor technology are increasingly being employed to assess and quantify the wearers physiology and their responses in real-time.

## EXAMPLE WHERE BURDEN OF DISEASE IN IMMUNE THROMBOCYTOPENIA (ITP) WAS ASSESSED BY ADELPHI USING PATIENT DATA FROM THE UK-I-WISH STUDY

- > Immune thrombocytopenia (ITP) is a disease defined by a platelet count of  $<100 \times 10^9/L$  with no diagnostic test for ITP but the exclusion of other thrombocytopenia conditions. Though platelet count is the main measure of disease activity in ITP, other factors such as fatigue are frequently reported. However, limited data are available on the burden of ITP for patients and the impact on QoL.
- > The aim of I-WISH was to investigate differences between patients' perceptions of symptom burden, treatment goals and disease management. Adelphi Values PCO team worked with the pharmaceutical company sponsor and completed supportive work focusing on the psychometric properties of the Immune Thrombocytopenia Life Quality Index (ILQI), concluding that the ILQI PRO questionnaire effectively measures a wide range of ITP impacts. This aspect of the psychometric evaluation of the ILQI questionnaire is important in supporting the key conclusions of the I-WISH study.<sup>10</sup>
- > The analysis of the ILQI questionnaire data highlighted the multifaceted burden of ITP on patients' lives; in an analysis of responses from UK patients, it was concluded that fatigue remains a major unmet need, therefore improvements in the management of fatigue in ITP patients would be beneficial.

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