

## Article title

### Can a Patient Reported Outcome be adequate without assessing quality of life in lower urinary tract dysfunction?

#### Abstract

A think tank was convened at the sixth ICI-RS meeting held in the UK, September 2015, to consider the adequacy of patient reported outcome (PRO) measurement if quality of life (QoL) evaluation were excluded. Rigorous methodology is proposed for the development of PROs and much is written about this process but the necessity for QoL inclusion is rarely discussed. The decision was therefore taken to consider what QoL evaluation provides and what these data provide. Discussions highlighted the need to question our aim for including QoL evaluation in clinical practice and research in order to ensure its necessity for the intended purpose. Improved understanding of the usefulness of QoL data, in particular in relation to important health indicators was also identified as an area of unmet need. The think tank ended with a collaborative research proposal to pool existing QoL databases to explore the correlations with other outcome measures and types of associations present. It was suggested that these findings would enable clinicians and researchers to make more informed decisions regarding PRO selection, use and interpretation.

#### Background

Since 2009, the ICI-RS meetings have introduced a platform for research active individuals with expertise and interest in the area of incontinence to discuss current status and research needs within the field. This arena enables individuals to share experiences and discuss areas of unmet need in terms of research by comparison with the more traditional extensive reviews of 'what is already known'. This report is therefore an account of the think tank proceedings that were discussed at the sixth ICI-RS meeting to consider the adequacies of PROs in lower urinary tract dysfunction if quality of life evaluation were excluded. The intention was to explore through group discussion, the inclusion of quality of life (QoL) evaluation and the value that adds to patient evaluation. From this, opportunities for research and questions that we cannot answer were identified rather than a comprehensive review of PROs or QoL research in lower urinary tract dysfunction (LUTD).

Benign conditions may cause significant costs for the National Health Services and impact negatively on patients' quality of life. In LUTD, deterioration of quality of life is a major driver of patient help seeking behaviour and its restoration is one of the obvious aims of treatment together with reducing the direct and indirect costs caused by the condition. LUTDs include ailments in which the quality of the outcome is difficult to measure as it highly depends on the type of outcome measures considered and for which no consensus exists as to the ideal quality measure. Regulatory agencies are particularly interested in patient reported outcome as they provide the sufferer evaluation of treatment outcome and offer a more holistic approach in medicine. Patient reported outcomes (PRO) are defined as "any report of a patient's health condition that comes directly from the patient"<sup>1</sup>. Instruments to measure these parameters have been developed and termed "patient reported outcome measures" (PROM), more specifically within the UK, "to assess the quality of care delivered to NHS patients from their perspective"<sup>2</sup>. The notion of robustly gathering the patients' insight with regard to their own outcomes appears obvious but unless PROs are developed accurately and robustly the data provided can simply pay lip service to this endeavour. In recent years, the research field surrounding PRO development has seen significant growth with influences from both the scientific and regulatory communities<sup>3</sup>. Rigorous guidelines have been proposed to support the development process of PROs, primarily to facilitate qualification of the instrument as an outcome measure to support pharmaceutical labelling claims submitted to the FDA. However, the methods described are those that have been recommended by experts in questionnaire design for a number of years and represent a gold standard formula for the production of high quality instruments<sup>4-7</sup> (figure 1).

Reprinted from: Food & Drug Administration. Guidance for industry - patient-reported outcome measures: Use in medical product development to support labeling claims. Silver Spring, MD: FDA; 2009<sup>1</sup>.

Within LUTD PROs are commonly used in clinical research as trial screeners and outcome measures, for long term follow-up and to support labelling claims in the pharmaceutical industry. Within clinical practice their use is growing to guide decision making with patient pathways, provide robust treatment evaluation and to enable health care practitioners to audit and publish their outcome results.

PROs are often used to evaluate QoL as they facilitate exploration of the patient's perception of their situation. QoL is defined by the WHO as 'perception of position in life related to goals, expectations, standards and concerns'<sup>8</sup>. It is recognised that QoL can be affected by various parameters such as social relationships, personal beliefs, psychological state, level of independence and, of particular relevance here, physical health, leading to the more specific definition of Health-related quality of life (HRQoL). HRQoL is described as:

- Attributes valued by patients including resultant comfort or sense of well being,
- Extent to which individuals can maintain physical, emotional and intellectual function,
- Degree to which individuals retain ability to participate in valued activities within the family, workplace and community<sup>9</sup>.

The authors were therefore tasked with convening a think tank at the ICI-RS 2015 meeting to discuss the necessity of inclusion of these concepts in PRO evaluation.

Where conditions are non-life threatening, as with incontinence, it can be argued that QoL becomes more relevant in terms of outcomes. Yet, it was suggested, the use of QoL as an outcome or a quality measure makes sense only if QoL is an independent component of outcome or quality, different for example from symptoms. Other commonly used outcomes include efficacy, effectiveness, costs and cost effectiveness. The importance of these other outcomes cannot be overlooked. Yet, given that LUTD is not life threatening but can be significantly life restricting, impact on QoL is undoubtedly a consideration.

Intrinsically linked to QoL evaluation are the individual patients. The many and varied characteristics of patients and variability within each patient, particularly in relation to a subjective phenomenon such as QoL, is unavoidable. Patients' perceptions of their health state and potential treatments will influence self-assessment along with transient events but through rigorous development PROs can offer a valuable tool in the spectrum of outcome evaluation.

An extensive review of PROs for lower urinary tract dysfunction (LUTD) was not the purpose of this think tank but it was recognised that a high number of robust PROs are available for assessment in the area of LUTD<sup>3</sup>. In contrast to generic 'health-state' instruments, which may overlook the subtleties of LUTD, condition-specific instruments have been developed to be sensitive to the specific nuances of these symptoms and can focus on different aspects such as symptoms, functioning and QoL, in isolation or in combination. We therefore initiated discussions with the broad question, "Is QoL evaluation required in PROs?".

### **Is QoL evaluation required in PROs?**

Discussions raised four main themes regarding the necessity for inclusion of QoL evaluation in the clinical area of LUTD (figure 2):

### *Depends on intended evaluation*

In LUTD, symptom presence may dominate assessment rather than the impact of those symptoms and determining the intended evaluation can clarify if QoL assessment is relevant in a given situation.

### *What are we missing if QoL evaluation is not included?*

Clinical evaluations focus more on physical features and findings do not necessarily correlate linearly with QoL evaluations. Patient evaluations tend to reflect a combination of mental, emotional and physical characteristics more accurately correlating with actual experience. Therefore can overlooking QoL evaluation miss important determinants of life satisfaction?

### *Is it more relevant in certain conditions?*

Chronic symptom complexes that are more difficult to manage may have more necessity for QoL evaluation. Balancing the improvement of symptoms with the reduction of side effects from interventions may be better reflected in QoL evaluation which may dominate where symptom resolution is not achievable. It must be recognised however, that resolution of symptoms and the advance of others can result in QoL stasis which may overlook actual changes that have occurred.

### *Routinely used in clinical trials but are these data given sufficient weight?*

QoL tools are increasingly incorporated into clinical trials but how often are they considered a primary endpoint? Inclusion as secondary outcomes is still of great value but how often are these reported sufficiently and what priority are these data given?

### *QoL, a moving target*

Clinical research has shown that patient perception of treatment outcome may change over time because priorities change in life and so does quality of life perception (surgical correction of lower urinary tract malformations aims at achieving continence but later on sexual and pregnancy issues may arise in the same young patient).

## **How does QoL relate to important health indicators?**

Our discussions highlighted, that in the area of LUTD where tools are available and uptake is in evidence, perhaps we do not fully understand the relationship of QoL with important indicators. It is important to consider the useful interpretation of these QoL data in order to explore the necessity for inclusion in PROs. Two areas of proposed exploration emerged in order to better understand the usefulness of QoL data (Table 1).

Better understanding of these relationships may enable clinicians and researchers to more adequately judge the usefulness of QoL data in order to use it more effectively rather than relying on symptom reports alone. As suggested by the WHO<sup>8</sup>, *“The measurement of health and the effects of health care must include not only an indication of changes in the frequency and severity of diseases but also an estimation of well being and this can be assessed by measuring the improvement in the quality of life related to health care”*. Attempts to include QoL PRO assessment to conform with expectations can be misguided and therefore appropriate selection of PROs requires education. A case study was provided that illustrated the necessity to consider the intended evaluation when identifying PROs for use rather than considering PRO incorporation as a ‘tick box’ exercise.

*A lady who had received a mid-urethral tape presented with no stress urinary incontinence but severe frequency and nocturia. Completion of two PROs was described: the ICIQ-UI Short Form<sup>10</sup>, which is a PRO specific to urinary incontinence, and Patient Perception of Bladder Condition<sup>11</sup>.*

*The ICIQ-UI Short Form provided a very low score indicating a low level of symptoms and impact imposed while the PPBC indicated severe problems.*

In this case study, consideration of the appropriateness of PRO selection was highlighted as a key step in identifying appropriate tools. The PPBC indicated a high level of problems for the individual as it evaluates broader symptoms related to bladder conditions. The ICIQ-UI Short Form indicated minimal symptoms as would be expected using an incontinence-specific questionnaire given that the patient was not experiencing incontinence. Whilst the ICIQ-UI Short Form is used widely it was not an appropriate tool to evaluate the symptoms being presented and would have provided misleading results if it had been used in isolation.

Evaluation of treatment outcome in LUTS highly depends upon the outcome measure considered<sup>12</sup> and the use of QoL instruments may help quantifying the overall outcome of treatments hopefully reflecting the complexity of the disease. QoL measures are ideally incorporated into PRO instruments and should be integrated by subjective and objective parameters of treatment outcome which may help identifying areas in which treatment was effective, failed or detrimental. Furthermore QoL measures may help in qualifying the clinical relevance of changes in objective parameters.

### **Further exploration of the importance of QoL evaluation**

The case study above highlights the need for improved education regarding PRO development and selection in order to make it a useful addition. The valuable discussion at the meeting also identified a number of areas for further exploration in order to better understand the importance of QoL evaluation in clinical practice and research:

- What is the patients' and clinicians' perspective on the importance of QoL evaluation in this area?
- We assume QoL data enables more targeted treatment and improved counselling regarding anticipated outcomes rather than absolute clinical outcomes but is this the case?
- How much influence do the QoL findings have?
- With the introduction of PRO qualification by the FDA will/has PRO use as primary endpoints altered?
- As QoL outcomes are often slower to respond are they better placed to evaluate prolonged treatment outcomes?

It is recognised that the questions above will not be answered in the short term so three pragmatic recommendations were suggested that could be more easily implemented in the short term.

### **Recommendations**

1. Ensure the correct development process is undertaken with new PRO development or existing PRO selection, namely inclusion of the concept elicitation phase to ensure the important areas of evaluation from the patients' and clinicians' perspectives are included.
2. We agree that QoL evaluation is probably required but whether we are doing it correctly requires further evaluation. A 'toolkit' was suggested to guide PRO selection.
3. Project proposal: retrospective evaluation of existing QoL databases held by ICI-RS members to explore the correlations with other outcome measures and types of associations present.

### **Conclusions**

Reiterating the principles of robust PRO design and challenging clinicians and researchers to question their intentions when using these tools was a useful exercise. The opportunity to revisit the key considerations underpinning the use of PROs was valuable and also highlighted unknown aspects of this area of PRO research. It was identified that while significant progress is being made in the field of PRO development and uptake of these tools is high in trial publications, perhaps our understanding of the usefulness of these data is not so well developed. In order to make QoL data really valuable in clinical practice and research we need to explore fully why we include it. We need to also consider how that links with health indicators to really evaluate, “So, what does this mean?”. The opportunity to collaborate with ICI-RS members using existing datasets would provide an opportunity to investigate correlations between objective/subjective outcome measures and QoL parameters in large numbers. Such a project would provide the basis for robust conclusions and recommendations regarding the inclusion of QoL evaluation in patient assessment.

The authors welcome further input regarding any of the issues raised and are very grateful for the group discussion at the ICI-RS meeting.

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