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Patient-reported outcomes (PROs): the significance of using humanistic measures in clinical trial and clinical practice

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Abstract. – Patient-reported outcome (PRO) is an "umbrella term" that covers a whole range of potential types of measurement but it is used specifically to refer to all measures quantifying the state of health through the evaluation of outcomes reported by the patient himself/herself. PROs are increasingly seen as complementary to biomedical measures and they are being incorporated more frequently into clinical trials and clinical practice. After considering the cultural background of PROs – that is the well known patient-centered model of medicine –, their historical profile (since 1914, the year of the first outcome measure) and typologies, the paper aims at debating their methodological complexity and implementation into practice. Some clinical trials and therapeutic managements utilizing patient-centered measures will be also analyzed.

Key Words:
Patient-reported outcome, Trial, Therapeutic management.

Introduction

Since the Sixties, the disease-centered model of conventional medicine has been widely criticized and the importance of a bio-psycho-social approach has been suggested[1].

The latter was largely developed by the American psychiatrist G. Engel[2]. It is characterized by a holistic approach that improves biological aspects with psychological and social considerations[3] and its implementation into clinical practice has started a new model, the so called "patient-centered" approach[4-14].

Patient-centered medicine is based on the claim that patients should be active participants in their care. In other words, patients become experts of their experience of disease (*illness*)[15].

During the Eighties, when the patient-centered model was conceptualized for the first time, it was considered a "soft" model for a small group of fans[16].

Nowadays, its role has expanded and it is the basis of many curricula of universities all over the world. Furthermore, it is of great importance within the *outcome research*, being cultural background of it.

Outcome Research

Outcome research is the assessment of the value of different types of health care treatments (from common drugs administration to complex care strategies) within real settings, using methodological approaches scientifically well-established and both clinical-economic (symptoms, severity, survival, Health Related Quality of Life costs, etc.) and humanistic outcome measures[17].

Its aim is to: a. obtain well-founded measurements to describe outcomes of interventions; b. conduct studies in order to produce well-founded evidences concerning the value of "real" interventions[17,18].

The idea of evaluating outcomes of health interventions is certainly not new.

Nevertheless, – as G. Apolone has noted[17] – the novelty of outcome research consists in: (1) an enlarged definition of intervention, including not only drug treatments but also, and above all, complex health care strategies; (2) the context in which results are applied and generalized (ideal and real settings). (3) and above all, an enlarged definition of outcome, including not only clinical and economic parameters, but also humanistic measures. In other words, when outcomes of healthcare treatments are assessed, both clinical-economic (e.g., generic and disease-specific mortality, markers as blood pressure levels, pathological events as infarcts, ictus or work days missed due to healthcare treatments, etc.)[19] and humanistic outcomes should be considered.

The way from clinic outcomes to humanistic ones, i.e. patient-reported outcomes (PROs) was long. A brief synthesis is the following.

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Historical Profile, Definition and Classifications

From a historical point of view, the first exhortations to assess health outcomes have been clearly raised from bioclinical context[20-21].

In 1914, the surgeon and anesthesiologist EA Codman observed that the hospitals of that period posted the number of patients treated, but not the benefits[22].

After a long silence, the term "outcome" reappeared during the Fifties, when PA Lembcke, a physician and epidemiologist at the Johns Hopkins University in Baltimore (USA), associated it with the concept of "quality" of services[23].

A few years later, a physician named A. Donabedian proposed a model for assessing health care quality based on three types of parameters or indicators: structure/process/outcome. He defined "structure" as the environment in which health care is provided, "process" as the method by which health care is provided, and "outcome" as the consequence of the health care provided[24,25]. So, the study of quality in health care and medical outcome research was born.

Nevertheless, from a conceptual point of view, outcomes held a prominent position, only between the Seventies and Eighties, when they began to be used as possible criteria to verify the reasonableness of costs.

Just in this health context, some works started, which will be important in order to develop today's PROs.

The RAND Health Insurance Experiment (RAND HIE) is the most famous among these: it was an experimental study of health care costs, utilization and outcomes in the United States, which assigned people randomly to different kinds of plans and followed their behavior, in 1974-1982.

The assessment tools of this research spread far and wide, and a review of them was used again within the Medical Outcomes Study (MOS), an observational study designed to examine the care patterns and outcomes of patients with chronic medical conditions (e.g., congestive heart failure, myocardial infarction, hypertension, diabetes) and depression among different provider specialties, treatment systems and payment mechanisms. The MOS will be fundamental in order to sanction the methodological elements that characterize today's PROs conceptualization.

PROs put together two terms (*patient-reported* and *outcome*) and – according to D.L. Patrick – they mean "any report coming directly from patients, without interpretation by physicians or others, about how they function or feel in relation to a health condition and its therapy"[26].

The term "PRO" is often used to refer to the things being measured (i.e., concepts and domains (discrete concepts within a multidomain concept)), the instrument used to measure the concepts (e.g. questionnaires, diaries, interview, etc.) and the actual end points (i.e., the outcomes as analyzed in a particular clinical trial).

In other words, PROs are "a useful terminology as an organizing tool for the many concepts and applications of self-reports in treatment evaluations and population surveys"[27].

There are several ways of categorizing instruments designed to measure PROs.

First of all, they can be subdivided into "generic instruments" and "specific" ones. Generic instruments measure the full range of domains without focusing on specific areas. They are designed for use across a wide variety of populations. Specific instruments are designed for application to individuals, conditions or diseases, domains, or populations.

More, the measures can be classified according to the following: (1) *source of the report* – information was gathered from the patient or proxy; (2) *mode of data collection* – the data was collected through self administration, interviewer-administered or computer administered tests; (3) *testing content* – use of adaptive or dynamic testing where the content varies for individuals and items are calibrated or standard content where everyone takes the same items; (4) *types of scores* – reflecting the level of aggregation across concepts and domains; (5) *range of population and concepts* included or covered; (6) *weighing system* used in scoring items – whether an indicator, index, profile, or battery, instruments can be divided into two broad categories[27].

Finally, PROs can refer to different dimensions: symptoms and pain; health status and social and psychological functioning; satisfaction with treatment and care.

Furthermore, they are characterized by three methodological elements: (1) patients' centrality and the consideration for which health care treatment could be assessed by their perceptions; (2) an operative definition of the concept of health according to the World Health Organization's instructions; (3) the use of standardized self-completed questionnaires.

The three elements were present – and this was new – within the questionnaire of the MOS (MOS 36-item short-form health survey or SF-36), a gold standard in the context of PROs for a long time.

Nevertheless, further circumstances has increased the use of PROs.

In the first place, the Engel's enlargement of the biological model of medicine in favor of the bio-psycho-social approach. To tell the truth, Sociology followed this line of reasoning for a long time, but the Author ignored it probably because the scientific and medical community looked warily at hints from social disciplines.

In the second place, the progressive inclusion of some no bio-medical aspects within diagnostic and prognostic protocols, as from the Fifties.

In the third place, the contribution of psychiatry, a field in which self-completed questionnaires for diagnoses (e.g. questionnaires to assess depression) appeared since the Fifties and Sixties.

In the fourth place, the wide spread of the Quality of Life (QoL), a well-known PRO, whose concept has become the subject of an impressive number of publications, and of the Health-Related Quality of Life (HRQoL), a multidimensional construct referring to patients' perceptions of the impact of disease and treatment on their physical, psychological and social function.

In the fifth place, some regulatory agencies such as the Food & Drug Administration (FDA) or the European Medicines Agency (EMA) have started the use of PROs in the evaluation of medical products[28-33]. This attracted substantial capitals to the PROs sector.

Finally, PROs are inereasingly used within the health tecnology assessment (HTA) processes[34-38].

Critical Points

As noted, the scientific community looked warily at hints from humanistic disciplines. Beyond the aspects of custom, PROs use raises several difficulties anyway. These difficulties could be summed up briefly as:

1. *Scientific value*: evidence has been collected confirming the scientific value of these instruments, but only under "ideal" conditions. Instead, studies on their "real" efficacy are few.

2. *Methodology*: the main methodological issues that the literature[34] has identified are the following: extent; difficulty of choosing; instability of defining some concepts that characterize them (e.g. health, quality of life, wellbeing, etc.); data collection timing within the follow-up (answers could vary according to temporal distance from administration of questionnaires); cultural validation process and, above all, standardization.
In this respect particular doubts arise over the efficacy of these instruments to the point that some Authors propose to de-standardize these measures.
The main strategies that have been suggested are:
- The Experience Sampling Method (ESM), a means for collecting information about both the context and content of the daily life of individual by asking individuals to provide written responses to both open- and closed-ended questions at several random points throughout each day of a normal week, whenever a signaling device prompts them to respond;
- The individualized approach, for which interviewer and interviewee set up together questionnaires. An example of them is the Schedule for the Evaluation of Individual Quality of Life (SEIQoL), for the assessment of quality of life;
- Computer adaptive tests, that could be defined as the computer based tests which are created and adapted specifically for each examinee based on the examinee's ability estimate, and based on the way in which each examinee has responded to the previous items that have been administered to them. An example is the PRO Measurement Information System (PROMIS) for the assessment of chronic diseases.

3. *Utility*: the "real" utility of the PRO has been the object of *The Outcome of the Outcomes Research*[40] by the U.S. Agency for Healthcare Research and Quality (AHCPR). It has illustrated the repercussion of using PROs by a pyramidal model. Results are pessimistic and indicates that PROs are under several studies but their implementation into decision-making culture is far.

Instead, Valderas et al.'s review[41] is not so pessimistic. According to them, some improvements in the standard of clinical practice (e.g. diagnosis or doctor-patient communication) could be reached by implementing PROs.

Conclusions

PROs are being increasingly used and the implementation of them into trials and health care strategies is wider. Nevertheless – as we have noted – scientific and methodological doubts are several.

However, some merits are unquestionable: in the first place, they have reduce the (positivistic) rift between medicine and humanistic disciplines; in the second place, the care process is more patient-centered thanks to them.

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