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Report - Oncology Working Party Health Related Quality of Life (HRQoL) workshop 2nd May 2012

Health Related Quality of Life

Health-related quality of life is a multi-domain concept referring to the effect of an illness and its therapy upon a patient's physical, psychological and social wellbeing, as perceived by the patients themselves. In clinical research, health-related quality of life measures can provide a means of capturing the personal and social context of the disease experience.

Aim

The intention of this workshop was to gather information/opinion in order to generate a Health Related Quality of Life/Patient Reported Outcome (HRQoL/PRO) appendix to the general Guideline on the 'Evaluation of anticancer medicinal products in Man'.

Disclaimer

The views reported in this document are those expressed by workshop participants; they should not be understood as being those of the Oncology Working Party and they are in no way binding to the Oncology Working Party.



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Stakeholder Presentations

Patient Perspective

One of the two patient representative's presentations considered the setting of incurable cancer where there are no further treatment options and where participation in clinical trials is the only available therapeutic option. Particularly in this setting, HRQoL was considered to be very important, as patient access to such trials can give hope. However, for some patients, there is also the potential of stress, related to whether one is on the active treatment or the control (often placebo) arm of the trial. For such patients, HRQoL is not only related to the disease process and drug, but also related to the whole process of participating in the clinical trial. Finally, it is possible that improvements in HRQoL that the patient may value significantly may not be captured by other endpoints, e.g. this improvement may be associated only with a partial tumour response, which underscores the importance of collecting HRQoL data.

The second patient and caregiver representative's presentation highlighted a potentially innovative way of collecting HRQoL data: patients and their families organise themselves online, outside formal clinical trial participation and exchange experiences and advice via online fora, such as www.patientslikeme.com. The patient representative also argued for the reporting of HRQoL data in the post-approval real life clinical settings (can inform about issues such as inequities and accessibility, reimbursement decisions), for collection of information from caregivers and for exchange of information, especially in the case of rare diseases. In conclusion, the patient representative stressed that an improvement in HRQoL is a valid and achievable objective for cancer treatment and HRQoL should have a central position in determining clinical benefit.

Industry Perspective

The industry presentation welcomed the announced HRQoL/PRO appendix to the general anticancer guideline, but highlighted the following issues: under what circumstances HRQoL measures or PRO measures should be used, that expertise should be employed in scientific advice (SA) and regulatory assessment of relevant measures used in clinical trials, that the use of these measures should be carefully considered and correctly/diligently employed, the potential burden on investigators, physicians, patients and caregivers, whether relevant information will play a role in benefit/risk assessment (compared to other endpoints like Overall survival [OS], Progression-Free Survival [PFS]) or reimbursement decisions and whether it will be reflected in the Product Information.

Industry supported that: PROs should be included to characterise the symptom burden of the treatment regimen(s) from the perspective of the patient, to help with benefit risk assessment (include all key symptoms related to the disease, the experimental regimen, and the comparator regimen); PROs may be included to support labelling claims related to improved efficacy or toxicity and facilitate the patient-physician discussion on the therapeutic options; PROs may support PFS or a surrogate endpoint; PROs may help if clinical significance of primary endpoint is not conclusive; PROs should be included as patient-relevant evidence for market access and reimbursement (e.g., EuroQoL-5 Dimensions, EQ5D); the assessment burden of multiple PROs on cancer patients and sites must be reasonable and if multiple HRQoL (PRO) comparisons are being made, it is important to have adequate statistical multiplicity control in order to avoid spurious findings; finally, PRO compliance and study design must be sufficient to allow interpretation of the data.

Health Technology Assessment (HTA) Perspective

For the Relative Effectiveness Assessment of pharmaceuticals, HRQoL is one of three important factors (mortality, morbidity, HRQoL). There have been cases where, even though the therapeutic benefit was modest for authorisation purposes, the HTA assessment was quite positive on HRQoL grounds. Both generic HRQoL and disease (or population) specific questionnaires used in clinical trials are useful. Treatment effects on HRQoL should be investigated in comparative, interventional trials. However, in some circumstances, 'real life' trial settings may reduce the influence of trial conduct on QoL results.

Where Cost-Utility assessment is required by an HTA body it will usually be necessary to present health gains in terms of quality-adjusted life years (QALYs). HRQoL needs to be translated into utility so that it can be incorporated into the calculation of the QALY. In choosing which HRQoL measure to collect in trials, it is important to consider the need to attach utility values to the health states within the model. This is usually done by using a generic health status instrument, such as the EQ-5D or the SF-36 (Short Form-36), for which a set of preference-based utility values has been elicited. The use of observational data sets to measure HRQoL may be particularly useful to obtain utilities for health states that are infrequently seen in trials.

Topics for discussion

Clinical Trial Design

As with other aspects of clinical trial design, good science applies to the assessment of HRQoL. No scientific method performs at its best when it is included as an add-on to a mature clinical development programme and careful thought must go into designing and implementing HRQoL in the oncology clinical trial setting.

[When should HRQoL assessment be included in the clinical development programme for oncology drugs?](#)

The optimal timing of HRQoL assessment in the clinical development programme for oncology drugs is hard to define. Proposals included assessment as early as in phase I trials with the use of in depth interviews with patients and pre-specification of symptom- or disease-specific measures as primary endpoints and as late as in the immediate post-authorisation setting. Other proposals included use in phase II trials, in order to inform decisions on the design of phase III trials or phase II/III adaptive designs.

[Should HRQoL measures be included in early exploratory \(phase I/II\) clinical trials?](#)

Most of the debate revolved around whether HRQoL assessment should occur in phase II trials. Although such early assessment of HRQoL was considered welcome by some participants, its utility was questioned by others in for example single arm trials. More specifically, assessment of HRQoL in phase II trials could help target further HRQoL assessment in phase III trials and thus inform further clinical development through the identification of either disease-specific or drug toxicity-specific HRQoL items (as opposed to more general HRQoL assessment). On the other hand, this may entail a component of subjectivity in the choice of the HRQoL items of interest (either disease- or drug toxicity-related).

Under what circumstances, if any, could HRQoL be the primary endpoint?

Some participants expressed the view that depending on the clinical setting, HRQoL could be acceptable as a primary endpoint the same way that PFS, OS or, in certain situations, Response Rate (RR) are acceptable primary endpoints in oncology trials. For HTA bodies, in addition to survival, patient-relevant endpoints are considered important and may be primary endpoints in oncology trials. However, as HRQoL is a complex, multidimensional concept, not measuring directly product effectiveness and harms is considered insufficient for HTA. HRQoL combined with clinical endpoints such as PFS and/or OS is fully acceptable for HTA. For regulatory purposes and in accordance with the EU main anticancer medicine guideline, control of cancer-related symptoms could be used as primary endpoint if shown to be related to the anti-tumour activity of the medicinal product.

Is HRQoL data considered to be of value if collected from open-label clinical trials and if so, under what circumstances?

Open-label trials may not be the best setting in which to assess subjective endpoints such as HRQoL. However, if a blinded design is not possible in a given situation, then there may be value in assessing HRQoL in such a trial. Moreover, some participants argued that there are rare situations in which a double-blind design could influence adversely HRQoL assessment: for example, if the benefit in terms of HRQoL from an experimental treatment comes from its alternative route of administration, then a double-blind, double-dummy trial would not allow this benefit to be demonstrated. Patient representatives considered more generally that a double-blind trial in the palliative setting could also impact on the patient's HRQoL due to the stress of not knowing whether they are on the experimental or control treatment arm, as already alluded to earlier.

HRQoL Instruments

An instrument can be described as a means to capture data, such as a questionnaire.

Are there any specific recommendations we can give regarding instrument selection?

Historically, there has been misuse of instruments and this sometimes misguides instrument selection. It is important to consider the rationale, the purpose and the expectations behind HRQoL assessment. Moreover, it is important to involve relevant expertise both in the design of studies that intend to assess HRQoL as well as in the assessment of these studies for authorisation or reimbursement purposes.

The use of multiple instruments in the same trial often results in overlaps between them and repetition which may discourage patients and/or physicians from using them. Computer Adaptive Testing, which is under development, may help in this respect.

What is the utility of non-validated instruments in settings where no instrument currently exists?

Availability of appropriate and adequate instruments was not considered to be a major issue, as validated tools can be used in most trial settings, and several groups have developed cancer specific tools which are validated and translated for most global trials. Informed selection and rigorous implementation of instruments in clinical trials, including use of part(s) of validated instruments, as well as adding ad-hoc questions to existing validated measures, was considered to be of importance.

Statistical Methods and Missing Data

Incorporating HRQoL instruments as clinical trial endpoint measures introduces challenges in the analysis of clinical trial data, particularly because of their multi-dimensional nature and often

unbalanced missing values, in addition to the selection bias that missing data entails. Moreover, patients' values and perspective are modified during the course of the disease which may further add to the complexity.

How can missing data be minimised in the oncology setting?

Perhaps the only effective way of addressing missing data is to minimise them. In addition to careful and expert planning in the assessment of HRQoL within clinical trials, the use of dedicated personnel for collection of data and data collection methods that allow patients to complete their PRO assessment from home may help towards this end. Baseline collection of HRQoL data may be used as inclusion criterion, particularly when HRQoL measures are the primary or key secondary endpoint of the trial. On the other hand, it was suggested that ethics committees may find it unacceptable not to include patients in a trial simply due to the absence of baseline HRQoL assessment.

With regard to the frequency of HRQoL data collection, no general rule can be provided: A proposal might be that assessment of symptoms could be daily to weekly, but functional assessment might preferably be performed less frequently, e.g. on a monthly basis.

With regard to data collection after progression/exit from study, certain long-term sequelae of medicines may warrant long follow-up of patients well after their exit from the study. However, HRQoL data post-study and particularly upon administration of next line therapy should be considered and assessed separately from HRQoL on study.

How should missing data be handled in the analysis?

The handling of missing data has been discussed extensively in the literature and in regulatory guidance; this guidance should be followed in principle (Guideline on Missing Data in Confirmatory Clinical Trials, EMA/CPMP/EWP/1776/99 Rev. 1). However and specifically for HRQoL, more emphasis should be put on the underlying reason for the missing data; random influences (administrative issues) should be separated from HRQoL-related issues (impaired health).

Clinical Importance and added value

HRQoL instruments should be capable of detecting clinically meaningful effects. The Minimal Important Difference (MID) may be defined as the smallest change perceived by the patient as an advantage/disadvantage or that could lead to a change of treatment.

Can we define what we mean by clinically meaningful HRQoL difference in oncology?

The minimal clinically meaningful difference is hard to define as it depends on the disease setting: from the curative setting to the setting of disease delay and to the palliative setting. It may also be influenced by cultural factors and the definition of the minimal clinically meaningful difference might be 'the difference large enough for the patient to notice there is one'.

From the opposite perspective, it is important but historically often difficult to know whether the absence of difference in terms of HRQoL measures is indeed an indication of equivalence or a result of employing an instrument that was incapable of detecting change.

What weight should we give to HRQoL data in a Benefit: Risk analysis?

To the extent that HRQoL measures could serve as (one of) primary or key secondary endpoints in confirmatory trials, they can be key factors in the benefit-risk assessment and their reporting in the Product Information of medicines will be commensurate to their weight in the benefit-risk decision. The fact that historically such data have not commonly played an important role in this respect is a consequence of the fact that they have rarely been shown to be meaningful.

In life-threatening situations accompanied by significant suffering, patients may value improvements in HRQoL more, even at the cost of life-threatening drug side-effects. Dilemmas such as 'better but shorter life' are ethical or philosophical in nature, hence with no straightforward answer. Similarly, to say that the weight of HRQoL is much more important in the palliative setting as opposed to the curative intent setting brings about the following question: Would an improvement in QoL in the palliative setting, at the cost of some (small?) loss in Overall Survival be acceptable? How could one value the length vs the quality of life?

Patient Reported Outcome Measures

A PRO may be defined as a measurement based on a report that comes directly from the patient about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else.

In an introductory presentation, it was highlighted that information collected systematically from patients (PROs) complements and enhances other evaluations made of treatment safety and efficacy. PRO data can support efficacy endpoints that either are not established as constituting clinical benefit per se or for which it is doubtful whether the magnitude of effect seen is clinically relevant. Moreover, PROs can inform the safety assessment because the manner in which all adverse events and side effects are collected in clinical trials is not always especially reliable and because several studies have shown that side effects are often underestimated. Multiple studies have shown that physicians, healthcare professionals and caregivers often report toxicities differently and in biased ways compared to patients themselves.

There is a need for clarification of terms as PROs reported by patients is an umbrella term used to cover single-dimension and multi dimensional measures of symptoms, HRQoL, health status, adherence to treatment, satisfaction etc. The notion of multidimensionality is a key component: single domain improvement cannot be considered as a basis for global HRQoL improvement in claims to be included in the Product Information. The correct PRO to be used obviously depends on the study. The US National Institutes of Health (NIH) has funded the Patient Reported Outcomes Measurement Information System (PROMIS). This is a large bank of items (questions mostly from standard HRQoL questionnaires) being compiled. Eventually this bank will be used in Computer Adaptive Testing which promises to permit more efficient, precise and psychometrically sound assessment; however, this would need to be adapted for EU use, including being appropriately translated according to current requirements.

Can we define in what setting PRO data should be collected?

There is probably no specific situation in which PROs or HRQoL measures implemented by the physician should be preferred. In general, PROs can be much more effective in HRQoL data collection compared to instruments implemented by the physician. Investigators in clinical trials have a tendency to report more systematically the more serious adverse events or ones for which there is a specific

treatment (ascertainment bias). Finally, reliability of instruments filled in by proxies (carers) of the patients is debatable and it can at best be considered similar to physician reported scores.

PROs are particularly important for the assessment of safety of medicines pre-authorisation, as documentation of side-effects of medicines may be less than exhaustive in clinical trials. In this respect, data from PROs can inform the management of side effects of medicines.

An important question is how demanding the PROs are to fill in and what educational status is required by the patient to be able to use them effectively. It is agreed that PROs should be used by patients who are both mentally and psychologically fit. However, PROs are developed through extensive testing in order to make them easy to understand and the language used in them as patient friendly as possible. Moreover, translations of such instruments in other languages are developed equally rigorously.

[Can we define types of PRO measures that should be included in clinical trials for certain patient groups?](#)

Identification of specific types of PROs and of clinical settings in which they should be used at a general level is not possible: the appropriate PROs for a certain clinical setting and their appropriate use within this setting should be judged on a case-by-case basis.