Reflection Paper on the use of patient reported outcome (PRO) measures in oncology studies

Draft

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Keywords

Patient reported outcome (PRO), Health related quality of life (HRQL)
Executive summary

The importance of the patient’s point of view on their health status is fully acknowledged and such information may in principle be used in drawing regulatory conclusions regarding treatment effects. This reflection paper on the use of patient reported outcome (PRO) measures in patients with malignancies focuses on the value of these data from a regulatory perspective. The possible add-on value from a licensure perspective of such data to conventional efficacy and safety data is therefore emphasised. In particular the use of PRO data in order to estimate patient perception of side effects of therapy is highlighted.

This document has been named “reflection paper” in order to underline its preliminary status and to spur an open discussion on the value of PRO data in the development of medicinal products for the treatment of malignancies and in acknowledgment that PRO methodology is developing and evolving.

Important definitions

PRO  A PRO includes any outcome evaluated directly by the patient himself and based on patient’s perception of a disease and its treatment(s). Patient reported outcome is an umbrella term covering both single dimension and multi-dimension measures of symptoms, health-related quality of life (HRQL), health status, adherence to treatment, satisfaction with treatment, etc.

HRQL  Health-related quality of life is a specific type of PRO and is a broad concept which can be defined as the patient’s subjective perception of the impact of his disease and its treatment(s) on his daily life, physical, psychological and social functioning and well-being. The notion of multidimensionality is a key component of the definition of HRQL.

1. Background

PRO measure is an umbrella term for the capturing of health status, symptoms, HRQL, adherence to treatment, satisfaction with treatment, etc with the emphasis placed upon the patient’s judgement. It is recognised that such data are subjective, change over time and are influenced by the treatment, the disease and other co-morbidities. HRQL is a concept referring to the effect of an illness and its therapy upon a patient’s physical, psychological and social wellbeing, as perceived by the patient themselves. In clinical research, such measures may provide an additional means of capturing the personal and social context of the disease and treatment experience, as objective clinical measures may not necessarily correlate to a patient’s own feeling of wellbeing.

Over the last decades, HRQL objectives have frequently been incorporated in confirmatory oncology studies. However longitudinal HRQL data have rarely been informative from a licensure perspective, a main reason being the absence of demonstrated difference between the study arms. Whether this is related to poor sensitivity of the instruments, high attrition rates and informative censoring, or simply reflects the resilience and dynamics of the individual’s perception of HRQL during the course of disease, remains unknown. In addition, there is often a lack of consensus regarding what degree of difference is clinically relevant, which together with poorly defined objectives may further hamper the usefulness of PROs from a licensure perspective.

More recently, time to significant deterioration in tumour related symptoms, as measured by PRO instruments, has been introduced and here differences have been demonstrated, paralleling what has been shown in terms of progression-free survival (PFS). This is of value, but it could be discussed whether repeat demonstration of parallelism between PFS and time to symptom deterioration, e.g. in...
the treatment of lung cancer, is of value. More importantly, these data do not provide estimates of longitudinal HRQL, i.e. do not provide a weighed approach of benefits and adverse reactions of therapy.

In most cases, for a particular tumour type and disease stage, there is no reason to assume that the potential benefit of a delay in tumour progression, if of similar magnitude, is product specific. However, the tolerability and toxicity profiles may differ considerably between medicinal products. The differential impact on patient wellbeing is harder to estimate from conventional adverse event reporting, even though withdrawal rates prior to tumour progression may provide some insights. In relation to active compound comparative trials and from a licensure perspective, PRO data derived from instruments capturing the consequences of adverse reaction on patient wellbeing, in an unbiased way and in relation to the study drugs, are welcomed. However, at the time of this paper there is no EMA/CHMP experience from the use of, e.g. the NCI’s Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).

In summary, PRO measures may provide important patient perspective on the disease and the treatment received; an evaluation that provides clinically important information that is not captured by conventional anti-tumour efficacy data and adverse event reporting. There are, however, methodological obstacles that historically have reduced the impact of PRO data on regulatory decisions. Key is careful planning and an in depth analysis of whether the inclusion of PRO measures is likely to provide added value in the clinical trial setting; can the collection of PRO data make a potential difference to the study conclusions.

2. Scope

This reflection paper covers general aspects of the use of PRO endpoints in oncology studies such as the designing and carrying out of clinical studies, the acceptability of instruments and the clinically important differences and added value. This reflection paper does not cover the validation of instruments nor does it make specific recommendations regarding the instrument to select.

3. Legal basis

This document should be read in conjunction with Directive 2001/83/EC, as amended and Regulation 726/2004. In addition, relevant CHMP guidelines should be taken into account. These include but are not limited to:

- Guideline on the evaluation of anticancer medicinal products in man -EMA/CHMP/205/95/Rev.4
- Statistical principles for clinical trials – CPMP/ICH/363/96 (ICH E9)
- Reflection paper on the regulatory guidance for the use of HRQL measures in the evaluation of medicinal products - EMEA/CHMP/EWP/139391/2004
- Guideline on missing data in confirmatory clinical trials EMA/CPMP/EWP/1776/99 Rev. 1
- Points to consider on multiplicity issues in clinical trials CPMP/EWP/908/99

4. Patient reported outcomes

A patient-reported outcome (PRO) is an umbrella term that can be defined as a measurement based on a report that comes directly from the patient about the status of a patient’s perception of the impact of
disease and treatment, without amendment or interpretation of the patient’s response by a clinician or anyone else. A PRO can be measured by self-report or by interview, provided that the interviewer records only the patient’s response. PRO measures must have acceptable responsiveness, reliability and validity, and may include reference to symptoms, functional status, treatment adherence or satisfaction with care. In clinical research, the use of a PRO measure is advised when measuring a concept best known to the patient or best measured from the patient perspective. Clinical studies in oncology may include PRO measures as secondary or exploratory outcomes and rarely as primary outcomes, incorporated as part of the initial trial protocol. The general recommendations for the incorporation of PRO measures in clinical studies include:

- The extent to which the inclusion of PRO measures can provide added value in the clinical trial setting; crucially can the collection of PRO data make a difference to the study conclusions.
- PRO endpoints should be incorporated into the protocol development at the earliest stage and should be explicitly stated as a specific clinical trial objective or hypothesis.
- For specific therapeutic claims in Section 5.1 of the SmPC, a clear hypothesis lead strategy is required and measures should be selected based on their ‘fit’ with the hypothesis.
- Questionnaires & instruments should be administered to study subjects at time points when there is a clear and hypothesis driven rationale for their use and when it is feasible to expect high levels of completion. PRO instruments should match the abilities of the patient population.
- PRO data should be treated like any other data in monitoring clinical site performance and collection methods.

4.1. Health Related Quality of Life (HRQL)

The impact of treatment and disease can be measured using self-reported questionnaires. HRQL is a multidomain concept that represents the patient’s general perception of the effect of illness and treatment on physical, psychological and social aspects of life. HRQL instruments attempt to measure complex aspects of life which are potentially modified by therapeutic interventions. HRQL is a personal perspective and varies with gender, experience, age, education and cultural background. The inclusion of HRQL assessment in clinical trials should have a strong scientific rationale and researchers should utilise existing validated instruments where available. HRQL complements the range of traditional indicators and the data can provide information regarding both positive and negative patient experiences. Reasons to include HRQL assessment in the clinical development programme for oncology medicinal products includes:

- Provide a patient focused assessment of the burden and impact of disease
- Understand how a novel treatment impacts on patient functioning
- Add information on the positive and negative effects of a therapy by complementing efficacy and safety data e.g. help assess the relationship between efficacy/clinical endpoints (OS, PFS, disease stabilisation) and HRQL
- Identify treatment-related symptoms that need additional management and supportive care
- Attempt to differentiate two treatments with similar efficacy
- Facilitate more accurate patient-physician communication in terms of the quality of the time remaining and the burden of treatment-related morbidities by detailing a more complete evaluation of cancer treatment.
5. Clinical trial design

General principles (see also Reflection paper on the regulatory guidance for the use of HRQL measures in the evaluation of medicinal products, Doc. Ref. EMEA/CHMP/EWP/139391/2004)

There is no standard approach to collecting, analysing or interpreting PRO data in clinical trials. As with other aspects of clinical trial design, good science applies and objectives need to be justified alongside realistic expectations. Careful thought must go into designing and implementing PRO measures in the oncology clinical trial setting in order to investigate a well-formulated predefined hypothesis, whether related to HRQL or a more targeted objective better captured by a more focused PRO instrument. In the majority of circumstances, the patient is the best informant and the most appropriate way to measure PRO is self-reporting direct from the patient. Importantly, measurements should not constitute an undue burden to the patient.

There has been a general perception that only truly double-blind studies can provide trustworthy PRO data. There is a paradox in this, as it implies that differences in side effects profiles should be sufficiently small not to be detected by patient and treating physician. Whether such small differences are sufficiently large to be detectable by PRO instruments are dubitable and such effects are perhaps also of minor clinical relevance. It is obviously true that possible differences in positive effects on tumour related symptoms might be detectable, but the added value to so called objective measures of tumour response and delay in progression might be of relevance mainly in studies without an active comparator. Thus whilst ideal from a “bias perspective”, informative double blind studies may be successfully conducted only in specific situations.

Whilst the concern in relation to open label studies remains, it might well be that data of clinical interest a priori can be produced only under open label conditions. One example being an experimental compound assumed to be more efficacious, but also more toxic or less well tolerated. Under these circumstances extensive planning in advance is required to increase the credibility of study data. For example, effects of neuropathy on functionality should be supported by conventional clinical measures of neuropathy. As emphasised, it is of major importance to discuss in detail in the study protocol why certain timings of assessments were selected and why the selected instrument is unbiased in relation to the toxicity/tolerability profiles of study drugs.

Frequency and duration of assessments

Timing and frequency of assessment are key issues and frequency can greatly influence the scores received. If assessments are too few, important changes may not be captured, if too frequent, the subject may become sensitised to the instrument. The overall frequency of assessment depends on the hypothesis being tested, the method of data analysis, the natural history of the disease and the nature of the investigative treatment and anticipated side effects. It is generally recommended to determine when expected changes in symptoms and or side effects are likely to occur over time and data collection should cover the clinically most important periods. The duration of assessment depends on the research questions being asked, but it is important to ensure that the duration of the clinical study and follow up is of adequate length to robustly support any planned analysis, including reversibility of adverse reactions.

In order to be able to accurately assess the PRO results on study therapy, continued assessment post-progression and during next-line therapy may also be needed. Such next-line PRO data allows contextualisation of the results observed on study treatment, which can be of particular importance in
the palliative or maintenance setting, and when therapeutic claims (in SmPC section 5.1.) are intended. For example, when an active treatment is compared against placebo or other less toxic therapy, worse scores for PROs may be seen during treatment in the active/experimental arm due to toxicity. In this situation, if there is no gain in OS, or if OS cannot be assessed (e.g. due to lack of power, immature data, or cross-over), next-line PRO data can help put the PFS gain into perspective and could potentially affect the benefit/risk (B/R) balance. Apart from the need for contextualisation, there is also a methodological rationale for collecting next-line or post-progression data when PROs are studied. Patients in the comparator arm are normally expected (as a group) to experience progression earlier than the patients in the experimental arm. Thus, if PRO assessments are stopped at progression, patients in the comparator arm will automatically have a shorter observation period compared with those in the experimental arm. This can be regarded as a form of informative censoring, affecting the possibilities to draw conclusions from the PRO data.

Data collection

High compliance has been attributed to comprehensive educational programmes prior and during the trial for both research staff and study participants. Assessments should be performed on schedule irrespective of whether study treatment has been given. Collecting PRO data from patients with advanced and progressive disease may be more difficult because of failing health and / or cognitive challenges. PRO data can be collected by administering PRO instruments through different modes – interviewing, telephone, mailing or self administration. Electronic data capture methods may offer more convenience to some patients and may increase data quality, reduce missing data (allowing automatic reminders to be sent) and potentially reduce data entry errors.

Statistical methods and missing data

Incorporating PRO instruments as clinical trial endpoint measures introduces challenges in the analysis of clinical trial data, particularly because of their multi-dimensional nature and missing values. The study protocol should describe the principal data analysis features in the statistical section with a detailed elaboration of the analysis in the Statistical Analysis Plan, including how to control for multiplicity. The clinical trial protocol should also describe how missing data will be handled in the analysis (e.g. use of imputational techniques, sensitivity analysis). Missing data should be put into context of underlying reason, but missing at random is hardly ever a justified assumption. It is therefore essential to minimise data loss and to employ strategies to increase patient compliance, such as, for example;

- Filling in baseline questionnaire as part of the eligibility criteria checklist
- Appoint a person responsible for PRO data collection in each study site
- Education and training to patients before completion of the questionnaire, including that there is no incorrect answer and explaining the purpose of the assessment
- Explore the use of automated electronic data collection
- Checking for completeness of forms for omissions, clarifying reasons for non-completion

Of importance, whilst use of electronic data recording might be of benefit in some patient groups, alternatives should be made available, e.g. for elderly patients so that differential loss of data is minimised.
Depending on the chosen instruments, lack of linguistic and cultural validation of instruments may be problematic in multinational and global studies. Investigation of PRO endpoints in a predefined sufficiently large subgroup, including patients representative for the EU target population, may be considered to avoid cross-cultural validity and translation issues. In these cases, implementation of all measures for a high compliance rate is expected in order to provide a substantial amount of interpretable longitudinal data.

### 5.1. Instruments

PRO instruments should be relevant, reliable, validated and responsive to change. An instrument can be described as a means to capture data, such as a questionnaire, plus all the information and documentation that supports its use. Generally, this includes clearly defined methods and instructions for administration or responding, a standard format for data collection, and well-documented methods for scoring, analysis and interpretation of results in the target patient population. Disease specific measures may be more acceptable to patients, providing a more in-depth relevant analysis. However, they may fail to capture unexpected changes. Generic measures are useful for comparisons across treatments. However, they may be less sensitive to change and the relative importance of the different PRO domains needs to be determined a priori.

#### Selection of an instrument

It is beyond the scope of this reflection paper to make specific recommendations regarding valid instrument selection, but in general, the instrument should be shown to measure the concept it is intended to measure, be appropriate for the research objective, the disease and patient population characteristics and the practical considerations (respondent burden, feasibility). Instruments should be culturally valid and translated versions should be as true to the original as possible (linguistic validation).

#### Carer/ proxy input

There is generally discordance between ‘patient’ reported PRO and ‘proxy’ reported PRO. The evaluation of PRO by carers or other proxy judges may be utilised where it is clear that the patient themselves cannot contribute (e.g. very small children, patients with cognitive impairment, severe ill health), but in general proxy reporting should be avoided.

### 5.2. Special patient populations

**Paediatric**

Specific issues to consider are development stage (maturation may also differ because of disease and or experiences) and meaning of self. As with adult patients, the best informants are the patients themselves and it is important to collect as much information directly from the patient wherever possible, using creative and age related approaches. However it is acknowledged that some patients will be too young or too sick to contribute to the data collection.

**Elderly**

Elderly patients present particular characteristics and instruments should be calibrated to the special requirements of older patients wherever possible. In elderly patients, concomitant diseases are more frequent, affecting psychological status and general performance. It is important to consider that HRQL...
is affected by comorbidities, multiple medications (polypharmacy), functional status, ability to carry out activities of daily living, mental status (depression, cognitive functioning) and social support.

**Palliative setting (for definition see 7.4, main anticancer document)**

Successful patient palliation has been described as disappearance or improvement of symptoms, improvement of a specific symptom from baseline, change in the severity of a specific target symptom, for example pain or composite outcomes of pain and analgesic requirements, a symptom difference perceived as beneficial by the patient, HRQL score changes or increased duration of survival. In patients with advanced cancer where the aims are palliative, the focus of care is promoting and maintaining remaining quality of life. This aspect should be carefully considered in the clinical study design, in particular as complicated multidimensional changes can occur relatively quickly and patient survival time is relatively short. If appropriate, longitudinal HRQL data should be collected alongside other PRO measures such as symptom assessment (see section 6).

### 6. Symptom PRO measures

Patients provide a unique and personal perspective of treatment effectiveness and measuring symptoms is important in understanding the burden of cancer. Symptom response rates and symptom control are particularly significant in the palliative setting. Assessment of palliation can be assessed by changes in symptom scores in general or change in symptom scores considering only certain prespecified symptoms. Symptoms (related to the disease, toxicity or multi-factorial) that are commonly found in the advanced setting include anorexia, anxiety, constipation, depression, dyspnoea, fatigue, insomnia, pain and neuropathy. However, patient reported symptoms to be investigated should be evidence based and derived from feedback from patients and carers, clinicians and other experts, as well as the literature. If symptom PRO measures are used to evaluate the impact on specific symptoms, these should be accompanied by multidimensional HRQL measures to ensure that a benefit in respect to specific symptoms is not accompanied by a negative impact on global HRQL. As important as selecting an instrument that properly captures disease related symptoms is to use an instrument that captures side effects of therapy in an unbiased way.

### 7. Clinical importance and added-value

PRO instruments and assessments should be capable of detecting clinically meaningful effects. The Minimal Clinically Important Difference (MCID) has been described as ‘the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management’. Situations where PRO measures, including HRQL, could potentially be of added value in terms of possibly affecting the benefit risk profile, include the late line palliative setting, maintenance therapy, and in studies comparing agents with similar efficacy but different safety profiles. In some disease settings, symptom response and especially time to relevant deterioration might in principle be used as primary outcome measures, provided that data are supported by ORR and PFS. Criteria used to assess the potential added value of PRO data include:

- The relevance, reliability and responsiveness of the instrument/ assessment
- The appropriateness of the frequency and duration of data collection, in light of the patient population, disease setting and treatment regimen
• The adequacy of the study design including the hypothesis and methods for appropriate handling of multiple outcomes in the statistical analysis

• The rationale for the anticipated magnitude of effect - statistical significance should correlate with clinically relevance

• Considerations of alternative explanations that may account for the observed changes or lack of changes

References


