EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28th November 2014

# Submission of comments on 'EMA Draft reflection paper on the use of patient reported outcome (PRO) measures in oncology studies'(EMA/CHMP/292464/2014)

## Comments from:

| Name of organisation or individual |
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**International Society for Quality of Life Research**
The International Society for Quality of Life Research (ISOQOL) thanks the EMA for the opportunity to comment on this timely and potentially valuable document.
The mission of ISOQOL is to advance the scientific study of health-related quality of life (HRQL) and other patient-centered outcomes, to identify effective interventions, enhance the quality of healthcare and promote the health of populations. With over 600 members representing 43 countries, ISOQOL is an international society with activities focused on promotion of high quality research in the science of HRQL measurement; 21 members provided detailed comments and suggestions on the EMA Reflection Paper; 81% from academia, and 19% from industry. This summary was produced by a Taskforce convened by the ISOQOL Executive Committee.

**ISOQOL Taskforce**
**Melanie Calvert**, Professor of Outcomes Methodology University of Birmingham, UK (Chair), Co-Chair of the ISOQOL Best Practices for PROs in Trials Taskforce.
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**Derek Kyte**, Lecturer in Health Research Methods, University of Birmingham, UK
**William Lenderking**, Senior Research Leader, Evidera, USA
**Rebecca Mercieca-Bebber**, Project Officer, Quality of Life Office, University of Sydney, Australia
**Josephine Norquist**, Patient Reported Outcomes Specialist, Merck Sharp & Dohme Corp. USA and Chair of the ISOQOL Industry Advisory Committee (IAC)
**Bryce Reeve**, Professor of Health Policy & Management, University of North Carolina, USA
**Lena Ring**, Adjunct Professor in Quality of Life Research in Health Care, University of Uppsala, Sweden

Our comments are intended to be constructive; we understand that the authors may not wish to include all of the points raised. Once again we thank you for this opportunity to comment.

Name of organisation or individual

*Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.*

*When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).*

## 1. General comments

| Stakeholder number<br>*(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)<br>*(To be completed by the Agency)* |
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| | **Scope and referencing**<br>The paper reflects on a broad range of methodological issues relating to the use of patient-reported outcomes (PROs) in oncology trials; however, since many issues are not described in depth we feel that increased referencing and signposting to seminal work, appropriate to each area, would increase the value of the document. Embedding references within the text would be helpful. To assist the oncology working party we have highlighted key references in our detailed comments below and have included a list of references for consideration at the end of this document.<br><br>Since the EMA requires rigorous assessment of PROs including HRQL to inform reimbursement decisions it may be useful to provide a summary of related documents early in the paper, perhaps following the definitions section, to ensure that readers immediately have a sense that this document should not be read in isolation to gain a deeper understanding of the use of PROs in oncology studies. | |
| | **EMA Experience**<br>Evidence in the form of number of oncology submissions and numbers with PRO labeling claims | |

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| | would be of major interest to readers but is currently lacking. Case studies would enrich the document. Ideally we would like to know how many products had PROs in the labels (numerator), but also how many requested PROs in the label (denominator), and the reasons why PRO labels were not approved. | |
| | **Definitions**<br>Within the first two pages there are three separate definitions of PROs (lines 27, 36 and 92); all slightly different. We would suggest that only one definition be used as follows, and that the second and third instances be deleted to allow more space to address other comments as detailed below. The suggested definition is:<br><br>"A patient-reported outcome (PRO) is a measurement that comes directly from the patient's perception about health, disease or treatment, without amendment or interpretation by a clinician or anyone else. PRO is an umbrella term that can refer to symptoms, functioning, treatment satisfaction, global health perceptions, health-related quality of life, treatment concordance, among other measures." | |
| | **Patient-Reported Outcomes and Health-Related Quality of Life** | |

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| | Over the last decade there has been a clear shift in the terminology used from HRQL to the broader umbrella term PROs (we wonder if greater explanation of this historical terminology may be provided as a footnote). Interestingly many of the reasons to include HRQL in the clinical development programme (section 4.1) equally apply to other PROs such as symptoms. As such we would suggest restructuring/combining the sections on page 4 (in particular the bullet points which are currently separated).<br><br>Furthermore the term COA *i.e., Clinical Outcomes Assessments) is now used by FDA as a greater umbrella term encompassing PROs as well as Clinician-reported outcomes (ClinRO), Observer-reported outcomes (ObsRO) and Performance outcome (PerfO) measures. COAs can be used to determine whether or not a drug has demonstrated treatment benefit. The FDA's Roadmap to Patient-Focused Outcome Measurement in Clinical Trials describes the process for choosing a COA. It would be valuable to refer to this process in the document since it is a systematic scientific approach where the concept of interest precedes the instrument of choice. | |
| | **Clinical Trial Design - Data Collection, Statistical Methods and Missing Data**<br>The '*Statistical methods and missing data'* heading (line 199, page 6) seems to be in the wrong place | |

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| | as many of the bullets refer to data collection. We believe this should read *'Data Collection and preventing avoidable missing data'*.<br><br>Each of these sections could be developed to highlight not only potential problem areas but also how to overcome them. Over the last decade, research has been conducted to optimize data collection, minimize missing data and develop statistical approaches to deal with PRO data. The EMA could usefully position this reflection document to detail past challenges and future opportunities.<br>Additional references are suggested for this section below:<br><br>Bernhard J, et al. Missing quality of life data in cancer clinical trials: serious problems and challenges. Statistics in Medicine. 1998;17(5-7):517-32.<br><br>Fielding S, et al. Investigating the missing data mechanism in quality of life outcomes: a comparison of approaches. Health Qual Life Outcomes. 2009;7:57.<br><br>Calvert M et al. Patient-Reported Outcome (PRO) Assessment in Clinical Trials: A Systematic Review of Guidance for Trial Protocol Writers. PLoS One. 2014 Oct 15;9(10):e110216. | |

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| | Kyte D et al. Systematic Evaluation of the Patient-Reported Outcome (PRO) Content of Clinical Trial Protocols. PLoS One. 2014 Oct 15;9(10) | |
| | **PRO trial reporting**<br>Although the article references the CONSORT-PRO Extension, the manuscript currently does not include a section on this. An EMA representative was involved in the development of CONSORT-PRO and as such we respectfully request the EMA to consider adding a brief section on this topic and lending their support to the use of CONSORT-PRO. Poor reporting of PRO data limits their use to inform clinical care, guidelines and health policy. | |
| | **Value of PRO data (lines 45-48)**<br>**'***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.'*<br><br>We understand that lack of HRQL difference between study arms might be seen as a challenge when using HRQL data from a licensure perspective. However, we also emphasize that if | |

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| | the HRQL outcome is robustly designed in a trial protocol (i.e., with a strong scientific rationale, using a well validated HRQL instrument and with an appropriate statistical plan, attention paid to training study staff on proper administration and suggestions to avoid missing data) and the results appropriately reported in later publications, the information derived will nearly always provide useful information to inform clinical decision-making and to evaluate overall treatment effectiveness. There are pivotal trials, for example in brain cancer patients, where HRQL differences between treatment arms have been found to be marginal but have indeed contributed to a better understanding of the "value" of the new treatment evaluated. (e.g. Taphoorn MJ, 2005). The lack of a HRQL difference between treatment arms should not be seen, per se, as a factor limiting the use of HRQL data.<br><br>*References:*<br>Taphoorn MJ, Stupp R, Coens C, et al., Health-related quality of life in patients with glioblastoma: a randomised controlled trial. Lancet Oncology. 2005 Dec;6(12):937-44 | |
| | **Patient engagement**<br>The last decade has seen growing interest in the contribution of patients as active research partners in health and social care research. Growing evidence reflects the beneficial impact of active | |

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| | patient engagement in enhancing the quality, relevance and validity of research (Gradinger et al, 2013; Brett et al, 2014). This has also been evidenced in PRO-related research (Staniszewska et al, 2012; de Wit et al, 2014): for example, identification of the outcomes that really matter to patients (Kirwan et al, 2007); improving the relevance and validity of PRO measures (Nicklin et al, 2010); seeking to enhance the acceptability of PRO-based assessment and hence improving completion rates. The manuscript raises issues associated with 'respondent burden' and PRO selection. These are issues that can be usefully explored with appropriate, active patient engagement. Of note, for many patients, completion of a relevant and appropriate measure may indeed be empowering; respondent burden may be more readily associated with completion of irrelevant and inappropriate measures. The manuscript would benefit from a section which considers the value of co-production of appropriate guidance by relevant stakeholders (as equal partners and co-creators) to inform PRO selection, PRO application and PRO interpretation.<br><br>*References:*<br>Brett J, Staniszewska S, Mockford C, Herron-Marx S, Hughes J, Tysall C, Suleman R. Mapping the impact of patient and public involvement on health and social care research: a systematic review. Health Expectations. 2014 Oct;17(5):637-50 | |

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| | de Wit MP, Abma TA, Koelewijn-van Loon MS, Collins S, Kirwan J. What has been the effect on trial outcome assessments of a decade of patient participation in OMERACT? The Journal of Rheumatology. 2014 Jan;41(1):177-84.<br><br>Gradinger F, Britten N, Wyatt K, Froggatt K, Gibson A, Jacoby A, Lobban F, Mayes D, Snape D, Rawcliffe T, Popay J. Values associated with public involvement in health and social care research: a narrative review. Health Expectations. 2013. Dec 10. doi: 10.1111/hex.12158. [Epub ahead of print]<br><br>Kirwan JR, Minnock P, Adebajo A, Bresnihan B, Choy E, de Wit M, Hazes M, Richards P, Saag K, Suarez-Almazor M, Wells G, Hewlett S. Patient perspective: fatigue as a recommended patient centered outcome measure in rheumatoid arthritis. The Journal of Rheumatology. 2007 May;34(5):1174-7.<br><br>Nicklin J, Cramp F, Kirwan J, Urban M, Hewlett S. Collaboration with patients in the design of patient-reported outcome measures: capturing the experience of fatigue in rheumatoid arthritis. Arthritis Care Res (Hoboken). 2010; 62(11): 1552-8. | |

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| | Staniszewska, S., Haywood K.L., Brett J., Tutton E. Patient and public involvement in patient-reported outcome measures: evolution not revolution. Patient. 2012; 5(2): 79-87. | |
| | **New oncology agents and their impact on PRO trial design.**<br>Whilst we recognize that this is a reflection paper, this may also be a useful place to consider new challenges in oncology PRO trial design. For example, while it is quite straightforward to link HRQL assessment to specific clinical events in case of a chemotherapy-based trial (e.g. administering questionnaires in conjunction with the clinical visit), the issue of "timing" becomes more challenging in other treatment scenarios. To illustrate, tyrosine-kinase inhibitors (TKI) (i.e., targeted therapies) are to be taken by patients on a daily basis (and in most cases for a prolonged period of months or years); so these newer therapies are introducing new challenges that Investigators need to consider when developing a protocol. Also, the challenge of "adherence to therapy" needs to be considered. We take for granted that the patient has received the recommended dose of chemotherapy or radiotherapy, as the patient has to attend a clinical | |

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| | visit in the hospital and receive treatment in the clinic. However, anticancer-targeted therapies are typically administered orally (and patients get their drugs without coming back to the hospital). It has been shown that adherence with targeted agents (e.g. leukemia patients) is not optimal and this affects both clinical and QoL outcomes. A brief mention to these new challenges introduced with newer anticancer-targeted agents could be helpful. | |

**2. Specific comments on text**

| Line number(s) of the relevant text<br>*(e.g. Lines 20-23)* | Stakeholder number<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes<br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome<br>*(To be completed by the Agency)* |
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| **EXECUTIVE SUMMARY**<br>**Line 18**<br>'patient reported outcome' | | **Comment:** Patient reported outcome should be hyphenated.<br>**Proposed change (if any):** Hyphenate throughout the text: i.e. 'patient-reported outcome'. | |
| **Line 27** | | **Comment:** PROs do not have to focus on ANY specific disease or treatment. They can be generic, both in standardized or individualized form, and they can be used to assess the health status of populations, that will include both healthy individuals and people with a number of different conditions.<br>**Proposed change (if any)**: To remove "and based on patient's perception of a disease and its treatment(s)" | |
| **Lines 27, 32, 33** | | **Comment:** Should avoid exclusive use of masculine "himself", "his".<br>**Proposed change (if any)**: Use gender-neutral terminology throughout document. | |
| **Line 29** | | **Comment:** Most theoretical models specifically include functioning as a construct measured by PROs.<br>**Proposed change (if any)**: To include "functioning" alongside the other constructs (see suggested PRO definition below). | |

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| **IMPORTANT DEFINITIONS**<br>**Line 30**<br>'quality of life (HRQL), health status, adherence to treatment, satisfaction with treatment, **etc.**' | | **Comment:** For readers who are not familiar with the terminology "etc." is unhelpful.<br>**Proposed change (if any):** Suggest the text is edited to state 'includes…., among other measures' (see suggested PRO definition below). | |
| **Line 30** | | **Comment:** Adherence to treatment has been abandoned in favour of concordance to highlight and improve patient centeredness.<br>**Proposed change (if any)**:To substitute adherence for concordance (see suggested PRO definition below). | |
| **Line 32** | | **Comment:** Don't need to qualify patient's perception as subjective.<br>**Proposed change (if any)**: Delete "subjective" from '. . . defined as the patient's subjective perception . .' (see suggested PRO definition below). | |
| **BACKGROUND**<br>**Line 36**<br>'PRO measure is an umbrella term …' | | **Comment:** We do not believe that PRO measures is accurate – the definition appears more appropriate to PROs rather than the tools by which to measure them.<br>**Proposed change (if any):** Suggest this should read 'PROs are an umbrella term including health status …..' (see suggested PRO definition below). | |

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| **Line 37**<br>'etc' | | **Comment:** We do not believe the use of etc is helpful.<br>**Proposed change (if any):** It may be more useful to give further examples or reference relevant literature. (see suggested PRO definition below). | |
| **Lines 39-40**<br>'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.' | | **Comment:** This could also state that this is from the patient perspective without interpretation by family, loved ones or health-care professionals.<br>**Proposed change (if any):** Consider suggested PRO definition below. | |
| ****SUGGESTED PRO DEFINITION**** | | **Comment:** We believe the following PRO definition (combining the suggestions above) should be used from the start of the document.<br>**Proposed change (if any):** Consider suggested | |

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| | | wording below.<br><br>"A patient-reported outcome (PRO) is a measurement that comes directly from the patient's perception about health, disease or treatment, without amendment or interpretation by a clinician or anyone else. PRO is an umbrella term that can refer to symptoms, functioning, treatment satisfaction, global health perceptions, health-related quality of life, treatment concordance, among other measures." | |
| **Line 43**<br>'may not necessarily correlate to a patients own feeling of wellbeing'. | | **Comment:** We would suggest rephrasing lines 41-43 as detailed below. A reference would be useful here.<br>**Proposed change (if any):**<br>We suggest editing to: 'In clinical research, PROs may offer additional information about the personal and social context of disease and treatment experience, which may not be evident from objective clinical assessment alone'<br>Or similar to convey that PROs are part of a comprehensive patient assessment.<br>Sneeuw KC. Sprangers MA. Aaronson NK. The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease. Journal of Clinical Epidemiology. 55(11):1130- | |

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| | | 43, 2002. | |
| **Lines 45-48** 'absence of demonstrated difference between the study arms' | | **Comment:** Please see general comments above – a finding of no significant difference between treatments or evidence of equivalence can still provide valuable information to inform treatment selection. In addition is this statement supported by evidence? If so, supporting references would be helpful.<br>**Proposed change (if any):** Consider editing this section in response to the general comment made on this point above. | |
| **Line 45** 'rarely been informative from a licensure perspective' | | **Comment:** A welcome addition to this paper would be evidence on the number of oncology approvals over a specific timeframe and how many had PRO/HRQL on the label. Ideally we would like to know how many products had PROs in the labels (numerator), but also how many requested PROs in the label (denominator), and the reasons why PRO labels were not provided.<br>**Proposed change (if any):** Add evidence based on the EMA experience. | |
| **Line 47** 'absence of demonstrated | | **Comment:** Failure to power studies adequately for the PRO endpoint can also be an issue<br>**Proposed change (if any):** Consider commenting on | |

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| difference between the study arms' | | the issue of sample size. | |
| **Lines 49, 50**<br>'in addition, there is often a lack of consensus regarding what degree of difference is clinically relevant,....' | | **Comment:** This is an important issue which has been the focus of research for over a decade within the PRO/HRQL research community, and guidelines are now available for the most commonly used cancer-specific PRO measures, the EORTC QLQ-C30 and FACIT FACT-G. There are some key references which should be included – we have added below:<br><br>**Proposed change (if any):**<br>'in addition, historically there was a lack of consensus regarding what degree of difference is clinically relevant, …'<br><br>*Relevant references are:*<br>• Cocks K, King MT, Velikova G, et al, on behalf of the EBIG collaborative group. Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer quality of life questionnaire core 30 (EORTC QLQ-C30). Journal of Clinical Oncology. 2011; 29 (1): 89-96.<br>• King MT. A point of minimal important difference (MID): A critique of terminology and methods. Expert Review of Pharmacoeconomics & Outcomes | |

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| | | Research. 2011; 11 (2): 171-184.<br>• Revicki D, Hays RD, Cella D, Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. Journal of Clinical Epidemiology. 2008; 61(2): 102-9.<br>• Norman GR, Sloan JA, Wyrwich KA. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Medical Care, 2003; 41(5): 582-592. | |
| **Lines 52-58**<br>Entire paragraph | | **Comment:** This paragraph could be rewritten to emphasize that data on HRQL can put PFS data into a context that is more meaningful for patients, especially in the absence of overall survival data. The emphasis in the current paragraph is on redundant information being provided when PFS and HRQL show parallel results, but in fact without the HRQL data, the PFS data are harder to interpret (This was a position taken by the US FDA for a lung cancer treatment).<br>**Proposed change (if any):** Rewrite paragraph as suggested above. | |
| **Lines 66-68**<br>'However, at the time of this | | **Comment:** This warrants further description or inclusion of key refs. ISOQOL would be happy to discuss potential collaboration in this area with the EMA. | |

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| 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).' | | **Proposed change (if any):** At a minimum suggest adding the following reference:<br><br>Basch E et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). J Natl Cancer Inst. 2014 Sep 29;106(9). pii: dju244. doi: 10.1093/jnci/dju244. Print 2014 Sep. | |
| **Lines 71-73** 'There are, however, methodological obstacles that historically have reduced the impact of PRO data on regulatory | | **Comment:** Many of these "methodological obstacles" are no longer so relevant to prevent a well-designed PRO assessment (please see general comments relating to this above).<br>**Proposed change (if any):** Consider rephrasing this to position PROs in a more positive light | |

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| decisions.' | | | |
| **Line 73**<br>**'...**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.' | | **Comment:** This is an overly narrow definition of the value provided by PROs.<br>**Proposed change (if any):** Add a more extensive list of the ways that PROs can add value. To that end, please see this reference and the table pasted below:<br><br>Au HJ et al. Added value of health-related quality of life measurement in cancer clinical trials; the experience of the NCIC CTG. Expert Reviews in Pharmacoeconomics and Outcomes Research. 2010 Apr;10(2): 119-28.*2010*<br><br>**Table 1. Classification of added value of health-related quality-of-life outcomes.**<br>Intended use / HRQoL outcomes<br>1. Choosing the 'best' treatment — 1.1. Used as the primary outcome for comparing treatments; 1.2. Support the primary trial outcome by improving understanding of treatment benefits or treatment risks; 1.3. Counterbalance the primary trial outcome by improving understanding of treatment benefits or treatment risks<br>2. Enriching the understanding of patient experiences (for counseling beyond treatment decision-making) — 2.1. Enhance understanding of treatment benefits or risks; 2.2. Provide prognostic information for counseling purposes; 2.3. Characterize under-evaluated populations<br>3. Improving clinical trials methods — 3.1. Prognostic determinant (stratification); 3.2. Measurement advances in HRQoL research | |

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| **SCOPE**<br>**Lines 79-80**<br>'This reflection paper does not cover the validation of instruments nor does it make specific recommendations regarding the instrument to select.' | | **Comment:** It would be exceptionally helpful to provide key references for interested readers.<br>**Proposed change (if any):** Add the following ref:<br><br>**Selecting a PRO measure:**<br>Luckett T, King MT. Choosing patient-reported outcome measures for cancer clinical research – Practical principles and an algorithm to assist non-specialist researchers. European Journal of Cancer. 2010; 46(18):3149-57. | |
| **LEGAL BASIS** | | **Comment:** It is unclear why this section is entitled legal basis.<br>**Proposed change (if any):** We would recommend placing this earlier in the document – perhaps calling it 'Related Documents for Review'. | |
| **PATIENT REPORTED OUTCOMES**<br>**Line 95**<br>'A PRO can be measured by self-report or by interview, | | **Comment:** As PROs are commonly completed in the form of questionnaires, it might be helpful to state this explicitly.<br>**Proposed change (if any):** Rephrase to " A PRO can be measured by self-report, generally in the form of a questionnaire, or by interview…" | |

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| provided that the interviewer records only the patients response.' | | | |
| **Lines 99-100**<br>'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.' | | **Comment:** Suggest delete the word **"rarely"** (for RCTs with PRO as "primary endpoint") as it really depends on the research question and does not reflect the current situation. We have data on 600 recent cancer RCTs (from 2004 to 2013) across a wide range of cancer specialties and know that 24% of RCTs had a PRO as a primary endpoint (http://promotion.qimema.it) (paper to be submitted). Also, even earlier evidence (up to 2008 and conducted in diseases other than cancer) has shown that it is not so "rare" that RCTs have PRO as a primary endpoint (Brundage et al, 2011). An example of a cancer clinical trial with a PRO co-primary endpoint was Hussain et al (2013).<br><br>*References:*<br>Brundage M, Bass B, Davidson J, Queenan J, Bezjak A, Ringash J, Wilkinson A, Feldman-Stewart D. Patterns of reporting health-related quality of life outcomes in randomized clinical trials: implications for clinicians and quality of life researchers. Qual Life Res. 2011; 20:653-64. | |

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| | | Hussain M, Tangen CM, Berry DL, et al. Intermittent versus continuous androgen deprivation in prostate cancer. N Engl J Med 2013;368(14):1314-1325.<br><br>**Proposed change (if any):** Delete 'rarely' and consider making reference to the points made above. | |
| **Lines 103-104** '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.' | | **Comment:** It may be useful to describe this in the context of rationale for PRO assessment.<br>**Proposed change (if any):** Comment on the clinical rationale within his section. Further examples are also warranted: e.g. advanced stage disease studies when survival differences based on treatment are expected to be small; when one treatment may be expected to cause worse toxicities; when treatment modalities differ or the design is an agent versus placebo; or where survival is not the primary outcome. We also refer you to our response to line 73, in which we outline a number of ways in which PROs provide value, beyond making a difference to the study conclusions. | |
| **Lines 112-113** PRO data should be treated like any other data | | **Comment:** Arguably you may need more rapid follow up for missing PRO data due to the recall period. We cannot retrospectively capture PRO data in the same way as some clinical data. | |

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| in monitoring clinical site performance and collection methods. | | **Proposed change (if any):** Note that retrospective PRO data capture, unlike some clinical outcomes e.g. overall survival, may not be possible (due to recall bias). | |
| **Line 113**<br>Bullet points | | **Comment:** We believe a further bullet point would be helpful as described below.<br>**Proposed change (if any):** Suggest add another bullet that PRO collection may give rise to PRO Alerts, i.e. exposure of trial staff to PRO data displaying 'concerning levels of psychological distress or physical symptoms that may require an immediate response'. Where applicable, an *a priori* plan for the management of alerts should be included the protocol and clearly communicated to all appropriate trial staff. Consider the following supporting reference:<br><br>Kyte DG, Draper H, Calvert M. Patient-Reported Outcome Alerts: Ethical and Logistical Considerations in Clinical Trials. JAMA. 2013; 310(12): 1229-1230. | |
| **Line 114**<br>Bullet points | | **Comment:** We believe a further bullet point would be helpful as described below.<br>**Proposed change (if any):** Suggest add another bullet that in general, PRO measures should be | |

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| | | administered at the beginning of a clinic visit prior to medical interviews or procedures, in the event that adverse medical information or immediate toxicities from chemotherapy would bias retrospective evaluation. | |
| **Line 116**<br>'multidomain' | | **Comment:** Use the term multidimensional rather than multidomain for consistency.<br>**Proposed change (if any):** Edit to multidimensional. | |
| **Lines 123-124**<br>'Reasons to include HRQL assessment in the clinical development programme for oncology medicinal products includes:' | | **Comment:** Unclear why PROs and HRQL have been split in this way.<br>**Proposed change (if any):** Many of the points listed apply equally to other PROs such as symptoms. Suggest restructuring of this section. | |
| **Line 130** | | **Comment:** In this section, symptom status is included in the definition of HRQL.<br>**Proposed change (if any):** Add to first definition (lines 31-34). | |
| **Lines 141-143**<br>'Careful thought | | **Comment:** Perhaps it would be useful to mention that "exploratory studies" can still be possible and | |

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| 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.' | | informative. Sometimes Investigators have no preliminary evidence based on which to formulate a clear HRQL hypothesis, but inclusion of HRQL can still be very helpful.<br>**Proposed change (if any):** Note that exploratory PRO data may also be useful. | |
| **Lines 145-146** 'Importantly, measurements should not constitute an | | **Comment:** It would be useful to cite relevant references here to clarify what is meant by undue burden.<br><br>It should be mentioned that although the completion of | |

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| undue burden to the patient.' | | PRO measures is time-consuming, it is likely to be less burdensome than blood draws, IV placement, or other invasive medical procedures.<br>**Proposed change (if any):** Edit the text to provide a more considered view of 'burden', for instance:<br>PRO experts suggest limiting estimated completion time of baseline PRO assessments to 20 minutes and 10-15 minutes completion for subsequent assessments.<br>*Reference:*<br>Basch E, et al. Recommendations for Incorporating Patient-Reported Outcomes Into Clinical Comparative Effectiveness Research in Adult Oncology. Journal of Clinical Oncology. 2012;30(34):4249-55. | |
| **Lines 148-149**<br>'There has been a general perception that only truly double blinded studies can | | **Comment:** This is based upon the perception that if patients know which treatment they are taking (as in an open-label study); their responses are more likely to be biased. Why would this consideration not apply to the collection of adverse events in open-label studies? These are not considered invalid. In fact, there is value in the collection of PRO data in open-label | |

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| provide trustworthy PRO data.' | | studies, and functional unblinding occurs in randomized, blinded studies as well.<br>**Proposed change (if any):** Consider revising the text accordingly. | |
| **Lines 160-161**<br>'For example, effects of neuropathy on functionality should be supported by conventional clinical measures 160 of neuropathy.' | | **Comment:** The patient may report neuropathy but this may not be supported by clinical measures of neuropathy, or those measures are not included in the trial because they are expensive/add to burden on patients.<br>**Proposed change (if any):** Suggest deleting the statement - it again implies that PRO only serve as added information to the "gold standard" "objective measure". | |
| **Lines 164-189**<br>Entire paragraph | | **Comment:** This paragraph is very good, but a mention of the challenges of deciding "timing and frequency" of assessments with the newer "anticancer targeted agents" would be helpful (please see general comments above **- New oncology agents and their impact on PRO trial design**).<br>**Proposed change (if any):** Comment on timing and frequency of assessments and new challenges/opportunities. | |

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| **Lines 166-167**<br>'If assessments are too few, important changes may not be captured, if too frequent, the subject may become sensitised to the instrument.' | | **Comment:** We interpret "sensitised" as meaning the respondent/patient becomes familiar with the questionnaire and knows what questions will be asked (and familiar with the response options). We don't think there is anything wrong with the patient being familiar with the questionnaire. In fact, it could be a benefit, as they will complete the questionnaire quicker than someone who is "naïve" to the questionnaire. There is nothing about being familiar with a questionnaire that would compromise the validity of the patient's response (at least in the context of PRO measurement in oncology clinical trial settings). What could be a concern is more frequent assessments could add to burden, especially if the patient is extremely sick and doesn't feel up to completing daily/weekly surveys. This could result in more missing data which is a problem.<br>**Proposed change (if any):** Suggest removing the term sensitised.<br>We all agree that we don't want to burden respondents with unnecessary PRO measurements. It would be useful for the EMA to correct the notion/impression among those unfamiliar with PROs that completing PRO surveys are "burdensome". We are not collecting painful blood or tissue samples. Patients are simply tapping on a computer screen or using a pencil on paper to answer | |

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| | | questions on their health status. Most assessments can be minimized to 15-20 minutes at most. In addition, if more frequent assessment is needed, it is possible to create short questionnaires (e.g., < 5 minutes) that can be administered at time points between longer assessments with the shorter questionnaire focusing on the primary PRO of interest (e.g., pain). In addition, it should be noted that we find that patients don't mind completing PRO questionnaires. They enjoy the idea that information they provide will help future cancer patients.<br><br>A useful reference relating to this issue is:<br>Stone AA, Broderick JE, Schwartz JE, Shiffman SS, Litcher-Kelly L, Calvanese P. Intensive momentary reporting of pain with an electronic diary: Reactivity, compliance, and patient satisfaction. Pain. 2003: 104; 343-351. | |
| **Lines 165-174**<br>Entire paragraph | | **Comment:** It would be good to stress the importance that all studies that plan to collect PROs should collect a "baseline" assessment of as many of the domains we measure (e.g., fatigue, lack of sleep, anxiety, depression) that are relevant before the intervention starts. This will allow researchers to know where a patient started to see how they changed once on | |

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| | | treatment.<br>**Proposed change (if any):** Comment on the importance of baseline assessment. | |
| **Line 169-171**<br>'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.' | | **Comment:** This should also take into account the recall period of the questionnaire.<br>**Proposed change (if any):** Note that recall period is of importance. | |
| **Lines 175-176**<br>'In order to be able to accurately | | **Comment:** Data should be collected in the same ways across treatement groups.<br>Next line therapy PRO data may be influenced by 2nd line treatments and may be more vulnerable to patient attrition. They also make a study more expensive to do. | |

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| assess the PRO results on study therapy, continued assessment post-progression and during next-line therapy may also be needed.' | | We believe the document devotes too much time to this section and suggests that these PRO data are more illuminating and worthwhile than they have been demonstrated to be.<br>**Proposed change (if any):** Emphasize the need to collect data in the same way across treatment groups. Suggest shortening this section and adding the caveats noted above. | |
| **Lines 186-189** | | **Comment:** We think the idea of analyzing PROs similar to Progression Free Survival (e.g., Progression Free Symptom experience) is interesting and could be a valuable alternative, and complementary approach, to differentiate treatment arms. However, we would not endorse stopping PRO assessments in one arm (e.g., the comparator arm as used in the text) if the symptoms get worse. We recommend continuing to collect the PRO data over the course of the study as this will give decision makers (regulators, trialists, patients, clinicians) a better picture of the trajectory of the PRO experience.<br>**Proposed change (if any):** There should be complete data collection on both arms for comparisons of the | |

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| | | trends over time. Although the authors seem to be saying that it is important to continue to collect PRO data after progression has been reached, this point needs to be emphasized as it seems to get lost in the subsequent discussion. | |
| **Lines 192-193**<br>'High compliance has been attributed to comprehensive educational programmes prior and during the trial for both research staff and study participants.' | | **Comment:** This is an important point – signposting to relevant references would be useful.<br>**Proposed change (if any):** Signpost to the following reference:<br>**Staff education:**<br>Hansen LK, Moinpour CM, Ermete RB. Enhancing Nurse Contributions To SWOG Clinical Trials Objectives. Seminars in Oncology Nursing. 2014; 30(1): 26-31. | |
| **Lines 196-198**<br>'Electronic data capture methods may offer more convenience to some patients | | **Comment:** We agree but need to ensure that ePROs are equivalent to paper based version.<br>**Proposed change (if any):**<br>Add the following reference:<br>Coons SJ, Gwaltney CJ, Hays RD, Lundy JJ, Sloan JA, Revicki DA, Lenderking WR, Cella D, Basch E; ISPOR | |

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| and may increase data quality, reduce missing data (allowing automatic reminders to be sent) and potentially reduce data entry errors.' | | ePRO Task Force. Recommendations on evidence needed to support measurement equivalence between electronic and paper-based patient-reported outcome (PRO) measures: ISPOR ePRO Good Research Practices Task Force report. Value Health. 2009 Jun;12(4):419-29. | |
| **Line 209**<br>'Filling in baseline questionnaire as part of the eligibility criteria checklist.' | | **Comment:** Suggest adding to the sentence: "*and prior to randomization* and administration of treatment"<br>**Proposed change (if any):** Edit as above. | |
| **STATISTICAL METHODS AND MISSING DATA**<br>General point relating to the section. | | **Comment:** Much of this section relates to data collection and should be merged with the section above<br><br>**Proposed change (if any):** Move information on data collection to the section above.<br><br>Mention the importance of powering a study to detect a | |

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| | | difference in HRQL (or another concept measured by a PRO) based on the group Minimally Clinically Important Difference (MCID) for that instrument. The statistical analysis section should also make reference to the criterion for a clinically significant difference for the key PRO score. | |
| **Line 214**<br>'Checking for completeness of forms…' | | **Comment:** Checking for completeness must be done at the moment the patient hands in the form—it is not possible to capture the data later.<br>**Proposed change (if any):** Note that checking for missing data must occur at the point of assessment or very soon after to minimise recall bias. | |
| **Line 223**<br>'to avoid cross-cultural validity and translation issues.' | | **Comment:** Cultural validation is an area of concern.<br>**Proposed change (if any):** Note or reference that forward and backward translation methods ensure a consistent comprehension of items in an instrument - this would help with ensuring cross-cultural validity, for example, the EORTC Translation Guidelines and the ISPOR Task Force paper.<br><br>*Reference:*<br>Dewolf, L, et al. 2009. EORTC Quality of Life Group Translation Procedure, 3rd Ed. EORTC, Brussels. http://groups.eortc.be/qol/sites/default/files/archives/translation_manual_2009.pdf | |

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| | | Wild, D, et al 2005. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: Report of the ISPOR Task Force for Translation and Cultural Adaptation. Value in Health, Vol. 8, Issue 2, 2005 pp 95-104 http://www.ispor.org/workpaper/research_practices/PROTranslation_Adaptation.pdf | |
| **Lines 224-233** Entire paragraph | | **Comment:** This section could usefully be expanded to provide examples.<br>**Proposed change (if any):** Suggest describe the existence of "treatment" specific measures (e.g. the FACT-Bone Marrow Transplantation-BMT). In the discussion of "Generic" measures, you could include some example like the PROMIS measurement system. | |
| **Line 225** 'PRO instruments should be relevant, reliable, validated and responsive to | | **Comment:** PRO measures should also be acceptable to the population in which they will be administered, both in terms of the questions they ask (e.g. are they appropriately worded?) and the overall burden to the patient (e.g. is the completion time for the PROM agreeable?). PRO instruments must also be easily interpretable, i.e. the meaning of differences in PROM score should be clearly understood. | |

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| change.' | | **Proposed changes:** Include: "PRO measures should also be acceptable to the population in which they will be administered, both in terms of the questions they ask (e.g. are they appropriately worded?) and the overall burden to the patient (e.g. is the completion time for the PROM agreeable?). PRO instruments must also be easily interpretable, i.e. the meaning of differences in PROM score should be clearly understood."<br><br>Consider the following supporting reference:<br><br>Mokkink L, Terwee C, Patrick D, et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. Journal of Clinical Epidemiology. 2010; 63: 737-745. | |
| **Lines 224- 233** Paragraph describing instruments. | | **Comment:** Both types of instruments have advantages. **Proposed change (if any):** We would often recommend using a combination of both generic and disease-specific instruments - generic instruments can capture changes in HRQL that disease specific | |

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| | | instruments do not. | |
| **Lines 238-239**<br>'Instruments should be culturally valid and translated versions should be as true to the original as possible (linguistic validation).' | | **Comment:** For translated instruments, the field has moved away from the thought that "linguistic validation" (or linguistic equivalence) is the highest priority. Of more importance is the notion of "measurement equivalence" or "conceptual equivalence". It has been found that the same word(s) translated into different languages can be interpreted differently based on cultural issues. It is recognized that it is okay to have different words for an item as long as the result is that one is measuring the same "concept" (PRO). Thus, obtaining measurement equivalence should be the key target.<br>**Proposed change (if any):** Refocus the section on measurement equivalence and provide appropriate references. | |
| **Lines 242-245**<br>'The evaluation of PRO by carers or other proxy judges may be utilised where it is clear that the | | **Comment:** If proxy reporting has occurred, this should be described and discussed in the main trial publication.<br>**Proposed change (if any):** Comment that any proxy reporting should be discussed in the final trial publication. | |

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| patient themselves cannot contribute (e.g. very small children, patients with cognitive impairment, severe ill health), but in general proxy reporting should be avoided.' | | | |
| **Lines 251-252** 'However it is acknowledged that some patients will be too young or too sick to contribute to the data collection.' | | **Comment:** This statement may be viewed as a get out clause. Trialists can work with experts in childhood PRO assessment to maximise data collection. Different approaches can be tailored to maturity.<br>**Proposed change (if any):** Consider re-writing this section and adding the following references:<br><br>Connolly MA, Johnson JA. Measuring quality of life in paediatric patients. Pharmacoeconomics. 1999;16:605–25. | |

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| | | Eiser C, Morse R. Can parents rate their child's health-related quality of life? Results of a systematic review. Quality of Life Research. 2001;10:347–57.<br><br>Matza LS, Patrick DL, Riley AW, Alexander JJ, Rajmil L, Pleil AM, et al. Pediatric Patient-Reported Outcome Instruments for Research to Support Medical Product Labeling: Report of the ISPOR PRO Good Research Practices for the Assessment of Children and Adolescents Task Force. Value in Health. *2013;16(4):461-79.*<br><br>Matza LS, Swensen AR, Flood EM, Secnik K, Leidy NK. Assessment of Health-Related Quality of Life in children: a review of conceptual, methodological & regulatory issues. Value in Health. 2004:7(1)79-92.<br><br>Wakefield C, Patterson P, McDonald FEJ, et al. Assessment of psychosocial outcomes in adolescents and young adults with cancer: a systematic review of available instruments. Clinical Oncology in Adolescents and Young Adults. 2013 February; 3: 13-27. | |

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| | | | |
| **Line 253 Elderly** | | **Comment:** Given the large number of health-related factors that could affect older adults it would be important to consider extra provisions for PRO assessment in this group.<br>**Proposed change (if any):** It may be worth emphasizing potential support for elderly patients that may be useful e.g. support for completion (interviews), or provision of grip-pens. | |
| **Lines 285-287** 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 | | **Comment:**<br>This is a key concept, but MCID is not the only term used in the literature. A suitable reference here would be the comprehensive review by King which provides an explanation and chronology of this and related definitions<br>**Proposed change (if any):**<br>Insert this reference:<br>King MT. A point of minimal important difference (MID): A critique of terminology and methods. Expert Review of Pharmacoeconomics & Outcomes Research. 2011; 11 (2): 171-184. | |

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| excessive cost, a change in the patient's management'. | | | |
| **Lines 289-291** "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." | | **Comment:** This inappropriately gives primacy to the clinical outcomes.<br><br>**Proposed change (if any):** Rephrase to avoid this issue. | |
| **Line 300** 'clinically' | | **Comment:** Typo<br>**Proposed change (if any):** Should read 'clinical'. | |
| **Lines 301-302** Considerations of alternative explanations that may | | **Comment:** We believe that there should be a separate reporting section that ideally references and endorses the use of CONSORT-PRO.<br>**Proposed change (if any):** Add a separate section on trial reporting with reference to CONSORT-PRO. | |

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| account for the observed changes or lack of changes | | **References:**<br>Brundage M, Blazeby J, Revicki D, Bass B, de Vet H, Duffy H, Efficace F, King M, Lam CL, Moher D, Scott J, Sloan J, Snyder C, Yount S, Calvert M. Patient-reported outcomes in randomized clinical trials: development of ISOQOL reporting standards. Quality of Life Research. 2013 Aug;22(6):1161-75. doi: 10.1007/s11136-012-0252-1. Epub 2012 Sep 18.<br><br>Calvert M, Blazeby J, Altman DG, Revicki DA, Moher D, Brundage MD; CONSORT PRO Group. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. JAMA. 2013 Feb 27;309(8):814-22. doi: 10.1001/jama.2013.879. | |
| **REFERENCES**<br>Ref: Ganz and Cotay | | **Comment:** Typo<br>**Proposed change (if any):** Should read 'Ganz and Gotay'. | |
| **REFERENCES** | | Consider adding the following references.<br>**References**<br><br>***General References:***<br><br>Fayers P & Machin D. Quality of Life: The Assessment, Analysis and Interpretation of Patient-reported | |

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| | | Outcomes, Wiley 2nd edition.<br><br>Fairclough D. Design and Analysis of Quality of Life Studies in Clinical trials, Chapman and Hall 2nd edition.<br><br>***Examples: Value of PRO Data***<br>Taphoorn MJ, Stupp R, Coens C, et al., Health-related quality of life in patients with glioblastoma: a randomised controlled trial. Lancet Oncology. 2005 Dec;6(12):937-44<br><br>Sneeuw KC, Sprangers MA, Aaronson NK. The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease. Journal of Clinical Epidemiology. 55(11):1130-43, 2002.<br><br>Au, HJ, Ringash, J, Brundage, M, et al. Added value of health-related quality of life measurement in cancer clinical trials; the experience of the NCIC CTG. Expert Reviews in Pharmacoeconomics and Outcomes Research. 2010 Apr;10(2): 119-28.<br><br>**Selecting a PRO measure:**<br>Luckett T, King MT. Choosing patient-reported outcome measures for cancer clinical research – Practical | |

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| | | principles and an algorithm to assist non-specialist researchers. European Journal of Cancer. 2010; 46(18):3149-57.<br>Mokkink L, Terwee C, Patrick D, et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. Journal of Clinical Epidemiology. 2010; 63: 737-745.<br><br>***PROs as a Primary Outcome***<br>Brundage M, Bass B, Davidson J, et al. Patterns of reporting health-related quality of life outcomes in randomized clinical trials: implications for clinicians and quality of life researchers. Qual Life Res. 2011; 20:653-64.<br><br>Hussain M, Tangen CM, Berry DL, et al. Intermittent versus continuous androgen deprivation in prostate cancer. N Engl J Med 2013;368(14):1314-1325.<br><br>***Equivalence***<br>e-PROs:<br>Coons , Gwaltney , Hays , et al; ISPOR ePRO Task | |

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| | | Pharmacoeconomics & Outcomes Research. 2011; 11 (2): 171-184.<br><br>Revicki D, Hays RD, Cella D, et al. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. Journal of Clinical Epidemiology. 2008. 61(2): 102-9.<br><br>Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Medical Care. 2003. 41(5): 582-592<br><br>Wyrwich, K, Norquist JM, Lenderking, W, and Acaster S. Methods for interpreting change over time in patient-reported outcome measures. Qual Life Res. 2013 Apr;22(3):475-83<br><br>***Patient Engagement/Patient & Public Involvement***<br>Brett J, Staniszewska S, Mockford C, et al. Mapping the impact of patient and public involvement on health and social care research: a systematic review. Health Expectations. 2014 Oct;17(5):637-50<br><br>de Wit, Abma Koelewijn-et al. What has been the effect | |

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| | | on trial outcome assessments of a decade of patient participation in OMERACT? The Journal of Rheumatology. 2014 Jan;41(1):177-84.<br><br>Gradinger Britten, Wyatt, et al. Values associated with public involvement in health and social care research: a narrative review. Health Expectations. 2013. Dec 10. doi: 10.1111/hex.12158. [Epub ahead of print]<br><br>Kirwan, Minnock, Adebajo, et al. Patient perspective: fatigue as a recommended patient centered outcome measure in rheumatoid arthritis. The Journal of Rheumatology. 2007 May;34(5):1174-7.<br><br>Nicklin, Cramp, Kirwan, et al. Collaboration with patients in the design of patient-reported outcome measures: capturing the experience of fatigue in rheumatoid arthritis. Arthritis Care Res (Hoboken). 2010; 62(11): 1552-8.<br><br>Staniszewska, S, Haywood KL, Brett J, Tutton E. Patient and public involvement in patient-reported outcome measures: evolution not revolution. Patient. 2012; 5(2): 79-87. | |

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| | | ***PRO Reporting***<br>Brundage M, Blazeby J, Revicki D, et al. Patient-reported outcomes in randomized clinical trials: development of ISOQOL reporting standards. Qual Life Res. 2013 Aug;22(6):1161-75. doi: 10.1007/s11136-012-0252-1. Epub 2012 Sep 18.<br><br>Calvert M, Blazeby J, Altman DG, et al for the CONSORT PRO Group. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. JAMA. 2013 Feb 27;309(8):814-22. doi: 10.1001/jama.2013.879. | |
| **Other remarks** | Terminology | **Comment:** Need to be careful of the distinction throughout the paper between HRQL and PRO—they are not synonymous, and methods such as Q-TWiST can be employed to measure quality of life in certain types of cancer even without the use of a PRO measure.<br>**Proposed change (if any):** Consider the appropriate use of the distinctions between PRO and HRQL throughout the document. | |

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| | Phase of study | It would be useful to consider collection of PRO in phase I and phase II clinical trials. There may be a general perception that PRO are only included within phase III randomized clinical trials. Although licensing decisions by regulatory authorities may be based primarily on phase III data, collecting PRO data within context of phase I or phase II data can be informative in drug development process.<br>**Proposed change (if any):** Perhaps the EMA document can provide guidance on this issue. | |