Current state of quality of life and patient-reported outcomes research

5th EORTC Quality of Life in Cancer Clinical Trials Conference Faculty; Calvert, Melanie

DOI:
10.1016/j.ejca.2019.08.016

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
5th EORTC Quality of Life in Cancer Clinical Trials Conference Faculty & Calvert, M 2019, 'Current state of quality of life and patient-reported outcomes research', *European Journal of Cancer*, vol. 121, pp. 55-63. https://doi.org/10.1016/j.ejca.2019.08.016

European Journal of Cancer 121 (2019) 55–63

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Current Perspective

Current state of quality of life and patient-reported outcomes research

Andrew Bottomley [a,*], Jaap C. Reijneveld [b], Michael Koller [c], Henning Flechtner [d], Krzysztof A. Tomaszewski [e,f], Eva Greimel [g] on behalf of the 5th EORTC Quality of Life in Cancer Clinical Trials Conference Faculty[1]

[a] *Quality of Life Department, European Organisation for Research and Treatment of Cancer, Brussels, Belgium*
[b] *Department of Neurology and Brain Tumor Center, Amsterdam University Medical Center, Amsterdam, The Netherlands*
[c] *Center for Clinical Studies, University Hospital Regensburg, Germany*
[d] *University Clinic for Child and Adolescent Psychiatry, Otto-von-Guericke-University, Magdeburg, Germany*
[e] *Faculty of Medicine and Health Sciences, Andrzej Frycz Modrzewski Krakow University, Krakow, Poland*
[f] *Scanmed St. Raphael Hospital, Cracow, Poland*
[g] *Department of Gynecology, Medical University Hospital, Graz, Austria*

Received 6 August 2019; accepted 8 August 2019

KEYWORDS
Quality of life;
Patient-reported outcomes;
Symptom assessments;
Cancer treatment;
Cancer patients;
Cancer survivorship

Abstract The 5th EORTC Quality of Life in Cancer Clinical Trials Conference presented the current state of quality of life and other patient-reported outcomes (PROs) research from the perspectives of researchers, regulators, industry representatives, patients and patient advocates and health care professionals. A major theme was the assessment of the burden of cancer treatments, and this was discussed in terms of regulatory challenges in using PRO assessments in clinical trials, patients' experiences in cancer clinical trials, innovative methods and standardisation in cancer research, innovative methods across the disease sites or populations and cancer survivorship. Conferees demonstrated that PROs are becoming more accepted and major efforts are ongoing internationally to standardise PROs measurement, analysis and reporting in trials. Regulators are keen to collaborate with all stakeholders to ensure that the right questions are asked and the right answers are communicated. Improved technology and increased flexibility of measurement instruments are making PROs data more

* *Corresponding author*: Quality of Life Department, European Organisation for Research and Treatment of Cancer, 83/11 Avenue E. Mounier, Brussels, 1200, Belgium.
E-mail address: andrew.bottomley@eortc.be (A. Bottomley).
[1] See Addendum.

https://doi.org/10.1016/j.ejca.2019.08.016

robust. Patients are being encouraged to be patient partners. International collaborations are essential, because this work cannot be accomplished on a national level.

1. Introduction

The 5th EORTC Quality of Life in Cancer Clinical Trials Conference presented the current state of quality of life (QOL) and other patient-reported outcomes (PROs) research from the perspectives of QOL researchers, regulators, industry representatives, patients and patient advocates and health care professionals. PROs are any clinical outcome reported directly by the patient and captured either through self-reporting or interview (as long as the interviewer directly records the patient's responses). Health-related QOL is a multidimensional concept referring to the patient's subjective perception of the effect of their disease and treatment on physical, psychological and social aspects of daily life. PROs are particularly important today, because a clinical response to treatment might well be observed, but at the expense of worsening the patient's condition. Indeed, drug efficacy in cancer clinical trials is assessed by end-points such as overall survival or tumour growth, but cancer treatments are often accompanied with side-effects that can adversely affect QOL. Symptom assessment can offer greater precision in describing the patient's experience, and these can strengthen the response to change in intervention trials, especially when they focus on a key treatment benefit or expected toxicity. The challenge, although, is being able to separate disease-related symptoms from treatment toxicity [1].

Information concerning the trajectory of symptoms can be obtained by collecting PROs data in an organised, longitudinal manner. In Edmonton, Canada, a retrospective observational study collected the data of 391,305 patients diagnosed with cancer between January 2007 and December 2014 with a recorded 3,277,585 symptom assessments. Considering the assessment of pain, e.g. the study found that in most cancer types, the proportion of patients with pain is fairly stable over the disease course, the trajectory depends on the type of cancer, and pain is higher in lung cancer and lower in gastrointestinal cancers [2]. However, for head and neck cancers, the worst pain occurs after treatment. Such information has important implications for patients, and this study shows that patients, together with their health care provider, should prepare a detailed treatment plan on how to address post-treatment pain.

2. Regulatory challenges in using PROs

Key drivers affect the regulatory environment: new and emerging science, medicines and technologies; public demand for greater transparency and openness; calls for a patient-centred approach and involvement. Regulators have to balance the benefits and risks of drug products. As for risks, clinical trial adverse events will capture disease-related symptoms and treatment-related symptoms together, which can be difficult to differentiate from each other. Also, safety is not the same thing as tolerability which has a component of patients' decision to adhere to a therapy that can be affected by symptomatic adverse events. It is very difficult to label how patients feel and function on a treatment, and these comprise underlying reasons for regulatory interest in PROs, and both the United States of America (USA) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have published guidance on PROs [3,4]. Differences among FDA, EMA and Health Canada in the way PROs are handled and interpreted can limit the capacity of external stakeholders to optimise clinical trial design and PROs data collection to meet regulatory decision-making requirements [5]. This makes continued international collaboration among regulators and payer groups using these data important.

In practice, obtaining scientific advice from regulators helps to ensure that developers perform the appropriate tests and studies. A recent study of 96 trials from 2007 to 2017 for cancer products concluded that implementation of procedures was needed to help improve PROs completion rates and reduce missing data [6]. To help this forward, both the EMA and FDA have established programmes to provide parallel scientific advice to sponsors which focus on sharing information and perspectives, achieving harmonisation and increasing convergence.

PROs provide a patient-focused assessment of the impact of a treatment on the patients' symptoms and functional ability, and as such, PROs fit well within personalised medicine. Challenges in using patient-reported outcome measures (PROMs) include the increasing molecular sub-classification of disease leading to insufficient numbers of similar patients to reach statistical power in clinical trials. Data to support regulatory decision-making may rely on extrapolation of the data on similar molecular tumour types at different

anatomical locations, e.g. basket studies. Smaller studies are more susceptible to the effects of variability, and missing data are more likely to impact the study conclusions. Smaller pre-market exposure equates with increased importance of, and emphasis on, post-market monitoring and data collection. Consequently, the use of real world evidence (RWE) is gaining attention as a way to support regulatory decision making [7].

Study design is important, and when deployed PROs end-points should be stated as specific clinical trial objectives in the study protocol and statistical analysis plan. The extent to which the inclusion of PROMs can provide added value to the clinical trial should be defined. Here, it should be noted that the most appropriate and valid PROMs have involved patients in their development. PROMs are best considered early in the development programme, and patients should be involved early in the study design process. PROMs should be administered to study subjects at time points when there is a clear rationale for their use. Excessively high numbers of questions can constitute an undue burden to the patient, and efforts to select only those questions that are relevant to the trial context may decrease high drop-out rates and missing data. When reporting results, a balanced view of PROs-QOL should be presented, and any disconnect between QOL results and other safety and efficacy end-points should be addressed.

3. Sponsor's perspective on QOL

It could be said that in the past, clinical trial end-points were not defined to compare QOL between treatments, did not start with a clear hypothesis to explore the differences in QOL, nor measured aspects of disease and treatment most relevant to patients. Today, however, there is greater alignment on core concepts of interest from the perspectives of regulators, patients and health care providers, e.g. disease symptoms, physical functioning, instrumental activities of daily living, treatment burden, as well as alignment on well-defined tools and end-points.

Looking forward, there is still room for clearer end-point definitions, better alignment between sponsors and regulators balancing rigor and feasibility, better up-front communication between regulators and sponsors, clearer alignment between payers and regulators on requirements for clinical evidence, clearer expectations of filing requests at pre–phase III meetings, and clearer alignment between payers and regulators on requirements for clinical evidence. Comparative tolerability of a medical product should include direct measurement from patients on how they are feeling and functioning while on treatment. In addition, the future will see an increase in the use of new study designs, a movement towards decentralised, yet still international, clinical trials and systematic patient input into trial design and feasibility.

An increase in novel treatments, such as cell and gene therapies, where limited empirical evidence is available at approval, points towards an increased importance for RWE. In rare cancers, where patients are scarce, PROs as part of routine care can provide valuable information on the patient's experience.

4. QOL assessment in clinical trials

PROs data relating to a new treatment are an important complement to the clinical evidence in demonstrating the value of a treatment; however, the lack of standardisation can lead to variation in result analysis and end in potential differences in data interpretation.

Carefully validated static questionnaires such as the EORTC QLQ-C30 and modules have become the norm, and this is good news. However, sometimes it is desirable to measure the core domains with greater flexibility to achieve greater precision (e.g. primary outcome), allow patients to answer fewer questions or capture higher levels of functioning or more severe symptoms (expand measurement range). With this in mind, the EORTC Quality of Life Group (QLG) is introducing a new flexible strategy for QOL assessment that builds on their traditional approach. To optimise measurement precision and flexibility, a computerised adaptive test (CAT) version of the EORTC QLQ-C30 has been developed. With CAT, the selection of items is tailored to the individual based on responses to previous items [8]. The EORTC CAT enables increased precision and requires a smaller sample, provides reduced response burden, reduced floor and ceiling effects, offers a questionnaire length selected for each study or person individually with immediate calculation of scores and remains compatible with the QLQ-C30.

Multiple hurdles must be overcome before we can effectively measure, appropriately specify, properly analyse, clearly report and successfully apply PROs findings from clinical trials in clinical practice. In this light, the Patient-Reported Outcomes Tools: Engaging Users and Stakeholders consortium has set out to ensure that patients, clinicians and other decision-makers have PROs data from clinical trials to make the best decisions they can about treatment options, and they are doing this by partnering with key stakeholder groups to disseminate and implement tools that have been developed to optimise the use of PROs in clinical trials [9–15].

The relationship between PROs and survival is well-established, although the mechanisms that explain why PROs predict survival do need to be identified [16,17]. Still, there is considerable potential to use these data in cancer care. PROs could be used as eligibility criteria or stratification factor in cancer clinical trials, opening the

possibility of PROs becoming integrated into cancer care, or to be used to provide interventions to improve PROs and survival time.

Modern cancer therapy has been advanced through a better understanding of genetics and the underlying molecular biology. Trials of diagnostics, surgical and radiotherapy techniques and targeted systemic therapies demonstrate that more patients are being cured or are living with their cancers for longer periods of time [18]. Even so, questions remain. Is lengthier survival worth treatment side-effects, and what survival benefit is needed to trade off disadvantages and harms? Certainly, current research suggests a flawed logic behind the idea that patients will accept high toxicity for minimal benefits. Indeed, if there is no clear survival benefit between treatments, then differences in QOL between those treatments are crucial and may influence patient choices. However, is there sufficient QOL data to inform patient decision-making [19]?

In response to these questions, Patient-Reported Outcomes in cancer, impact of Age and Carer/role demands associated with Treatment has developed and validated a Patient Roles and Responsibilities Scale to enable a broader evaluation of the impact of cancer and cancer treatment and measuring 'real world' roles and responsibilities such as caring for others and financial and employment responsibilities [20]. From the patients' perspective, whether something is worthwhile is an individual thing. It is important to know if treatment will allow them to carry on those daily activities that give their lives meaning.

Patient advocates see an opportunity for PROs to move centre stage in research as a means towards developing and understanding pathways of care. PROs tools, methods and support need development. The rounded holistic view provided by longitudinal studies is highly desired. Patient advocates point out that research participation is linked to high numbers of satisfied patients, and research delivery is linked to improved outcomes (both in institutions and in patient populations).

5. Innovative methods and standardisation in cancer research

Guidelines are recommendations intended to assist providers and recipients of health care and other stakeholders to make informed decisions, are conditional, and generally gain support with implementation [21]. Recommendations can be confusing in practice, so GRADE (Grading of Recommendations Assessment, Development and Evaluation) has developed a unifying, transparent, system for grading the certainty of evidence and making decisions [22]. The practical use of this tool can be seen, e.g., by applying it to situations in conjunction with the European Breast Guidelines. As an example, mammography screening programmes are organised for women more than 50 years old, but should you attend if you are 45–49 years old? GRADE, an interactive decision aid, considers the problem, desirable as well as undesirable effects, certainty of evidence, value, balance of effects, resources, the certainty of evidence of required resources, cost effectiveness, equity, acceptability, and feasibility to reach a suggestion for intervention. In this example, GRADE suggested the intervention: 'For asymptomatic women aged 45–49 years with an average risk of breast cancer, the European Commission Initiative on Breast Cancer Guideline Development Group recommends mammography screening over no screening, in the context of an organised screening programme (conditional recommendation, moderate certainty in the evidence)'.

Clinical trial protocols enable research teams to deliver a high-quality study. As such, protocols should provide sufficient detail to enable funders, reviewers and institutional review boards to appraise scientific, methodological and ethical rigor. These are, therefore, a major determinant of the quality of PROs data and the subsequent evidence. An international, consensus-based, PRO-specific protocol guidance was developed, an official Standard Protocol Items: Recommendations for Interventional Trials-Patient reported outcomes (SPIRIT-PROs) extension, to ensure that PROs data will be of high-quality and thus able to better inform patient care [10].

The EORTC Quality of Life core questionnaire, the QLQ-C30, maintains a sufficient degree of generalisability to allow for cross-cultural comparison along with a level of specificity adequate for addressing research questions of particular relevance in a given cancer clinical trial. It uses a modular approach applicable to all people with cancer. The current EORTC portfolio includes QLQ-C30 questionnaires available in over 110 languages, the QLQ-C15-PAL short version for palliative care, the QLQ-F17 short version with only functional scales and stand-alone questionnaires on, e.g. information and satisfaction with care. Apart from that, there are a total of 27 fully validated disease-specific modules that can be used in conjunction with the QLQ-C30 and are available for academic and commercial use.

If a researcher would like to assess QOL in a clinical trial, but there is no suitable EORTC instrument, then the EORTC item library can be consulted. EORTC QLG strategy supports the combining of static and flexible measures. Currently, the library has over 900 items (i.e. questions) from over 60 questionnaires, up to 110 language versions per item, and researchers are able to create and download item lists. Using item lists can reduce patient burden by minimising the number of measures required as well as provide increased flexibility and efficiency that can be more tailored to the needs of specific treatments and populations. However, the item

lists are not fully validated and may not be able to compare across trials.

The USA National Cancer Institute (NCI) developed the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PROs-CTCAE) to integrate the patient perspective into adverse event reporting [23]. The PROs-CTCAE item library contains 124 patient-reported items representing 78 symptomatic adverse events (e.g. dysphagia, nausea, sensory neuropathy). Items assess frequency, severity, interference with daily activities, presence and amount. Covered adverse events are drawn from the NCI's CTCAE.

Setting International Standards for the Analysis of Quality of Life (SISAQOL) led by the EORTC [24], is an international multi-stakeholder consortium with shared interest in improving the standards for the statistical analysis of PROs. Its current focus is on randomised clinical trials (RCTs) in oncology. A common PROs objective is, e.g. will treatment A improve physical functioning relative to treatment B. So, which statistical measure is appropriate to test this? Each statistical method focuses on a different aspect of the data and responds to a different research objective, and SISAQOL has developed a taxonomy of research objectives that can help inform the statistical method to be used. SISAQOL's ultimate goal is to draw robust and clear conclusions based on PROs assessments so that treatments can deliver better patient outcomes. That said, within a treatment arm for a given PROs objective, you might not feel better with the treatment, but you might not feel as bad as you would with the other.

QOL is increasingly assessed as an important end point in cancer clinical trials, and there is a simultaneously growing interest to improve the interpretation of QOL data. Interpreting QOL scores merely via statistical significance might be misleading, because small differences in mean scores can be statistically significant, even when clinical relevance is absent. Therefore, the notion of minimally important difference (MID) aids in interpreting differences and changes in QOL scores as clinically meaningful. A recent EORTC study, however, found that a global rule for MIDs applicable to all settings is unlikely [25]. MIDs vary by EORTC QLQ-C30 scale, direction of change and disease setting, and there is need to update and diversify current MID standards.

Lessons can be learned by looking back at analyses of QOL in clinical trials. EORTC trial 18071, e.g. is overpowered for QOL differences, and because of the multiple tests conducted, differences would be rated according to their magnitude rather than statistical significance [26]. The MID = 10 points, thus differences of <10 points are not considered clinically relevant. So, expecting QOL improvement needs more than efficacy improvement, and this is difficult to achieve. Patients not responding well tend to drop out, and consequently there is a selection effect. In EORTC trial 62072, longer progression-free survival led to longer pazopanib administration and, therefore, QOL data were collected for a longer time period. QOL assessment is limited until progression, so the question of the added value of delayed progression arises [27]. Here, post-progression QOL data collection is required. Blinding has an impact on QOL: the expectations are unchanged, uncertainty is added and adverse events are seen as positive (as patients then presume that they are in the experimental arm). Finally, it can be argued that the general QOL scale is insensitive in that the overall QOL is greater than the sum of symptoms and is subject to coping mechanisms, response shifts, remedial therapies, etc.

A systematic review of 46 RCTs of biomedical interventions and 20 RCTs of psychosocial interventions was conducted in 2003 to determine the contribution of QOL to decision-making [28]. In adjuvant therapy of breast cancer, QOL provided additional information for clinical decision-making beyond that of traditional medical outcomes to primary local management, but did not contribute to adjuvant chemotherapy or treatment of metastatic disease, and the authors of the study recommended targeting specific symptoms and psychological outcomes. A more recent analysis conducted between 2001 and 2017 found that among 66 studies reporting PROs results from RCTs of adult patients with advanced breast cancer receiving anti-cancer treatments, only eight (12%) studies reported a specific PROs research hypothesis [29].

Finally, on another note, wearable electronic devices offer the possibility of obtaining ePROs and the promise of less missing data, more facile data monitoring, circumvention of transmission and calculation errors as well as the realisation of capturing QOL data in real time. From a cost perspective, patients could essentially bring their own device and, thereby, reduce cost. Efforts are ongoing concerning validation of such devices.

6. Innovative methods across disease sites and populations

There are a number of unique challenges faced when QOL researchers develop QOL measurement instruments. For one, validated questionnaires need to be translated into the local language to be used by patients in a given country. To accomplish this, the EORTC first assesses the translatability of a questionnaire. This is followed by forward translations, reconciliation, backward translations, review, proofreading, pilot-testing on patients, discussion of the results and finalisation of the project. This procedure is followed during development of new instruments as well as after validation, when questionnaires are requested by external users.

Measuring sexual health (SH) in the oncology setting is another challenge, because communication about SH lacks a proactive approach by most health care

providers. Cancer patients and survivors expect health care providers to discuss sexual issues, but it often remains an unmet need during the course of treatment. The EORTC SHQ-22 is a cross-cultural validated measure applicable in multiple countries and nationalities, which can be used to assess SH of cancer patients in clinical trials as well as in clinical practice. It is short, easy to understand and well accepted by patients, and the measures may facilitate physician–patient communication and help to identify SH problems throughout the course of treatment [30]. Neurological tumours present another sort of challenge. There is an increasing number of clinical trials and studies in glioma patients that include QOL measures, but compliance with QOL is often limited. This hampers interpretation of the results and leaves clinically relevant questions unanswered. COmbining clinical trial DAtabases in GLIOma patients and RANO-PRO (Response Assessment in Neuro-Oncology–PRO) are two projects which have been formed to address this need [31,32]. RANO-PRO is a broad initiative which also includes radiological and other outcome measures. Finally, the experiences of adolescents and young adults (AYAs) with cancer are unique: the types of cancer, the way it changes their body, plans and life are different than for adults [33]. For instance, compared with their peers, children or adults with cancer, AYAs are at increased risk of poorer psychological functioning, less likely to comply with treatment, more likely to engage in risk taking behaviour and place a higher importance on their peer relationships. Consequently, their needs and experiences might not be fully captured by existing instruments [34].

7. Cancer survivorship

In 2016, there were an estimated 15.5 million cancer survivors living in the USA, and 62% were 65 years or older. The population of cancer survivors is expanding, there is a need to coordinate post-treatment care and the increased comorbidity experienced by these survivors from cancer treatments. Aging increases the risk of chronic diseases such as heart disease, cancer, chronic lower respiratory diseases, stroke, diabetes, dementia and kidney disease, and the late effects of cancer treatment may overlap with conditions associated with aging [35].

Given the increasing number of cancer survivors, cancer clinical trials are now being designed to include long-term follow-up to assess survival, late effects and QOL. Long-term PROs follow-up was not always a part of phase III RCTs once the primary end point was reached, and this resulted in challenges from institutional review boards when trying to approach these patients later on. Alongside this reality, there is a need to develop PROMs that capture the full range of issues relevant to disease-free cancer survivors. The EORTC QOL cancer survivorship questionnaire is being developed to, first, capture the full range of physical, mental and social QOL issues relevant to disease-free cancer survivors and, second, at what point following the completion of treatment should the questionnaire be used [36]?

In a first of its kind effort to identify the research priorities of cancer patients and survivors, National Cancer Research Institute (NCRI) partnered with the James Lind Alliance in a United Kingdom–wide survey and gathered more than 3500 responses from patients, caregivers and health and social care professionals. The Top 10 Living with and Beyond Cancer Research Priorities were announced at the 2018 NCRI Cancer conference [37]:

1. What are the best models for delivering long-term cancer care including screening, diagnosing and managing long-term side-effects and late-effects of cancer and its treatment (e.g. primary and secondary care, voluntary organisations, self-management, carer involvement, use of digital technology, etc)?
2. How can patients and carers be appropriately informed of cancer diagnosis, treatment, prognosis, long-term side-effects and late effects of treatments, and how does this affect their treatment choices?
3. How can care be better coordinated for people living with and beyond cancer who have complex needs (with more than one health problem or receiving care from more than one specialty)?
4. What causes fatigue in people living with and beyond cancer and what are the best ways to manage it?
5. What are the short-term and long-term psychological impacts of cancer and its treatment and what are the most effective ways of supporting the psychological wellbeing of all people living with and beyond cancer, their caregivers and families?
6. How can the short-term, long-term and late effects of cancer treatments be (a) prevented, and/or (b) best treated/managed?
7. What are the biological bases of side-effects of cancer treatment and how can a better understanding lead to improved ways to manage side-effects?
8. What are the best ways to manage persistent pain caused by cancer or cancer treatments?
9. What specific lifestyle changes (e.g. diet, exercise and stress reduction) help with recovery from treatment, restore health and improve QOL?
10. How can we predict which people living with and beyond cancer will experience long-term side-effects (side-effects which last for years after treatment) and which people will experience late effects (side-effects which do not appear until years after treatment)?

8. Conclusions

The 5th EORTC Quality of Life in Cancer Clinical Trials Conference brought together researchers, regulators, industry representatives, patients and patient

advocates as well as health care professionals to discuss the current state of PROs research. PROs are becoming increasingly accepted by all stakeholders, and major efforts are ongoing globally to make standards for PROs assessment, analysis and reporting in cancer clinical trials. A combination of improved technology and more flexible instruments allows collection of more robust PROs data. Regulators have joined in this effort and are keen to collaborate with all stakeholders to ensure that researchers ask the right questions and communicate the right answers. Patients, too, are encouraged to be patient partners. Finally, although there is a place for national studies, international collaborations are essential and can provide a greater impact.

Funding

This work was supported by the EORTC Quality of Life Group; an unrestricted educational grant form Celgene and an unrestricted educational grant form RWS Life Sciences.

Conflict of interest statement

Andrew Bottomley reports unrestricted educational grants for the EORTC from Boehringer Ingelheim, Genentech, Merck, and BMS for work outside the submitted project and grants from EORTC Cancer Research Fund, the EORTC Quality of Life Group, Celgene and RWS Life Sciences for the conduct of the conference. Andrew is a member of the EORTC. Michael Koller reports EORTC QLG grants and consulting contracts payments with Lilly and MSD. Jaap C. Reijneveld, Henning Flechtner, Krzysztof A. Tomaszewski and Eva Greimel report no conflicts of interest.

Acknowledgements

Medical writing assistance was provided by John Bean PhD, Bean Medical Writing, Halle, Belgium and was funded by the EORTC Quality of Life Group. The 5th EORTC Quality of Life in Cancer Clinical Trials Conference was managed by Davi Kaur, Danielle Zimmerman, Said Laghmari, Pat Vanhove, Laurence Decroix, Frederic Rince and Gwydion Lyn of the EORTC Communication and Events Team, and Melodie Cherton and other staff of the EORTC Quality of Life Department, Brussels, Belgium.

Addendum. 5th EORTC Quality of Life in Cancer Clinical Trials Conference Faculty

Patricia A Ganz, Jonsson Comprehensive Cancer Center, UCLA Schools of Medicine & Public Health, Los Angeles, CA, USA; Jolie Ringash, The Princess Margaret Cancer Centre, The University of Toronto, Canada; Maxime Sasseville, Health Products and Food Branch, Health Canada, Canada; Daniel O'Connor, Medicines and Healthcare Products Regulatory Agency, London, UK; Paul G Kluetz, US Food and Drug Administration, Silver Spring, MD, USA; Alicyn Campbell, Patient Relevant Evidence, CA, USA; Giovanni Tafuri, EUnetHTA, The Netherlands; Mogens Grønvold, Department of Public Health and Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark; Claire Snyder, Johns Hopkins Schools of Medicine and Public Health; Baltimore, MD, USA; Carolyn Gotay, School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada; Dame Lesley Fallowfield, Sussex Health Outcomes Research & Education in Cancer, Sussex, UK; Kathi Apostolidis, ECPC-European Cancer Patient Coalition, Brussels, Belgium; Roger Wilson, Sarcoma UK, London, UK; Richard Stephens, NCRI Consumer Forum, UK; Kathy Oliver, International Brain Tumour Alliance, Surrey, UK ; Holger Schünemann, Department of Health Research Methods, Evidence and Impact, McMaster University, Canada; Melanie Calvert, Centre for Patient Reported Outcomes Research, Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, UK; Bernhard Holzner, Medical University of Innsbruck, Austria; Jammbe Z Musoro, Quality of Life Department, EORTC, Brussels, Belgium; Sally Wheelwright, EORTC QLG Project & Module Development Committee, University of Southampton, UK; Francesca Martinelli, Quality of Life Department, EORTC, Brussels,Belgium; Amylou C Dueck, Alliance Statistics and Data Center, Mayo Clinic, Scottsdale, AZ, USA; Madeline Pe, Quality of Life Department, EORTC, Brussels, Belgium; Corneel Coens, Statistics Department, EORTC, Brussels, Belgium; Galina Velikova, Leeds Institute of Cancer and Pathology, University of Leeds, St James's Hospital, Leeds, United Kingdom; Dagmara Kulis, Quality of Life Department, EORTC, Brussels, Belgium; Martin J B Taphoorn, Leiden University Medical Center/Haaglanden Medical Center, Leiden/The Hague, Netherlands; Anne-Sophie Darlington, School of Health Sciences, University of Southampton, UK; Ian Lewis, NCRI, Cardiff, UK; Lonneke van de Poll-Franse, Tilburg University, The Netherlands.

References

[1] Kluetz PG, Slagle A, Papadopoulos EJ, Johnson LL, Donoghue M, Kwitkowski VE, et al. Focusing on core patient-reported outcomes in cancer clinical trials: symptomatic adverse events, physical function, and disease-related symptoms. Clin Cancer Res 2016;22:1553–8. https://doi.org/10.1158/1078-0432.CCR-15-2035.

[2] Bubis LD, Davis L, Mahar A, Barbera L, Li Q, Moody L, et al. Symptom burden in the first year after cancer diagnosis: an analysis of patient-reported outcomes. J Clin Orthod 2018;36:1103–11. https://doi.org/10.1200/JCO.2017.76.0876.

[3] European Medicines Agency. European Medicines Agency. Appendix 2 to the guideline on the evaluation of anticancer medicinal products in man: the use of patient-reported outcome (PRO) measures in oncology studies. 2016.

[4] Fax D. Guidance for industry patient-reported outcome measures: use in medical product development to support labeling claims clinical/medical guidance for industry patient-reported outcome measures: use in medical product development to support. Labeling Claims 2009:301–443.

[5] Gnanasakthy A, Barrett A, Evans E, D'Alessio D, Romano CD. A review of patient-reported outcomes labeling for oncology drugs approved by the FDA and the EMA (2012-2016). Value Health 2019;22:203–9. https://doi.org/10.1016/j.jval.2018.09.2842.

[6] Roydhouse JK, King-Kallimanis BL, Howie LJ, Singh H, Kluetz PG. Blinding and patient-reported outcome completion rates in US Food and drug administration cancer trial submissions, 2007–2017. J Natl Cancer Inst 2019;111:459–64. https://doi.org/10.1093/jnci/djy181.

[7] Calvert MJ, O'Connor DJ, Basch EM. Harnessing the patient voice in real-world evidence: the essential role of patient-reported outcomes. Nat Rev Drug Discov 2019. https://doi.org/10.1038/d41573-019-00088-7.

[8] Liegl G, Petersen MA, Groenvold M, Aaronson NK, Costantini A, Fayers PM, et al. Establishing the European Norm for the health-related quality of life domains of the computer-adaptive test EORTC CAT Core. Eur J Cancer 2019;107:133–41. https://doi.org/10.1016/j.ejca.2018.11.023.

[9] "PROTEUS" patient-reported outcomes tools: Engaging Users & Stakeholders. 2019. https://www.pcori.org/research-results/2018/proteus-patient-reported-outcomes-tools-engaging-users-stakeholders. [Accessed 27 May 2019].

[10] Calvert M, Kyte D, Mercieca-Bebber R, Slade A, Chan A-W, King MT, et al. Guidelines for inclusion of patient-reported outcomes in clinical trial protocols: the SPIRIT-PRO extension. J Am Med Assoc 2018;319:483–94. https://doi.org/10.1001/jama.2017.21903.

[11] Reeve BB, Wyrwich KW, Wu AW, Velikova G, Terwee CB, Snyder CF, et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. Qual Life Res 2013;22:1889–905. https://doi.org/10.1007/s11136-012-0344-y.

[12] Bottomley A, Pe M, Sloan J, Basch E, Bonnetain F, Calvert M, et al. Moving forward toward standardizing analysis of quality of life data in randomized cancer clinical trials. Clin Trials 2018;15:624–30. https://doi.org/10.1177/1740774518795637.

[13] Calvert M, Blazeby J, Altman DG, Revicki DA, Moher D, Brundage MD, et al. Reporting of patient-reported outcomes in randomized trials. J Am Med Assoc 2013;309:814. https://doi.org/10.1001/jama.2013.879.

[14] Snyder C, Smith K, Holzner B, Rivera YM, Bantug E, Brundage M, et al. Making a picture worth a thousand numbers: recommendations for graphically displaying patient-reported outcomes data. Qual Life Res 2019;28:345–56. https://doi.org/10.1007/s11136-018-2020-3.

[15] Wu AW, Bradford AN, Velanovich V, Sprangers MAG, Brundage M, Snyder C. Clinician's checklist for reading and using an article about patient-reported outcomes. Mayo Clin Proc 2014;89:653–61. https://doi.org/10.1016/j.mayocp.2014.01.017.

[16] Ediebah DE, Quinten C, Coens C, Ringash J, Dancey J, Zikos E, et al. Quality of life as a prognostic indicator of survival: a pooled analysis of individual patient data from Canadian cancer trials group clinical trials. Cancer 2018;124:3409–16. https://doi.org/10.1002/cncr.31556.

[17] Gotay CC, Kawamoto CT, Bottomley A, Efficace F. The prognostic significance of patient-reported outcomes in cancer clinical trials. J Clin Oncol 2008;26:1355–63. https://doi.org/10.1200/JCO.2007.13.3439.

[18] Fallowfield LJ. Quality of life assessment using patient-reported outcome (PRO) measures: still a cinderella outcome? Ann Oncol 2018;29:2286–7. https://doi.org/10.1093/annonc/mdy481.

[19] Fallowfield LJ, Catt SL, May SF, Matthews L, Shilling VM, Simcock R, et al. Therapeutic aims of drugs offering only progression-free survival are misunderstood by patients, and oncologists may be overly optimistic about likely benefits. Support Care Cancer 2017;25:237–44. https://doi.org/10.1007/s00520-016-3408-7.

[20] Shilling V, Starkings R, Jenkins V, Cella D, Fallowfield L. Development and validation of the patient roles and responsibilities scale in cancer patients. Qual Life Res 2018;27:2923–34. https://doi.org/10.1007/s11136-018-1940-2.

[21] WHO. Guidelines for WHO Guidelines. 2003.

[22] Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383–94. https://doi.org/10.1016/j.jclinepi.2010.04.026.

[23] Dueck AC, Mendoza TR, Mitchell SA, Reeve BB, Castro KM, Rogak LJ, et al. Validity and reliability of the US national cancer institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). JAMA Oncol 2015;1:1051–9. https://doi.org/10.1001/jamaoncol.2015.2639.

[24] Bottomley A, Pe M, Sloan J, Basch E, Bonnetain F, Calvert M, et al. Analysing data from patient-reported outcome and quality of life endpoints for cancer clinical trials: a start in setting international standardsvol. 17; 2016. https://doi.org/10.1016/S1470-2045(16)30510-1.

[25] Musoro ZJ, Hamel J-F, Ediebah DE, Cocks K, King MT, Groenvold M, et al. Establishing anchor-based minimally important differences (MID) with the EORTC quality-of-life measures: a meta-analysis protocol. BMJ Open 2018;8:e019117. https://doi.org/10.1136/bmjopen-2017-019117.

[26] Coens C, Suciu S, Chiarion-Sileni V, Grob J-J, Dummer R, Wolchok JD, et al. Health-related quality of life with adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): secondary outcomes of a multinational, randomised, double-blind, phase 3 trial. Lancet Oncol 2017;18:393–403. https://doi.org/10.1016/S1470-2045(17)30015-3.

[27] van der Graaf WTA, Blay J-Y, Chawla SP, Kim D-W, Bui-Nguyen B, Casali PG, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012;379:1879–86. https://doi.org/10.1016/S0140-6736(12)60651-5.

[28] Goodwin PJ, Black JT, Bordeleau LJ, Ganz PA. Health-related quality-of-life measurement in randomized clinical trials in breast cancer–taking stock. J Natl Cancer Inst 2003;95:263–81. https://doi.org/10.1093/jnci/95.4.263.

[29] Pe M, Dorme L, Coens C, Basch E, Calvert M, Campbell A, et al. Statistical analysis of patient-reported outcome data in randomised controlled trials of locally advanced and metastatic breast cancer: a systematic review. Lancet Oncol 2018;19:e459–69. https://doi.org/10.1016/S1470-2045(18)30418-2.

[30] Nagele E, Den Oudsten B, Greimel E, EORTC Quality of Life Group. How to evaluate sexual health in cancer patients: development of the EORTC sexual health questionnaire for cancer patients. Transl Androl Urol 2015;4:95–102. https://doi.org/10.3978/j.issn.2223-4683.2014.11.08.

[31] Coomans M, Dirven L, K Aaronson N, Baumert BG, van den Bent M, Bottomley A, et al. The added value of health-related quality of life as a prognostic indicator of overall survival and progression-free survival in glioma patients: a meta-analysis based on individual patient data from randomised controlled trials. Eur J Cancer 2019;116:190–8. https://doi.org/10.1016/j.ejca.2019.05.012.

[32] Dirven L, Armstrong TS, Blakeley JO, Brown PD, Grant R, Jalali R, et al. Working plan for the use of patient-reported outcome measures in adults with brain tumours: a Response Assessment in Neuro-Oncology (RANO) initiative. Lancet Oncol 2018;19:e173–80. https://doi.org/10.1016/S1470-2045(18)30004-4.

[33] Sodergren SC, Husson O, Robinson J, Rohde GE, Tomaszewska IM, Vivat B, et al. Systematic review of the health-related quality of life issues facing adolescents and young adults with cancer. Qual Life Res 2017;26:1659–72. https://doi.org/10.1007/s11136-017-1520-x.

[34] Hullmann SE, Brumley LD, Schwartz LA. Medical and psychosocial associates of nonadherence in adolescents with cancer. J Pediatr Oncol Nurs 2015;32:103–13. https://doi.org/10.1177/1043454214553707.

[35] Armstrong GT, Kawashima T, Leisenring W, Stratton K, Stovall M, Hudson MM, et al. Aging and risk of severe, disabling, life-threatening, and fatal events in the childhood cancer survivor study. J Clin Oncol 2014;32:1218–27. https://doi.org/10.1200/JCO.2013.51.1055.

[36] van Leeuwen M, Husson O, Alberti P, Arraras JI, Chinot OL, Costantini A, et al. Understanding the quality of life (QOL) issues in survivors of cancer: towards the development of an EORTC QOL cancer survivorship questionnaire. Health Qual Life Outcomes 2018;16:114. https://doi.org/10.1186/s12955-018-0920-0.

[37] LWBC Home. The National Cancer Research Institute. n.d. https://www.ncri.org.uk/LWBC/. [Accessed 29 May 2019].