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Bottomley, A, Pe, M, Sloan, J et al. (36 more authors) (2016) Analysing data from patient-reported outcome and quality of life endpoints for cancer clinical trials: a start in setting international standards. *Lancet Oncology*, 17 (11). e510-e514. ISSN 1470-2045

[https://doi.org/10.1016/S1470-2045\(16\)30510-1](https://doi.org/10.1016/S1470-2045(16)30510-1)

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Analysing data from patient-reported outcome and quality of life endpoints for cancer clinical trials: a start in setting international standards

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Abstract

Measures of health-related quality of life (HRQL) and other patient-reported outcomes (PRO) generate important data in cancer randomized controlled trials (RCTs) to assist in evaluating the risks and benefits of cancer therapies, and fostering patient-centered cancer care. However, the various ways these measures are analyzed and interpreted make it difficult to compare results across trials, and hinders the application of research findings to inform publications, product labelling, clinical guidelines and health policy. To address these problems, the Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) initiative has been established. This international multidisciplinary consortium, directed by the European Organization for Research and Treatment of Cancer (EORTC), was convened to provide recommendations to standardize the analysis of HRQL and other PRO data in cancer RCTs. This article discusses the reasons why this project was initiated, the rationale for the planned work, and the expected benefits to cancer research, patient/provider decision-making, care delivery, and policymaking.

Introduction

Patient-centeredness is increasingly identified as a critical component of quality health care.¹ With an enhanced emphasis on patient-centered care, health-related quality of life (HRQL), and other patient-reported outcomes (PRO) that quantify how a patient feels and/or functions, are assuming a more prominent role as important endpoints in cancer clinical trials.^{2,3}

The terms “PRO” and “HRQL” have at times been used interchangeably, leading to confusion in terminology.⁴ However, PRO and HRQL are two distinct terms that complement each other. Patient-reported outcome is defined as any clinical outcome that is reported directly by the patient; PRO can be captured either through self-report or interview, as long as the interviewer directly records the patient’s responses.^{5,6} Health-related quality of life, which is often assessed as a PRO, is a multidimensional concept that refers to the patient’s subjective perception of the impact of his/her disease and treatment(s) on physical, psychological, and social aspects of daily life.^{6,7} Many HRQL questionnaires also cover symptoms of disease, functional impairments, and adverse effects of treatment. This distinction between PRO and HRQL implies that PRO can be used to measure constructs other than HRQL (e.g., adherence, experiences of care) on the one hand, and HRQL can be measured by means other than PRO (e.g., observer or proxy reports) on the other hand.

Expanding adoption of PRO measures has revealed important challenges: the diverse ways of analyzing and interpreting PRO endpoints make it difficult to compare results across various cancer clinical trials. A continuing lack of standardization risks the suboptimal use of these findings to inform both policy and treatment decisions, and results in an inefficient use of increasingly finite research funding.⁸ Moreover, improved standardization of endpoint definitions, as well as the analysis and presentation of PRO data would strengthen the rationale for the use of PRO endpoints and generate rigorous data needed to power future trials that could statistically test important PRO hypotheses, thereby complementing

traditional radiologic and survival based endpoints.⁹ What is promising is the increased awareness in the research community that this issue needs to be addressed. Efforts to standardize specific aspects of PRO evaluations in cancer clinical trials are underway. For example, recent and ongoing efforts have focused on standardizing the outcomes to be measured,¹⁰⁻¹² the content that should be included in protocols (Standard Protocol Items: Recommendations for Interventional Trials in Patient Reported Outcomes -- SPIRIT-PRO),^{13,14} and the reporting of clinical trials findings (ISOQOL reporting standards; CONSolidated Standards of Reporting Trials in Patient Reported Outcomes -- CONSORT-PRO).^{15,16} While these efforts have emphasized standards for collecting and reporting PRO data, guidelines and best practices for the analysis and interpretation of PRO endpoints in cancer clinical trials are lacking.

Main Objective

SISAQOL is a collaborative initiative assembled by the EORTC to address this gap. This international consortium will develop recommendations for standardizing the analysis and interpretation of PRO endpoints in randomized cancer clinical trials.

These recommendations will not be tailored to a specific questionnaire; rather they will be broad enough to be applicable across different types of PRO measures (e.g., traditional fixed-length questionnaires, as well as more flexible assessment tools such as computer adaptive tests). Indeed, although the algorithm to compute the outcome scores from different types of measures may differ, the challenges encountered to analyze and interpret these scores are similar.

As an initial goal, SISAQOL will focus on standardizing the analysis of HRQL as measured by PRO, with a view towards broadening its scope to include other ways of measuring HRQL (e.g., observer or proxy-reports) and other types of PRO (e.g., treatment adherence, satisfaction with care).

Individuals or parties interested in contributing to this consortium, please visit us at (enter website here) for more details.

What is the problem?

Imagine that a randomized controlled trial (RCT) was conducted to assess the relative efficacy of two cancer treatments (A and B). Patients reported their level of physical functioning (measured using a multi-item scale) at baseline and every 6 weeks thereafter until disease progression or study discontinuation.

Several analyses could be conducted, for example: a)

time to deterioration of patient-reported physical functioning compared to

baseline; b) between-group differences in overall means; and c) cross sectional comparison at a specific

time point (i.e., end of treatment; hypothetical findings are shown in Figure 1). Results would reveal that the time to deterioration analysis favored Treatment B (12 weeks vs 42 weeks), overall means would not favor either treatment, and examining differences at end of treatment would tend to favor treatment A. What conclusions could then be drawn from this trial?

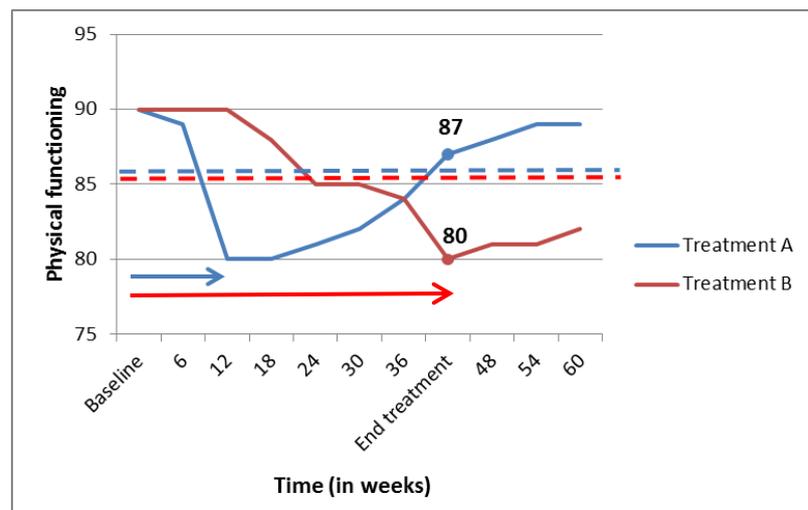


Figure 1. Mean physical functioning scores at every assessment point for each treatment group. Results from a) time to deterioration analysis are represented with arrows, b) comparison of group means across time are represented with dashed lines, and c) comparison of group means at a single time point are represented by the bold faced values.

Although this is a hypothetical example, several examples do exist in the literature where different methods of analysis applied within one RCT or variations in applied methods in different RCTs in the same patient population produced seemingly contradictory results.¹⁷⁻¹⁹ Such inconsistencies cast doubt on HRQL and other PRO findings in RCT publications, and

may impact the overall risk/benefit assessment of drugs and the decisions to register, reimburse and/or use these agents in the clinic.

How did this problem emerge?

The problem of inconsistency in the analytic approach to HRQL endpoints does not stem from the relevance of the data or the quality of the information that can be extracted from the data. Rather, the problem is that many different research questions can be asked about HRQL and other PRO outcomes. Therefore, clear and well-defined research questions must be selected *a priori* and matched with appropriate study design and analyses. Furthermore, while guidelines^{7,20} would suggest that the analytic considerations for HRQL and other PRO endpoints are similar to those for other trial endpoints, the data generated from HRQL and other PRO measures are more complex, requiring researchers to make different decisions for each part of the analysis. Specifically, many PRO instruments that measure HRQL are multidimensional, with several subscales to characterize the impact on aspects of patient functioning, and sometimes an overall score can be derived from these subscales to summarize the patient's self-reported health. Moreover, HRQL instruments could also include additional subscales or single questions that capture physical or mental symptoms of disease and/or adverse effects of treatment. This rich disaggregated data may not be part of the original *a-priori* planned HRQL endpoint analysis, but are still important to report descriptively as they not only provide the patient perspective on treatment effectiveness and toxicity, but also generate new research hypotheses that can be further tested in the future. It is, however, crucial that such unplanned analyses (i.e., exploratory analyses) should be stated as exploratory and the findings should be interpreted with caution. Finally, this information can also supplement other data, e.g., clinician-reported toxicity using Common Terminology Criteria for Adverse Events (CTCAE) and is important to the delivery of patient centered care.²¹

Second, complexity is increased given the repeated measurements required to capture changes in HRQL, and the interaction between HRQL and the treatment under evaluation.

Lastly, missing HRQL data are an inherent problem, and can be dependent on patient status (e.g., patients who drop out of the study because they are not doing well); thus, statistical analyses must account for data that are missing not at random.^{22,23} The multi-dimensional nature of HRQL, combined with repeated measurements and the prevalence of missing data, invites multiple statistical tests and inflated type 1 error. Many of these issues are also relevant when measuring more proximal, unidimensional PRO and/or HRQL concepts such as individual symptoms or physical function. We believe that a lack of clear guidance and the lack of internationally recognized standardized methods to analyze and report HRQL and other PRO data have contributed to a problem that is already complicated.

Ultimately, researchers plan to conduct the most appropriate analysis of HRQL and other PRO measures. However, the lack of specific research questions and the many possible ways to analyze HRQL and other PRO data can lead to different analytic decisions and in the absence of guidance, the researcher is left to decide how the analysis should be conducted. Some investigators favor ease of reporting to clinicians (e.g., produce descriptive statistics), whereas others favor statistical correctness (e.g., complex modelling approaches that may not be as easily communicated to clinicians). Ideally, the most appropriate would be a combination of the two: pre-specified robust statistical modeling complemented by reporting (including graphical presentation) that is easily interpreted by clinicians. It is, therefore, not surprising that HRQL and other PRO findings in RCTs stem from a variety of statistical approaches,^{24,25} leading to results that may not be directly comparable. This is a critical issue that cannot be ignored, especially as clinical research and care move towards a more patient-centered approach in which HRQL and other PROs play a central role in healthcare delivery.

Towards a solution

A multi-disciplinary expert Consortium (represented by the authors) has been established to develop consensus on international standards for the analysis of HRQL and other PRO data in cancer clinical trials. In assembling the expert Consortium, it is crucial that key

stakeholders are involved so that the insights gathered from this initiative are technically correct, comprehensive, and balanced. Therefore, the group is comprised of not only leading HRQL researchers and statisticians, but also key individuals from various international oncologic and medical societies, advisory and regulatory bodies, academic societies, pharmaceutical industry, cancer institutes and, crucially patient advocacy organizations. It is our hope that with this collaborative work we will be able to set standards for the analysis of HRQL and PRO data that will be acceptable to all parties.

Our first step has been to explore the different perspectives and views of the Consortium members. There was a clear consensus that standards and best practices for the analysis of HRQL and other PRO data are lacking and that such guidance is urgently needed. We developed an initial work plan, which focuses on appropriate statistical analyses for PRO data generated from HRQL instruments in cancer RCTs. We will then expand to other clinical trial designs (e.g., non-randomized trials, single arm studies, adaptive design), and other types of PRO (e.g., daily diaries).

To date, the Consortium noted that there is a limited consensus regarding the definitions of basic terminology such as compliance rates, baseline, minimally important differences (MID) and minimal clinically important differences (MCID), and the population that needs to be examined. We intend to identify the critical terms where consensus definitions are lacking and work towards having standardized definitions. Discussion points include, for example, (a) having one definition of compliance rate versus having different types of compliance rates (such as number of participants with HRQL at baseline or number assigned to HRQL), and (b) the definition of the population data set to be used for analysis as the intention-to-treat (ITT) population may not always be appropriate because of the high rates of drop out typical of cancer RCTs or the design might not require all randomized patients to be part of the HRQL and other PRO assessments.

Next, as mentioned above, a critical issue that surrounds HRQL and other PRO measures in RCTs in cancer is missing data. There are many different ways to handle missing data. For example, some researchers choose to ignore the missing data, analyzing only available data. Others may impute missing data with replacement values such as last value carried forward. Yet other approaches use complex statistical models that allow for missing data under specific assumptions.²⁶ These different approaches to missing data also influence the interpretation of HRQL results. International guidance and other PRO standards with respect to how missing data should be treated would make an important contribution to improving the rigor and reproducibility of HRQL findings.

Moreover, to address the issues around the multiple ways of analyzing and reporting HRQL and other PRO measurement results, we plan to conduct a critical review of the literature to identify the common statistical analyses used in cancer RCTs and to examine the possibility of matching statistical methods to appropriate research questions.

Finally, for each recommended statistical method, best practices need to be developed to ensure a uniform and correct implementation across different statistical assumptions of the underlying data. For instance, in what circumstances should models or effect estimates be adjusted for baseline measures? What are the considerations for inclusion of other patient-specific covariates in the analysis? Are sensitivity analyses needed, for example, in relation to patterns of missing data, and if so, what types of sensitivity analyses should be conducted? Decisions on these more specific options should not be neglected. Even if a statistical methodology is broadly agreed upon for a specific research question, a lack of consistency in the details of implementing the method can have an important impact on the findings. As we move forward, it is crucial that we build on past knowledge and that we consider recommendations proposed by the different regulatory bodies (e.g., U.S. Food and Drug Administration and European Medicines Agency) and academic societies (e.g., International Society for Quality of Life Research, International Society for Pharmacoeconomics and Outcomes Research). We will systematically identify relevant

guidance, review their recommended methods and determine how the guidance can be incorporated into the SISAQOL initiative.

In developing international consensus on rigorous and reproducible approaches to the analysis and interpretation of HRQL data in cancer clinical trials, we will also emphasize a pragmatic approach, thereby ensuring that our recommendations are interpretable and informative for researchers, clinicians, patients and regulators/policymakers. The overarching goal of this initiative is to support the design, interpretation and reporting of HRQL and other PRO endpoints in cancer clinical trials, thereby allowing for new insights into the patient experience of treatment effects, and providing reliable and valid information for stakeholder decision-making.

Future steps

The objective of the SISAQOL initiative is to produce a suite of tools, guidance and international consensus standards for the analysis of HRQL and other PRO data from clinical trials. We also aim to provide template macros to be used in a number of commonplace missing data settings and illustrative macros to address these requirements. We expect that having freely available guidelines and tools to facilitate their implementation will result in more reliable and faster dissemination of findings that stem from higher quality use of statistical methods and improved interpretability due to greater familiarity with standardized reporting.

We are aware that standardizing statistical analyses for HRQL and other PRO data in cancer clinical trials is an ambitious goal. However, the need for such standards has become prominent given the expanding interest in HRQL and other PRO endpoints. Trials cost substantial time, money and effort. Moreover, study participants, in the interest of improving their situations and helping others, voluntarily give up their time to complete measures for these trials. Therefore, the data we gather from these trials must be exploited to the full, with statistical analyses conducted in the most rigorous and standardized fashion, and with

results that clearly highlight clinical benefits (not just statistical significance).⁹ HRQL and other PRO findings also have a large potential impact on treatment benefit evaluations; and as resources to cover costs of cancer care become scarcer and treatment costs increase, it is imperative that these findings are based on valid and reliable statistical methods. For these reasons, choosing methods that reflect the best possible available evidence and the expertise of a diverse group of stakeholders is crucial. Members of the SISAQOL initiative have a shared interest in addressing this gap by working together to articulate a set of standards, best practices, and tools for the analysis and interpretation of HRQL and other PRO endpoints in cancer clinical trials.

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Disclaimer

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Contributors

The manuscript was conceptualized with the attendees of the SISAQOL kick-off meeting in Brussels on January 26, 2016. All authors reviewed and contributed to revisions of the article. All authors approved the final draft of the manuscript.

Conflict of Interest

A. Bottomley reports grants from Boehringer Ingelheim, grants from EORTC cancer research fund during the conduct of the study; grants from Merck outside the submitted work; and is a member of the EORTC Quality of Life Group executive committee.

F. Bonnetain reports grants, personal fees and non-financial support from Novartis, grants, personal fees and non-financial support from Roche, personal fees from AMGEN, personal fees from Merck Serono, personal fees from Ipsen, personal fees from Bayer, personal fees from BMS, personal fees from Nestle, personal fees from INTEGRAGEN, personal fees from CHUGAI, personal fees from JANSEN outside the submitted work.

M. Calvert reports other from ISOQOL, personal fees from Astellas Pharma, personal fees from Ferring Pharma, outside the submitted work; and M. Calvert is Director of the Centre for Patient Reported Outcomes Research University of Birmingham and is involved in a number of local and international initiatives to promote best practice for PROs in trials including the development of a SPIRIT-PRO Extension and CONSORT-PRO.

A. Campbell reports that she is an employee of Genentech.

N. Devlin reports that the Office of Health Economics receives funding from the Association of the British Pharmaceutical Industry. N.Devlin is a member of the EuroQoL Group, the European-based international group which developed the EQ-5D. N. Devlin is a member of the Board of Directors of ISPOR.

I. Griebisch is an employee of Boehringer Ingelheim, Germany. Boehringer Ingelheim provided an unrestricted educational fund to initiate this work.

M. Koller reports grants from EORTC Quality of Life Group, personal fees from Mundipharma outside the submitted work.

K. Oliver reports grants from Roche, GSK, Lilly, Novocure, Novartis, Celldex, MagForce, Accuray, Photonamic, Medac, to-BBB, Apogenix, Pfizer, AbbVie, Northwest Biotherapeutics, VBL Therapeutics, The Sontag Foundation, The Brain Tumour Network, Ivy Foundation outside the submitted work; honoraria and personal fees from GSK, Lilly, Novartis, Bayer, Bristol-Myers Squibb, Sarcoma Patients Euronet (SPAEN) outside the submitted work.

M. Taphoorn reports personal fees from Hoffman-La Roche outside the submitted work.

G. Velikova reports that she is the past chair of the EORTC Quality of Life group and past president of the International Society for Quality of research (ISOQOL).

The other authors declared no conflict of interest.

Acknowledgements

EORTC received an unrestricted education grant from Boehringer Ingelheim GmbH to initiate this work and additional financial support was provided by the EORTC Cancer Research Fund. Andrew Bottomley confirms final responsibility for the decision to submit for publication.