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Moving forward towards standardizing analysis of quality of life data in randomized cancer clinical trials

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Running Head

PRO analysis in cancer trials

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Abstract

Background

There is currently a lack of consensus on how health-related quality of life nd other patient-reported outcome (PRO) measures in cancer randomized clinical trials are analyzed and interpreted. This makes it difficult to compare results across RCTs, synthesize scientific research, and use that evidence to inform product labelling, clinical guidelines, and health policy. The Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data for Cancer Clinical Trials (SISAQOL) Consortium aims to develop guidelines and recommendations to standardize analyses of PRO data in cancer RCTs.

Methods and Results

Members from the SISAQOL Consortium met in January 2017 to discuss relevant issues. Data from systematic reviews of the current state of published research in PROs in cancer RCTs indicated a lack of clear reporting of research hypothesis and analytic strategies, and inconsistency in definitions of terms, including “missing data”, “health-related quality of life”, and “PRO.”

Based on the meeting proceedings, the Consortium will focus on three key priorities in the coming year: developing a taxonomy of research objectives, identifying appropriate statistical methods to analyze PRO data, and determining best practices to evaluate and deal with missing data.

Conclusion

The quality of the Consortium guidelines and recommendations are informed and enhanced by the broad Consortium membership which includes regulators, patients, clinicians, and academics.

Keywords: guidelines, standards, cancer clinical trials, health related quality of life, patient-reported outcomes

Background

The patients' voice is increasingly part of the evaluation of risks and benefits of cancer therapies. As such, data on patient-reported outcomes (PROs) that quantify how a patient feels and/or functions, are frequently collected in cancer clinical trials.[1] However, the lack of standards and clear guidelines on how these patient-reported data should be analyzed and interpreted diminishes their added value and make it difficult to compare results across different trials.[2] This hinders research findings from informing important processes such as clinical decision making, product labelling, clinical guidelines, and health policy.[3]

To explore the perspectives of multiple stakeholders, the European Organisation for Research and Treatment of Cancer convened a multidisciplinary international consortium focusing on "Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data for Cancer Clinical Trials" (SISAQOL). This manuscript summarizes the Consortium's work to date and provides a critical backdrop for future recommendations.

Methods and Results

The European Organisation for Research and Treatment of Cancer's kick-off meeting in January 2016 solicited attendees' views on the need for developing standards, guidelines, and recommendations for PRO analysis in trials. There was a clear consensus that standards and best practices for PRO data analysis are lacking, such guidance is urgently needed, and a multidisciplinary team of experts is crucial to ensure technically correct, comprehensive, and balanced

recommendations. Based on this input, SISAQOL moved forward. A summary of this initial meeting has been previously reported.[3]

The SISAQOL Consortium's second consensus meeting was convened a year later to discuss concrete strategies regarding standardizing PRO analysis, with the end goal being to produce internationally recognized guidelines. Participants were leading PRO researchers and statisticians and representatives from international oncological and medical societies, advisory and regulatory bodies, academic societies, the pharmaceutical industry, cancer institutes, and patient advocacy organizations (see author list).

Perspectives

Regulators/advisory bodies

Regulators and advisors from the European Medicines Agency network, the US Food and Drug Administration, Health Canada, and the Institute for Quality and Efficiency in Health Care discussed the current role of PROs in their organizations' decision-making processes.

It was clear that these groups recognize the importance of the patient's experience and perspective and their added value in the benefit-risk assessment of cancer treatment, and efforts are underway to identify methods to best incorporate the patient's voice into their programs.[4–7]

However, it was also evident that regulators have reservations about the conclusions drawn from PRO data to date. Poorly defined research objectives (and hypotheses) and lack of rigorous standards in analyzing PRO data in regulatory submissions have hampered the usefulness of such data for regulatory decision-making. To assess the potential added-value of patient-reported data in trials, one key criterion is to establish international standards in data analysis.

Patient

It was emphasized that throughout a patient's cancer journey, clear communication between the patient and the stakeholders involved in treatment on risks, benefits and potential side effects is crucial.[8] Patients need to be heard regarding side effects, their feelings about their treatments, and how they are functioning physically, mentally, emotionally, and socially. Such information needs to be collected and synthesized across patients to increase the knowledge base about patient experiences in a way that will be useful for future patients. Identifying the best ways to involve patients and survivors in initiatives such as SISAQOL, which focus primarily on technical research issues, is challenging. The discussion of missing PRO data provided a clear opportunity for possible patient participation. Missing data is a critical issue in any trials missing data present difficulties in analysis and drawing robust conclusions about treatments. Minimizing avoidable missing assessments is critical. While researchers have identified many factors that contribute to avoidable missing data, patients themselves generate PRO data, and SISAQOL provides an opportunity to work with patients to get their ideas about how to minimize the amount of avoidable missing PRO data in clinical trials[9] and to communicate the importance of providing complete data.[10]

Literature

Five systematic reviews provided a summary of the current quality of hypothesis reporting and analysis of PRO data in published trials in locally advanced and metastatic breast cancer,[11] advanced non-small cell lung cancer,[12] small cell lung cancer,[13] as well as two reviews on methods for dealing with missing data.[14, 15] For the purposes of this report, three key findings from these reviews are highlighted.

Hypothesis. Clear research objectives and a priori hypotheses are needed prior to statistical analysis. Otherwise, statistical analyses are exploratory, and no conclusions can be drawn. In the systematic reviews for metastatic breast[11] and advanced non-small cell lung cancers,[12] findings showed that only 7% of the articles (metastatic breast: 4 of 58 articles; advanced non-small cell lung cancer: 2 of 27 articles) reported specific a priori PRO research hypothesis. In a systematic review evaluating the quality of PRO reporting in trials published between 2002-2008, only around 50% of the 794 trials reported a PRO hypothesis.[16, 17] These findings imply that although PRO data are being included in trials, statistical analyses are often being conducted without clear reported PRO research objectives and hypotheses. This causes uncertainty regarding whether the results reported are based on: a) a priori hypotheses with an a priori statistical analysis plan that allow conclusions to be drawn, or b) exploratory analyses intended to generate future hypotheses, but where findings from this trial remain inconclusive.

Statistical methods. In the three systematic reviews, preliminary findings showed that at least 10 different statistical methods were used to evaluate PRO data.[11–13] This is a problem, since the variety of statistical techniques employed makes it challenging not only to compare findings across trials, but also to build on previous work to make the results more generalizable and conclusive.

Another problem is the failure to correct for type 1 error (or alpha adjustment) for multiple testing. This problem is particularly relevant for PRO data due to the possibility of calculating scores for an entire measure, subdomains and/or at a range of time points. If multiple scales and/or assessment points are tested independently from one another, and the alpha level is not adjusted for multiple testing (e.g. it remains at 0.05 for each of the tests), the probability of observing at least one

significant result simply due to chance is inflated. This then leads to findings that are difficult to interpret. This was a limitation found in this literature. All three reviews[11–13], less than 40% of the articles controlled for type 1 error when it was needed (metastatic breast cancer: 40%, 23 of 58 articles; advanced non-small cell lung cancer: 4%, 1 of 27 articles; small cell lung cancer: 27%, 9 of 33 articles).

Missing data. Missing data is a common problem in PRO analysis in trials. How missing data are considered in analysis, especially when the amount of missing data is substantial, may bias the analysis and critically influence the conclusions that can be drawn. For this reason, reports need to specify the analytic approach used to address missing data.[18, 19] In the systematic reviews for metastatic breast cancer[11] and advanced non-small cell lung cancer,[12] only 24% (14 of 58 articles) and 19% (5 of 27 articles) of the articles, respectively, reported how the analysis addressed missing data. Furthermore, the statistical methods across reports ranged from simple imputation (e.g. last observation carried forward) to model-based methods (e.g. pattern mixture modelling). These findings demonstrate the lack of standardization on how to handle missing PRO data.

Implications

Developing hypothesis

The systematic reviews show a lack of clearly reported research hypotheses. New guidelines for protocol development (i.e., SPIRIT PRO) [20, 21] and PRO reporting (i.e., CONSORT-PRO) [16] also recognize this issue. It was proposed that three components are necessary to specify in an a priori research hypothesis, specifically:

- the domains of interest;
- how the reference arm is expected to behave within the time frame of interest;
- how the treatment arm is expected to behave relative to the reference arm.

A rationale and evidence-based arguments informed by clinical and patient experience are needed to support these components of the hypothesis.

To address standardized classification of such hypotheses, the Consortium agreed to develop a taxonomy of PRO objectives, including underlying assumptions. This taxonomy has the potential not only to help researchers to be more precise in hypotheses in protocols, but also to allow comparison of objectives and findings across trials. The taxonomy is currently under development.

Statistical methods

The systematic reviews[11–13] demonstrate that the current trials literature does not provide a good foundation to determine which statistical method is recommended for a specific research objective. Not only is there a lack of clearly reported research objectives, but there is also no consensus on which statistical methods to use. Rather than recommending a specific statistical method, it was agreed that a more useful approach is to define essential statistical properties for analyzing PRO data. For example, an important statistical property is adjusting for covariates. Covariate adjustment is a common practice in trials for stratification, controlling for potential imbalance between treatment arms, or improving precision of the treatment effect (especially when the covariate has an important influence on the outcome).[22, 23]

The Consortium will compile a systematic list of statistical properties, with a recognition of the importance of balancing feasibility and accuracy. Following consensus on identifying essential statistical properties, the Consortium will determine statistical methods that fit these criteria, which can then be matched with research objectives identified in the previously mentioned taxonomy.

SISAQOL also emphasized the importance of developing criteria for descriptive statistics (including visualization) that can provide more complete documentation of

patient reports. For example, it is common practice to report the mean (or median) levels of a PRO measure per treatment arm over time. However, although this summary statistic may be useful, it is not sufficient to use it alone. Rather, this should be accompanied by a measure of variability to provide an indication of the diversity of responses. For example, an average score of “3” in a possible range of scores from 1 to 5 could mean that all participants reported a “3” or that half of the participants reported “1” and the other half reported a “5”. A measure of variability can capture this difference, whereas the average would not. SISAQOL Consortium members will work toward developing guidelines to standardize descriptive analyses and visualization approaches across all trials.

Missing data

Before undertaking statistical analysis, the researcher needs to be certain that the dataset is valid for analysis. Guidelines often indicate that a substantial amount of missing data can invalidate any analysis[18]. The Consortium questioned the definition of substantial, given that this is not consistent in the literature. The Institute for Quality and Efficiency in Health Care standard approach (e.g. Regofaranib,[24] p. 3) is to consider valid any analysis from a dataset that includes baseline data with at least one follow-up from at least 70% of patients. However, this criterion is not used consistently across the literature. Different definitions of missing data and their calculation may lead to varying practices and results and call out for guidelines.

It is not currently clear if it will be possible for international consensus on a fixed threshold that defines an acceptable percentage of missing data. For example, in a hypothetical situation where 65% of PRO data are missing, some investigators would agree that drawing conclusions on treatment efficacy based on these patient reports would be futile. However, others may argue that analyzing the 35% of patients for

whom data are available could be useful to understand more about patient well-being in this subgroup, although generalization to the larger trial population would not be possible. Exploring the potential to identify a fixed threshold for an acceptable percentage of missing data to have a valid analysis and robust findings is a priority question for the SISAQOL Consortium.

Another SISAQOL goal is to develop and validate a set of macros, an automated way to systematically examine missing data patterns and the impact of different imputation methods on findings. An initial pilot test of macros developed by the Mayo Clinic team was performed on a Mayo trial dataset. Capabilities of these macros include producing percentages of missing values over time and providing more detailed information on missing data patterns. Moreover, these macros also implement and test the effects of several imputation methods, which could then be used for sensitivity analysis.

The macros (or others) may prove useful following further testing and validation with other clinical trial datasets and guidelines on the appropriate use and interpretation of findings from these missing data macros are needed.

Terminology

An evidence-based review on the history on terminology of patient-reported indicators (such as quality of life, health-related quality of life and PRO) in the context of cancer and trials demonstrate the relatively recent emergence of terms (see Table 1). Indeed, widespread consensus on the exact meaning of these terms is not yet set, and new terminologies continue to surface: e.g. patient-generated health data, patient experience and patient-centered outcome.

Currently, definitions have been offered by regulatory bodies[5,6]), and academic societies (e.g. International Society for Quality of Life Research[25]). Although not all

definitions are the same, health-related quality of life is generally seen as a subcategory within the broader PRO construct, which may include other patient-reported variables. Currently, as seen in Table 1, the most citations and research information are based on “quality of life” and “health-related quality of life” endpoints than for the broader “PRO” concept. It is not within the remit of the Consortium to find consensus on these non-statistical terminologies. Regardless of the terminology used, Consortium members cited likely considerable overlap in data analytic approaches for all PROs, given that all come from the same source (the cancer patient).

Conclusion

Based on discussions and evidence extracted from systematic reviews of published literature, the SISAQOL Consortium has confirmed the priority need to develop guidelines and standards in analyzing PRO data in trials. The Consortium is focusing on three key priorities: developing a taxonomy of research objectives, identifying appropriate statistical methods to analyze PRO data, and determining how best to evaluate and deal with missing data. SISAQOL’s work will provide a toolbox for analysis of PRO outcomes in trials that is urgently needed and will advance the international research agenda now and into the future.

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Declaration of conflicting interests

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Table 1. Citations on quality of life related terms found by searching PubMed

Term	1st mention	“Critical mass” (N)**	2015/16 (N)
Symptom	1939	1975 (79)	1,846
Quality of life	1968	1979 (79)	4,603
Health-related quality of life	1989	1999 (90)	681
Patient-reported outcome	2003	2013 (81)	182
Patient-centered outcome	2004	NA (25 total)	9

Note. as of January 22, 2017.

N = number of citations

NA = not available

** Based on qualitative visual examination of upward trajectory maintained over time