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Evaluating Health-Related Quality of Life in Cancer Clinical Trials: The National Cancer Institute of Canada Clinical Trials Group Experience

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ABSTRACT

Introduction: The National Cancer Institute of Canada (NCIC) Clinical Trials Group (CTG) Quality of Life (QOL) Committee was initiated in 1986.

Purpose: The purpose of this review is to describe the evolution of the Committee's work and to highlight key developments such as the formulation of a policy regarding health-related quality-of-life (HRQOL) assessment, the provision of guidelines to ensure completion of HRQOL data within the protocol requirements, the rationale behind the choice of HRQOL instruments, the timing of assessments and the development of data analytic methods. These developments are illustrated with examples from CTG studies.

Recommendations: There is a lack of concordance between conventional toxicity data and HRQOL data and comparative studies designed to elucidate these differences are to be encouraged. Also, more studies are required to compare different analytic strategies and to determine how much missing data is acceptable, particularly in oncology studies where attrition is inevitable.

Keywords: assessment, clinical trials, oncology, QOL, quality of life.

The Quality of Life Committee—Description

The experience of the National Cancer Institute of Canada (NCIC) Clinical Trials Group (CTG) in health-related quality-of-life (HRQOL) assessment began in 1986 with the formation of a Quality of Life (QOL) working group. The role of the working group was to provide educational opportunities to the CTG clinical investigators and other CTG personnel. A standing QOL Committee was established in 1987 [1]. Subsequently, HRQOL assessment in the CTG has evolved gradually in keeping with developing worldwide knowledge. In several ways, the CTG has been instrumental in introducing new information during this evolution. Some of these advances are detailed in this article, which gives particular emphasis to how our policy and procedures have led to useful methods and results, and how this experience may be useful for developing Food and Drug Administration guidance for labeling claims.

Policy

The Committee developed a policy pertaining to HRQOL assessment in the context of clinical trials [1]. The policy stated that "there should be a statement about the anticipated impact on quality of life with every proposed Phase III clinical trial and whether QOL measures will be incorporated in the protocol."

As a result of this policy, almost all of the 71 trials initiated by the CTG since its adoption in 1987 include HRQOL components. This provides the CTG with extensive experience to determine which procedures have worked best in given situations, and the results have provided new information. Between 1992 and 2006, the QOL Committee published 45 full articles, 69 abstracts, and 6 miscellaneous publications. The presence of a CTG policy, however, does not always lead to the inclusion of HRQOL assessments in intergroup trials if the lead group does not feel it necessary to include such assessment.

Writing Guidelines

The QOL Committee provides writing guidelines for the inclusion of HRQOL assessment in clinical trials protocols [1,2]. HRQOL components should be a part of the main protocol and not an add-on. Inclusion of HRQOL components in the main protocol is desirable because adding on separate protocols creates the impression that HRQOL assessment is either not very important or that it is an afterthought.

The writing guidelines provide explicit instructions for the sections of the protocol dealing with the

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introduction, rationale and hypothesis, objectives of HRQOL assessment, eligibility criteria, study design, sample size, instrument description, instructions for administration of the instruments, timing of assessments [3], analysis, and wording of the consent form.

Instructions to Clinical Research Associates (CRAs)

At the outset, the QOL Committee developed instructions for the integration of HRQOL measurement into Phase III clinical trials [1]. These instructions are used by CRAs, office data managers, and others who will be involved in collecting the data. They include the rationale for the HRQOL component, how to present HRQOL questionnaires to patients, how to collect them after completion, and how to transmit the completed questionnaires to the central CTG office. As a result, all personnel involved with an HRQOL component in a trial understand the need for measuring it and the procedure for standardized collection of the data. Because central office staff who conduct the main part of the clinical trial are the same individuals who receive the HRQOL data, there is integration of all components of the trial by one group of personnel. We believe that this is an advantage over having separate personnel dealing with the HRQOL component and with the primary component of the trial (i.e., the primary objective).

A particularly important instruction to the CRAs is that they should obtain a completed HRQOL questionnaire on a patient before calling the central office for randomization instructions. This is intended to make certain that questionnaire completion rates at baseline are high. Nevertheless, if a patient is not able to answer a questionnaire because of language barriers, but meets all the other inclusion criteria, the patient is not excluded from participation in the study.

Liaison with Disease Site Groups (DSGs)

The QOL Committee members provide liaison to DSGs and educational resources to members of the CTG. Members of the QOL Committee act as liaison members between the QOL Committee and specific DSGs so that the HRQOL component of a proposed trial can be incorporated into the protocol at an early stage of the planning process. In addition, feedback to the DSGs on the success of collection of the HRQOL data can be provided as the trial progresses. To ensure that DSGs are well acquainted with the need to collect QOL data and what this entails, the QOL liaison person is a member of the executive committee for each DSG.

Completion Rates of HRQOL Instruments (Compliance)

The above policy and procedural instructions are intended to produce high questionnaire completion rates so as to keep avoidable (random) missing data to a minimum. Completion rates are determined as follows: number of questionnaires received with sufficient items answered to be deemed complete [4]; the number of questionnaires received over the number of patients enrolled in the trial; and the number of questionnaires received over the number expected (number of patients still on study and required to complete questionnaires according to the protocol). To date, almost all trials with HRQOL components have baseline completion rates higher than 97% [5–7]. On-study completion rates are lower, but the number completed over the number that can be expected to be completed is usually more than 80% (unpublished data) [5–7]. These completion rates are among the best in the world, and we believe that they are a consequence of the diligent efforts of our CRAs and central office personnel.

Choice of HRQOL Instruments

When the QOL Committee was formed, there were only a small number of HRQOL instruments from which to choose. Only two or three had been developed for use in patients with cancer. One of the members of the QOL Committee became a liaison member from the CTG to the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Study Group and was made aware of the properties of the Quality of Life Questionnaire (QLQ) being developed by that group [8]. The details of the questionnaire's reliability and validity were reviewed by the CTG QOL Committee, and it was decided to adopt the use of this questionnaire for CTG purposes. The decision was made to use this questionnaire as our standard questionnaire in clinical trials for a number of reasons. First, it provides separate domain and single-item scores rather than a single aggregated or summary score. Having separate scores allows a detailed picture of how different domains of HRQOL are affected by a disease and its treatment. Although a single aggregated score is appealing because it is simpler to deal with, it hides changes in HRQOL domains that move in opposite directions or that may differ according to the treatment a patient receives. Second, using the same instrument in a variety of disease sites allows us to become very familiar with its properties and behavior in a variety of cancer populations. Third, it allows us to make comparisons across clinical trials at different disease sites if we wish to do so. Finally, the use of one questionnaire allows for simplicity of administration at the clinic level and in data management at the central office. Eventually, we began to use other questionnaires if we were participating in a trial initiated by another cooperative clinical trials group or if it was felt that another instrument had some properties that made it desirable for use in a particular trial. We have used 24 different instruments, but the EORTC QLQ-C30 (the core instrument with 30 items) has been used in 51 of 71 (71.8%) trials.