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Letters

Quality Control of EORTC Case Report Forms—Wider Implications for Trial Management

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THE EORTC STUDY GROUP on Data Management recently ran a quality assurance project on case-report forms (CRFs), whereby data managers were asked to indicate where they had problems of understanding the questions on the forms they used and where they had problems in obtaining the data from their patient charts. The comments received from the data managers not only showed specifically where CRFs should be amended, which had been the main aim of the study, but also revealed a number of aspects of clinical trial data management that urgently need improvement.

Twenty-eight data managers sent in 41 sets of comments covering the CRFs of 11 EORTC studies and the resulting 179 comments fell into the following categories: ambiguity or lack of specificity of the question (32%), layout (21%), items or codes missing from forms (13%), superfluous items (2%), different terminology from their own institute (4%), contradictions between forms and protocol (2%), suggestions for alterations (11%), comments showing lack of data management experience (7%) and irrelevant comments (8%). Items marked as "lack of data in file" were evaluated separately. Overall, the scale of the difficulty in understanding the questions was 5% (58 items over a total of 1240 items on the forms).

Across all the different types of comments a distinction was made between those which were limited to just that one particular set of forms, as opposed to those which were more general, being also relevant to the CRFs of other studies. A third turned out to have general implications and examples of such lack of definitions and unclear formulation are:

"Date of diagnosis" (should it be the date of the clinical or the pathological diagnosis?)
"Reason dose modification" (is this just for dose reduction, or for delay as well?)
"Ejection fraction" (if not stated, should this be at rest or on exertion?)
"Nausea/vomiting" (how should this be coded when prophylactic antiemetics have been administered?)
"Chronic diseases" (how severe do they have to be to be reported?)
"Tumour diameter" (clinical or histological?)
"Examinations—normal/abnormal" (does "abnormal" only mean the presence of tumour, or does it include other abnormalities?)
"Previous surgery—curative/palliative" (what should be filled in if the pathology report states "not radical"?)

Difficulties with the definition of overall/best response and date of onset of response

Difficulties with the distinction between "mild/moderate/severe" for some toxicities

"Total number of tumour sites" (number of lesions or number of organs?)
"Nadir values day 14" (shouldn't this be "nadir values on or after day 14"?)
"Round off" (is this up or down?)

One of the aims of this project was to assess the need for writing individual handbooks to accompany sets of CRFs, however, as can be seen here, the majority of these problems can be rectified by making the questions more explicit, and this is indeed preferable since there is no guarantee that handbooks will be read. A full report of these findings has been submitted to the EORTC Quality Control Committee [1] and has been copied to the EORTC Form Review Committee (FRC) who are now in a position to supervise all new CRFs. This committee, consisting of EORTC Data Centre staff, was set up in 1989 but most of the CRFs reviewed in this study had in fact been designed before its implementation and had therefore not been reviewed by them. Since the dissemination of these results, it has been agreed that the EORTC Study Group on Data Management will support the FRC by allocating one of a team of local data managers to review the CRFs before they are submitted to the FRC.

In addition, it is important that study coordinators are aware of the problems highlighted above when they are reviewing the data.

In some cases, discussion within the EORTC cooperative groups will be necessary before making changes to the CRFs, for example to provide more precise definitions for "hormone receptor status". Although the answers allowed are "positive", "negative" or "unknown", in practice only levels of receptor above a certain value are considered "positive" and this value is not stated on the CRFs.

Data managers had also been asked to indicate for which items data was not available in the patient file. A large proportion of data managers reported that frequently general items such as performance status, weight loss, number of lymph nodes examined, concomitant medication, details and dates of toxicity (or lack of toxicity) were not documented in the patient file; something which confirms the findings of K. Vantongelen *et al.* in an earlier study on the quality control of trial data [2]. Apart from making a data manager's work extremely difficult, this lack of source documentation is no longer acceptable according to the demands of Good Clinical Practice. We therefore recommend to all physicians and data managers that they impose the use of standard flowsheets in their hospitals, since these not only facilitate data collection by providing checklists for

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completeness, but also give comprehensive overviews of the trial endpoints for all concerned. Copies of such a flowsheet are now available from the EORTC Chemotherapy Quality Control subcommittee.

Apart from general data that was missing, the data managers reported that in two of the trials reviewed the surgery form and the radiotherapy form respectively required details that had to be supplied specifically by the surgeon and radiotherapist. This is a perfectly acceptable situation, although in such cases it is advisable to discuss these forms with the doctors involved before the trial starts so that they can ensure that the data required is retrievable.

Data managers reported that in some studies there were items of "unusual" data, such as "sediment cells", "weight loss in the 3 months prior to study", "size of metastases at progression" and "time of headache", which had not been documented in patient charts. These problems indicate that there is still room for intensification of the contact between the physician/oncologist and the data manager. If the CRFs are discussed prior to the start of the study special attention can then be paid to documentation of these unusual items.

A number of comments (7%) could only be categorised as "lack of data management experience" and it was particularly disturbing to see that even experienced data managers were still having problems with determining certain study endpoints, for example "best/overall response", "data onset response" and "reason off study". Although this is data that can be checked and corrected by the Data Centre, these are fundamental concepts which a data manager should learn early in his/her career. It is obvious from this that data management training is essential and these topics have therefore been given extensive coverage in the recent EORTC–ESO Data Management Course.

Another point which was apparently not clear, and which was therefore emphasised during the Data Management Course, is the difference in endpoints between phase II and phase III trials. For phase II the CRFs must collect precise and extensive details on drug dosage, concomitant medication, toxicity and response assessment, whereas for phase III trials this degree of detail is superfluous since the emphasis should be on the harder endpoint of survival. The organisation of data collection must take these differences into account: entailing close monitoring of patients during the treatment period for phase II and paying careful attention to prestudy prognostic factors and regular patient follow-up for phase III.

In conclusion, the difficulty of understanding the questions on the CRFs is in the order of 5% and can be reduced, if not eliminated, by more explicit wording of the questions on the forms. In any case it does not warrant the production of specific handbooks, as was originally supposed. The Cooperative Groups, the study coordinators and the EORTC Form Review Committee should be aware of the types of problems of interpretation that the data managers have highlighted and the EORTC FRC, with support from the EORTC Study Group on Data Management, now has an important role to play in the supervision of all new EORTC forms.

From the reports of missing data in the patient chart, it became obvious that improvements need to be made in hospital file management. We strongly recommend the use of standard flowsheets to ensure that all general items are documented and that responsible physicians and data managers cooperate more closely in order to arrange ahead of time that *all* the required data is collected.

During this exercise on quality control of trial data and study forms it came to light that there is a need for ongoing data management training and a number of topics have been highlighted to receive special attention in the EORTC–ESO course.

1. Franklin HR, Kerr M, Tarayre M, Bierhorst FJ, Van Glabbeke M. Quality Control of Case Report Forms: A collection of data managers' comments. Report to the EORTC Quality Control Committee, March 1991.
2. Vantongelen K, Steward W, Blackledge G, Verweij J, van Oosterom A. EORTC Joint Ventures in Quality Control: Treatment-related Variables and Data Acquisition in Chemotherapy trials. *Eur J Cancer* 1991, 27, 201–207.

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High-dose Folinic Acid, 5-Fluorouracil Bolus and Continuous Infusion in Metastatic Colorectal Cancer: a 3-day/3-week Schedule

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5-FLUOROURACIL (5FU) modulated by folinic acid is a standard treatment for metastatic colorectal cancer. Various combinations of the two drugs have been studied for an overall response rate of 30–50% and median survival of 10–15 months [1, 2]. We previously reported a 2-day schedule at 2-week intervals of high dose folinic acid, 5FU bolus and continuous infusion (LV5FU2, protocol C85) which obtained a 54% response and 18 months median survival at particularly low toxicity [3]. We had added a 5FU continuous infusion to a bolus at 2-day/2-week schedule in

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