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Special Article

Guidelines for the Preparation of E.O.R.T.C. Cancer Clinical Trial Protocols*

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Abstract—*A therapeutic clinical trial may be defined as a medical observation performed on patients in order to answer specific questions concerning new forms of treatment(s). The application of new therapeutic regimens to diseased persons requires ethical justification by means of experimental (animal), historical (literature), clinical (previous experience) and logical arguments.*

The written description of the objectives of the study, its rationale and logistics are contained in the "study protocol", a self-contained document.

The goal of this paper is to provide an aid to investigators in the preparation of their protocols by means of guidelines (Table 1) which are discussed hereafter. These guidelines should be followed for all protocols submitted to the E.O.R.T.C. Protocol Review Committee||. The design and analysis of cancer clinical trials are the subject of a number of publications [1–20] and will therefore not be discussed here.

I. BACKGROUND AND INTRODUCTION

THIS section of the protocol provides the rationale and the background for undertaking the trial. In addition, the natural history of the disease, the most important prognostic factors [21] affecting the patient's response or survival and the results of previous studies of related interest [22] should all be critically discussed and referenced.

Besides published results in medical journals, information on both past and currently ongoing trials are available from several media [23–27].

II. OBJECTIVES OF THE TRIAL AND AN OUTLINE OF MATERIALS AND METHODS

The objectives of the trial must be clearly specified in detail along with a brief description of the materials and methods used to achieve these objectives i.e., phase of the trial, type of patients (sex, age, menopausal status, prior therapy, etc.), type of disease (primary, loco-regional, advanced, etc.), ran-

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Table 1. *Protocol contents*

I.	Background and Introduction
II.	Objectives of the Trial and an Outline of Materials and Methods
III.	Patient Selection Criteria (Eligibility Criteria)
IV.	Trial Design
V.	Therapeutic Regimens, Dose Modification and Toxicity
VI.	Required Clinical Evaluations, Laboratory Tests and Follow-up
VII.	Criteria of Evaluation
VIII.	Registration and Randomization of Patients
IX.	Forms and Procedures for Collecting Data
X.	Statistical Considerations
XI.	Administrative Responsibilities
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domization (single or multiple), historical control (literature, concurrent) etc. It is often advantageous to include a schema which summarizes at a glance the main details of the study.

III. PATIENT SELECTION CRITERIA (ELIGIBILITY CRITERIA)

The population of patients to be studied should be defined as precisely as possible through the listing of patient inclusion and exclusion criteria such as:

1. The tumor site, the stage of the disease, the TNM or other classification, and the histological type [28–30].
2. The presence of evaluable disease, measurable or not measurable [31].
3. The patient's age, sex and performance status [32, 33].
4. The type and amount of previous treatment received.
5. The patient's hematological status and values of specific hepatic and renal function tests.
6. The presence of other diseases, concomitant therapy, a second tumor, or contraindications for any of the treatments under study.

IV. TRIAL DESIGN

This section gives a short summary of the trial to include:

1. The time at which patients are to be registered or randomized and what stratifications, if any, are done. Stratification by institution in multicenter trials is recommended, but the number of additional stratifying variables should be kept to a minimum (one or at most two) as too much stratification can create a larger imbalance than no stratification at all.
2. Definition of the treatment arms and duration of treatment.
3. Specification of the minimum duration of treatment, the time of evaluation and the treatment policy to be followed as a function of the response: should treatment be continued, crossed-over, left to the investigator's discretion, or should the patient be entered in a phase II study?
4. In multi-modality trials the maximum delay permitted between surgery, radiotherapy and the start of chemotherapy or immunotherapy.
5. The frequency of follow-up.
6. The end points of the study, e.g., survival, disease-free survival, disease-free interval, amount of tumor shrinkage, duration of response, markers, etc.

V. THERAPEUTIC REGIMENS, DOSE MODIFICATIONS AND TOXICITY

The dose, schedule, route, cycles and duration of treatment should be clearly spelled out. It should be indicated whether supportive therapy may be given during the course of the study, and if so, under what circumstances and in what amounts. Any medication which is contraindicated in the protocol must be clearly stated as such. Special instructions concerning drug supply, storage and availability are also necessary.

The most frequent toxicities for each treatment should be listed, along with the schedule for monitoring toxicity. In case of excessive drug-related toxicity, dose modifications should be presented in an easy to read form. Drug dosage may be reduced or administration may be delayed until partial or total recovery. In this case, the maximum delay

permitted between courses or the percentage of reduction must be spelled out. For drugs where the total allowable amount administered is limited due to toxicity, the total permissible dose should be clearly indicated along with what the treatment policy is once the maximum dose has been reached.

In adjuvant studies, the primary treatment must be standardized and described in detail.

VI. REQUIRED CLINICAL EVALUATIONS, LABORATORY TESTS AND FOLLOW-UP

The required pre-treatment and follow-up examinations should be listed along with the schedule at which they are to be performed. All patients should be examined at the same frequency and with the same methods in order to avoid possible bias.

When evaluating response to treatment, it is recommended, whenever possible, that the same clinician follows the same patient throughout the course of the study. The evaluation should, when possible, be blind with respect to the treatment received.

In multicenter trials, procedures from one laboratory to another should be standardized as much as possible in order to minimize inter laboratory variation.

VII. CRITERIA OF EVALUATION

The endpoints with respect to which the treatments will be evaluated should be given with all evaluation criteria being clearly spelled out. In patients with advanced disease precise objective definitions for terms such as complete response, partial response, no change, progression, early death and toxic death must be given along with the time points at which patients are to be evaluated. For some examples see Moertel and Hanley [34], Scott *et al.* [35], Hayward *et al.* [36], and Staquet [21]. In addition, starting and endpoints for evaluation criteria such as duration of survival, disease-free interval or survival and partial or complete response should be defined [31].

The protocol should specify how patients who are lost to follow-up, receive insufficient treatment or have protocol violations are to be evaluated. Ideally, all patient records should be reviewed by an independent extramural review committee to assess both patient eligibility and treatment results.

VIII. REGISTRATION AND RANDOMIZATION OF PATIENTS

Clear and precise instructions concerning when and who the clinician must contact to register or randomize a patient should be provided along with what information the clinician must supply at the time of registration or randomization. In multicenter trials, a *centralized* randomization by telephone or telex is essential for the following reasons:

1. To ensure that the randomization is done correctly since envelope randomization can easily be abused.
2. To know at all times how many patients have been entered on study.
3. To be able to request overdue forms for all patients entered on study.

IX. FORMS AND PROCEDURES FOR COLLECTING DATA

This section should include copies of the forms to be used and information concerning when and how often each form should be filled out and to whom the forms should be sent. It is essential that forms be kept simple and short in order to concentrate on obtaining all the relevant data.

X. STATISTICAL CONSIDERATIONS

Based on the principal endpoints and the expected accrual rate, one can calculate the total number of patients required, the expected duration of patient entry, and the expected duration of the study [37–42]. One should specify whether a fixed sample or sequential type of analysis will be performed, if a formal stopping rule will be used in the case of early treatment differences, and how often and to what use interim statistical analyses will be made.

XI. ADMINISTRATIVE RESPONSIBILITIES

Each study must have a study coordinator who is responsible for the trial. This paragraph should contain his name, address and telephone number as well as those of the chairman of each subcommittee (the Central Pathology Review Committee, for example) and of the data processing and statistical center.

In addition, the participating centers should

be listed along with the principal investigators in each center.

XII. REFERENCES

An up to date list of references is essential documentation which must be included in all protocols. For non-published work, the results of the study must be appended.

XIII. APPENDICES

Possible appendices would include the TNM classification [30] or staging system used (AJC, [29]), the performance status classification used (Karnofsky [32] or ECOG/Zubrod [33] 5 points scale) and a nomogram or table giving the body surface area as a function of the patient's height and weight [42].

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