

# Independent Data Monitoring Committees and Interim Analyses

Randomized phase II and phase III clinical trials

**POL004**

**Version 1.5**

(Always refer to the Intranet to check the validity of this document)

**Author**

Richard Sylvester

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

**Co-author**

Patrick Therasse

Jean-Claude Horiot

Catherine Legrand

**Approved by**

EORTC Executive Committee

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

**Distribution**

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1.0	Initial Release	Richard Sylvester	
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1.4	<ul style="list-style-type: none"> <li>- An IDMC is no longer mandatory in Intergroup trials, but rather it is recommended. It is mandatory in phase 3 trials where there are formal interim analyses with early stopping rules.</li> <li>- The choice of external members for a given protocol should be suggested by the study coordinator.</li> <li>-Permanent and external members should not be members of other EORTC review committees such as the PRC or the SAC. They should not be involved in the review of any trials for which they entered patients or were responsible for patient treatment, or for which they had an official function within the trial. Likewise they should not be an officer within the previous 5 years of the EORTC Group responsible for the trial. In case a permanent member must be replaced for a given trial, the other IDMC members will identify and approve an appropriate replacement.</li> <li>- A training will be provided for IDMC members by the EORTC Data Center staff a minimum of at least once every 3 years at the time of the changeover of IDMC members.</li> </ul>	Richard Sylvester	September 26, 2003
1.5	<ul style="list-style-type: none"> <li>Approval by the EORTC Executive Committee</li> <li>Addition of the IDMC Coordinator</li> <li>Agreement between the Group, Data Center and IDMC concerning the choice of external reviewers</li> <li>IDMC members should not review a protocol from a Group where they are an officer at the time of the review</li> <li>Addition of the reference to EORTC Policy 001 on Conflict of Interest</li> <li>IDMC Coordinator will prepare the first draft of the minutes of the meetings.</li> </ul>	Richard Sylvester	February 20, 2004

## Table of contents

<b>1.</b>	<b>OBJECTIVES</b>	<b>4</b>
<b>2.</b>	<b>DEFINITIONS</b>	<b>4</b>
<b>3.</b>	<b>TERMS OF REFERENCE FOR IDMCS</b>	<b>4</b>
<b>4.</b>	<b>POLICY FOR EORTC IDMC REVIEW</b>	<b>4</b>
<b>5.</b>	<b>MEMBERSHIP ON IDMCS</b>	<b>5</b>
<b>6.</b>	<b>THE IDMC MEETING</b>	<b>5</b>
6.1.	Before the IDMC Meeting	6
6.2.	The IDMC Meeting	6
6.3.	After the IDMC meeting	7
<b>7.</b>	<b>FINANCING IDMCS</b>	<b>7</b>
<b>8.</b>	<b>EORTC POLICY ON INTERIM ANALYSES</b>	<b>7</b>
<b>9.</b>	<b>APPENDICES AND REFERENCES</b>	<b>8</b>

## 1. Objectives

The purpose of this document is to describe the EORTC policy for the use of Independent Data Monitoring Committees in randomized phase II and randomized phase III clinical trials.

## 2. Definitions

**Independent Data Monitoring Committee (IDMC):** an independent committee of clinicians and statisticians whose task is to review the status of a clinical trial and make recommendations to the clinical research group concerning the trial's continuation, modification and/or publication.

**EORTC IDMC:** a permanent EORTC committee of experts including at least: a medical oncologist, a radiation oncologist, a surgical oncologist and a biostatistician.

**Coordinating Secretary (CS):** the EORTC secretary assigned to provide administrative support to the EORTC IDMC.

**IDMC Coordinator (IC):** an EORTC Data Center staff member assigned to supervise the functioning of the EORTC IDMC and the coordinating secretary.

## 3. Terms of Reference for IDMCs

Depending on the particular trial, the terms of reference may include:

- ◇ To recommend to the clinical research group whether it is ethical to continue randomizing patients when there are potential differences in treatment efficacy and/or safety and toxicity, (or more generally when there is evidence that the null hypothesis may not be true), or conversely whether the data suggest that there may never be any difference in efficacy (or more generally when it is unlikely that the null hypothesis will ever be rejected).
- ◇ To recommend to the clinical research group whether one may present or publish the results of the trial earlier than anticipated, i.e. prior to trial maturity (see EORTC "Disclosure of Results and Publication Policy" (Ref.: POL009)).
- ◇ To recommend to the clinical research group and the EORTC Protocol Review Committee whether a randomized phase II trial should be continued as a randomized phase III study.
- ◇ To review potential problems with respect to patient compliance or trial feasibility/quality and make recommendations as appropriate to the clinical research group.
- ◇ Upon request of the EORTC Executive Committee, to recommend whether a poorly accruing trial should be prematurely closed to patient entry because it is unlikely to meet its accrual objectives in a reasonable period of time or whether accrual in the trial should continue.

## 4. Policy for EORTC IDMC Review

EORTC IDMC review is mandatory in phase 3 trials where formal interim analyses and early stopping rules are foreseen.

EORTC IDMC review is also recommended in the following situations:

- ◇ Intergroup trials coordinated by the EORTC
- ◇ All trials requiring the randomization of more than 1000 patients or more than four years of patient accrual

- ◇ Trials with highly toxic regimens or particular safety concerns.
- ◇ Pivotal phase III trials which will be used for drug registration
- ◇ Randomized phase II trials that may be continued as a phase III trial without clear rules in the protocol.

The policy for carrying out interim analyses should be precisely stated in the protocol. For trials which are not reviewed by the EORTC IDMC, the Data Center team consisting of the trial coordinating physician, statistician and data manager will review the data on a regular basis as specified in the protocol. In the case of intergroup trials, the trial steering committee will also review the trial. If either feel that there may be ethical problems to continue the study, or if the clinical research group wishes a formal interim analysis to be carried out which has not been foreseen in the protocol or pose a question of principle (for example modification of an endpoint), then a written request should be made to the Data Center team (if the request does not originate from the Data Center team) and the Assistant Director for Biostatistics via the IDMC Coordinating Secretary detailing the reasons for the request. If they feel the request is justified, then the IDMC will review the trial.

## 5. Membership on IDMCs

The EORTC IDMC will be composed of a minimum of four permanent members. Two trial specific external experts will be invited to participate in the committee for each study.

The permanent members are nominated by the EORTC Executive Committee and approved by the board for a term of three years, renewable at the discretion of the Executive Committee and the board. The terms will be staggered so that not more than half of the members will leave the committee during the same year. The chairman of the EORTC IDMC is elected amongst the permanent members. Each of the following disciplines will be represented: Medical Oncology, Radiation Oncology, Surgical Oncology and Statistics.

Prior to the activation of the study, the choice of the external members of the IDMC should be suggested by the trial statistician with the agreement of the study coordinator and the chairman of the clinical research group. The IDMC may propose different names, but then this should be discussed with the clinical research group and the trial statistician in order to reach a mutually acceptable decision. The external members may be physicians and/or statisticians who agree with the objectives of the trial and are free of any conflict of interest that might be related to the particular trial.

Permanent and external members should not be members of other EORTC review committees such as the PRC or the SAC. They should not be involved in the review of any trials for which they entered patients or were responsible for patient treatment, or for which they had an official function within the trial. Likewise they should not be an officer of the EORTC Group responsible for the trial at the time of the review. In case a permanent member must be replaced for a given trial, the other IDMC members will identify and approve an appropriate replacement.

No pharmaceutical company representatives may be among the members of the IDMC reviewing the study.

An EORTC Conflict of Interest/Confidentiality Disclosure form for EORTC Officers is to be signed by each member of the IDMC in accordance with EORTC Policy 001 "Conflict of interest" (Ref.: POL001).

The IDMC members should be aware that the information included in the interim report is confidential and must not be disclosed, even partially, either orally or in writing, outside of the committee.

A training will be provided for IDMC members by the EORTC Data Center staff a minimum of at least once every 3 years at the time of the changeover of IDMC members.

## 6. The IDMC Meeting

Depending on the material to be discussed, there may either be a physical meeting of the IDMC or they may conduct their business via a telephone conference or e-mail.

## 6.1. Before the IDMC Meeting

The Coordinating Secretary will inform the study coordinator and/or the chairman of the clinical research group that they may write to the chairman of the IDMC via the Coordinating Secretary to draw his attention to issues of practical importance to the clinical research group (“Practical Implementation of EORTC Policy 004 for Independent Data Monitoring Committees” (Ref.: WP5201)). This information will be circulated to all the IDMC members before the IDMC meeting. This may include trial modifications suggested by the clinical research group, recruitment problems, unexpected safety problems, and new evidence from the literature that may affect the design or the expected outcome of the trial.

The members of the IDMC will receive the study protocol, a copy of the case report forms and the most recent trial status report two months prior to the meeting. They will receive the (unblinded) confidential interim report prepared by the trial statistician in accordance with EORTC “Reporting trial progress” (Ref.: WP1302) 4 to 5 weeks prior to the meeting with a deadline of two weeks for sending comments back to the Coordinating Secretary with the possibility to request additional information.

## 6.2. The IDMC Meeting

In an open session, the IDMC may seek information as appropriate from the study coordinator, the chairman of the clinical research group, other clinical research groups, regulatory bodies, the pharmaceutical industry, etc. During this open session, no information concerning treatment efficacy or other trial endpoints may be presented.

The following closed session is limited to the members of the IDMC. The Data Center team will attend to present the interim analysis report, provide clarifications, and answer questions from the IDMC members. In the case of intergroup trials, the IDMC may also invite other participants that it considers appropriate to attend this part of the session. The trial’s status may then be reviewed with the study coordinator, however no confidential information will be discussed at this time.

In the ensuing discussion prior to making their recommendations, only the IDMC members (and possibly Data Center team members as non-voting members at the discretion of the IDMC chairman) may be present. The outcome data will be discussed and the IDMC will recommend whether the trial should be continued as it is, modified or terminated (or decide whether early disclosure of the results is advisable in the case of an interim analysis performed after closing the trial to patient entry and advise on the timing of the publication). The IDMC might also request that another interim analysis be carried out after a specified period of time, after an additional number of events have been observed or after an additional number of patients have been entered or are off-treatment.

During a second open session (optional), the recommendations will be discussed with study representatives which may include the study coordinator, the group chairman, the trial statistician, coordinating physician, data manager and pharmaceutical company representatives. Only if the IDMC gives any recommendation other than continuing the trial unchanged should the relevant information be provided. Information about therapeutic efficacy or safety may only be revealed in case of recommending trial discontinuation, major trial modifications or early publication.

The IDMC members should consider the statistical early stopping rule only as a guideline. It is not a hard and fast rule. Rather than just looking at P values, the IDMC should also take into consideration all other aspects such as

- ◇ the number of patients and events observed (data maturity)
- ◇ the length of the confidence interval for the size of the treatment difference
- ◇ toxicity/safety
- ◇ quality of life (if assessed)
- ◇ feasibility
- ◇ information from other trials
- ◇ resources in terms of patients and finances

In reaching their conclusions they should also take into account both prior and current beliefs concerning the size of the treatment difference that would likely be necessary to change clinical practice and the amount of evidence that the trial furnishes in support of this difference. When a trial is stopped early, the size of the difference may not be able to be accurately estimated. Members of the IDMC should thus be aware of the dangers of drawing conclusions based on immature data and recommend trial closure or early publication only in very exceptional cases. If the IDMC considers that the trial should continue, they should actively encourage the participants to pursue the trial and to complete patient entry as quickly as possible. The IDMC should be as constructive as possible and try to be a positive influence on the trial.

### **6.3. After the IDMC meeting**

The IDMC Coordinator, under the supervision of the Chairman of the IDMC, will prepare the first draft of the minutes of the meeting which is to be sent to the EORTC IDMC members and trial statistician (for their specific study) for comments and approval.

For each protocol the minutes must contain a short summary of the scientific discussion, the recommendations of the IDMC, and the actions to be taken. The minutes will be divided into 2 parts: one which is confidential and only for internal use within the IDMC and one which can be distributed outside of the IDMC.

After review by the EORTC IDMC members and the trial statistician (for their specific study) and the approval of the chairman and secretary of the IDMC, the Coordinating Secretary will distribute the full minutes to the EORTC IDMC members. The external IDMC members and Data Center team will receive the full minutes pertaining only to their protocols.

The non-confidential recommendations will be distributed to the chairman of the clinical research group and the study coordinator responsible for the study. For Intergroup trials the study coordinators for each of the participating groups will also receive the non-confidential minutes. In case of a recommendation to stop a trial, to continue or not a randomized phase 2 trial as a phase 3 study, and for all poorly accruing trials they review, the chairman of the PRC and the Data Center Director will also be informed.

Information about therapeutic efficacy or safety may only be revealed in case of recommending trial discontinuation, major trial modifications (such as dropping a treatment group, important change in treatment regimen, change in endpoint, etc) or early publication. Only if the committee came to any conclusion other than continuing the trial without modification should the letter justify the decision. A copy of the minutes of the IDMC meeting will be kept in the trial master file for the study and at the EORTC Central Office (with appropriate mechanisms to safeguard the confidentiality of trial results and data).

The final decision, however, is the responsibility of the clinical research Group represented by its chairman. In the case of a trial modification, a protocol amendment should be prepared for submission to the chairman of the PRC requesting written approval for the suggested changes prior to their implementation.

If the Clinical Research Group decides not to follow the recommendations of the IDMC, the chairman of the clinical research Group should discuss the matter with the chairman of the IDMC and the chairman of the EORTC Protocol Review Committee. These three persons will be responsible for reaching a mutually acceptable decision. If no decision can be reached, the matter will be referred to the EORTC Board who has the final decision.

## **7. Financing IDMCs**

Travel expenses encountered by IDMC members, the study coordinator and Data Center members will be reimbursed by the EORTC treasury. For fully supported studies, operating and administrative expenses will be charged in the contract with the pharmaceutical company.

## **8. EORTC Policy on Interim Analyses**

Unless approved by an IDMC, it is the EORTC's policy not to release interim trial results for any reason before the required number of events have been observed for the primary endpoint (as defined in the

protocol), whether for designing the next trial, for presentation or for publication.

However if the decision has been made to continue a randomized phase II trial as a phase III study, the phase II response and toxicity data may be released for publication. As usual for phase II trials, no p values will be provided. Unless approved by an IDMC, no further results will be publicly released until the end of the phase III study when the final results become available.

See EORTC “Disclosure of Results and Publication Policy” (Ref.: POL009) for further details.

## 9. Appendices and references

Document title	Reference (file name)
Conflict of Interest, Confidentiality	POL001
Disclosure of Results and Publication Policy	POL009
Reporting trial progress	WP1302
Practical Implementation of EORTC Policy 004 for Independent Data Monitoring Committees	WP5201