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Independent Data Monitoring Committees for EORTC studies

POL004

Version 3.0

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1 PURPOSE

The purpose of this document is to describe the EORTC policy for the use of Independent Data Monitoring Committees in EORTC 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.
- **Independence:** will result from the joint expertise of the members of the IDMC. It is to be seen as absence of conflict of interest, direct or indirect, financial or scientific, for the study for which data monitoring is required. Therefore no pharmaceutical company representatives may be member of the IDMC or attend its closed meeting sessions.
- **Permanent IDMC for EORTC studies (EORTC IDMC):** a permanent committee of experts including at least: a medical oncologist, a radiation oncologist, a surgical oncologist and a biostatistician.
- **IDMC Chair:** the person elected by the EORTC Board to chair the IDMC.
- **IDMC Support Unit**: Unit of the EORTC Headquarters Unit assigned to organize the IDMC meetings and to facilitate the smooth functioning of the IDMC and to maintain the documentation of the IDMC meetings.
- **IDMC Support Unit officer ('IDMC secretary'):** the EORTC Headquarters staff providing administrative support within the EORTC IDMC Support Unit.
- **Head of IDMC Support Unit:** a member of the EORTC Statistics Department that is responsible for the IDMC support unit. The Head of IDMC Support Unit also provides support to the IDMC members in respect to methodology and procedures of EORTC. He /she reviews and approves all the IDMC reports prepared by EORTC statisticians.
- **Trial status report (TSR):** administrative report issued during the study conduct to inform principal investigators and other partners of study progress and protocol compliance, and to monitor treatment safety. The objective is to address and solve any arising problems that may compromise the conduct of the trial and/or the analysis and interpretation of the study's results.
- **IDMC analysis report (IDMCR):** confidential report on an interim statistical analysis issued before data maturity for review by the IDMC.
- **EORTC Headquarters Institutional Review Board (IRB):** a panel responsible for safeguarding the rights and welfare of subjects participating in clinical trials conducted with the support of the EORTC Headquarters. It validates the informed consent templates used in EORTC trials and ensures that EORTC activities are conducted without conflict of interest according to EORTC Policy "Conflict of Interest and Confidentiality" (POL001)
- **Study Management Group:** For an EORTC study the Study Management Group consists of the EORTC Headquarters core team in charge of running the study (clinical research physician, statistician, project manager and data managers) and the study coordinator.
- **Study Steering committee (SSC) (also named Study Executive Committee, or Study Executive Board):** The committee that provides the overall supervision of the study and has the executive power.

The SSC should monitor study progress and conduct and give advice on scientific credibility. The SSC will consider and act, as appropriate, upon the recommendations of the IDMC. Membership of the SSC shall, as a minimum, include the study coordinators, the representatives of collaborative groups involved, at least one representative of the EORTC Headquarters and the representative of the sponsor. When EORTC is the sponsor, the EORTC study clinical research physician is the representative of EORTC as sponsor. When no SSC has been formally set up for an EORTC study, SSC in this study will then refer to the study coordinators (principal and co-coordinators) and the Chairperson of the EORTC groups involved in the study, at least one member of the EORTC HQ team (usually the EORTC study Clinical Research Physician) and the representative of the study sponsor.

3 POLICY

The IDMC for EORTC studies is charged with the interim review of EORTC studies and intergroup studies where the EORTC is the coordinating group (including studies done together with the pharmaceutical industry). Any exception to this policy must be approved by the Director General of EORTC. For intergroup studies where the EORTC is not the coordinating group, the IDMC set up by the coordinating group will generally be used and is expected to be broadly compliant with the present policy.

The functioning of the permanent IDMC for EORTC studies is ruled by a charter (see link). If by exception, another IDMC than the central EORTC IDMC is used, a study specific IDMC charter may be developed together with the study sponsor per contractual agreement. Before their first review of a study, all IDMC members must sign that they agree with the terms of the IDMC charter.

The interim reviews should be planned upfront and precisely specified in the study protocol.

IDMC review is mandatory in all phase III and phase II trials where formal interim analyses and early stopping rules are planned and described upfront in the protocol. It is also mandatory for trials that are designed with planned adaptions of the sample size or of the study design that are based on interim analysis of the unblinded results of the trial.

EORTC IDMC review is also recommended and should be planned and specified in the protocol in the following situations:

- Intergroup trials coordinated by the EORTC.
- Trials requiring the randomization of more than 1000 patients or more than four years of patient accrual.
- Pivotal trials which will be used for drug registration.
- Randomized phase II trials that may be continued as a phase III trial.
- Trials testing treatments that carry particular safety concerns, for which it is expected that the independent advice regarding safety will be needed

3.1 Terms of reference for the IDMC

The IDMC should make recommendations to the Study Management Group and Study Steering Committee regarding the following aspects of the study; as is relevant in regard to the study design:

- whether it is ethical to continue randomizing patients when there is compelling evidence that the risk/benefit ratio favors one of the arms over the other(s) or conversely, where there is compelling evidence of futility (i.e., that the study will never lead to concluding against the null hypothesis) following protocol defined stopping rules

- whether one should present or publish the results of all or some of the study endpoints earlier than anticipated, i.e., prior to study maturity
- whether a randomized phase II study should be continued (or possibly expanded) into a phase III study
- whether a modification should be made to the study for safety reasons, for example, a modification of the eligibility criteria when the risk/benefit ratio seems unfavorable in specific subgroups of patients
- on modifications to the study sample size
- on study parameters that are planned according to an adaptive study design when the adaptions are effects based on an interim analysis of un-blinded results of the controlled study (generally involving comparative analyses of study endpoints or outcomes potentially correlated with these endpoints)
- on actions needed to manage identified issues related to patient compliance or study feasibility and/or quality

3.2 Reviews of safety data

Safety issues are identified by the Study Management Group during the study specific medical reviews. Findings will then be discussed with the Study Steering Committee, who will then take the appropriate measures..

The Study Management Group may defer to the IDMC any safety problems they identify as requiring external advice or identified as requiring IDMC review in the Medical Review Plan (ref: EORTC CM-010-SOP “Medical Review”). In that instance, the IDMC will review all (un-blinded) safety data for the study and provide recommendations concerning the possible continuation, modification or discontinuation of the treatment regimens under study and/or of the study protocol. Such safety reviews may be conducted using an expedited review process and generally require no disclosure of the efficacy outcome data other than the lethal adverse events.

3.3 Reviews of study efficacy data

It is the EORTC’s policy not to release interim efficacy results for any reason before the trial has been closed to recruitment and the data are mature for the analysis of the primary endpoint (as defined in the protocol), unless the data fulfil one of the conditions specified in EORTC POL009 (Disclosure of Results and Publication Policy), or unless the release of the information is authorized by the IDMC.

When interim efficacy analyses are conducted, they are performed according to the protocol-specific interim analysis plan. The IDMC Report (IDMCR) is provided confidentially to the EORTC IDMC members for their assessment. The IDMC then provides their signed recommendations to the Trial Steering Committee, to the other participating groups (for intergroup trials), and to the sponsor (when it is not EORTC), through the Study Management Group.

In the event that changes to the interim analysis plan regarding efficacy endpoints need to be made after the launch of a study, these must preferably be done prior to the first interim analysis. Such revisions of the statistical design must be performed by a statistician independent of the study conduct. Whenever such changes are implemented after having conducted earlier interim analyses, the IDMC itself needs to authorize the change to the interim analysis plan.

3.4 Other questions not involving data review

The study sponsor, the Study Steering Committee and the Study Management Group may also address questions of principle to the IDMC that do not require any immediate interim statistical analysis of the study data (for example a request to change the design to include an interim analysis of one or several efficacy endpoints, or a request to change the statistical analysis plan for the final analysis of the trial, or a request concerning a potential change of the study primary endpoint).

Such requests are transmitted to the IDMC by the Study Management Group, through the study statistician. Such requests should be made in the form of a letter to the IDMC that clearly formulates the questions addressed to the committee and provides all the necessary documentation in support. The IDMC Chair will then decide on the most appropriate process for the IDMC to address the request (e.g. include in the agenda of the next planned meeting of the IDMC, set up an rapid review safety review, or reject the request when it is judged unjustified).

4 COMPOSITION OF THE EORTC IDMC

No pharmaceutical company representatives may be members of the IDMC.

4.1 Permanent EORTC IDMC and its members

Besides its Chair, the EORTC IDMC has a minimum of five (5) permanent members representing at least the following disciplines: medical oncology, radiation oncology, surgical oncology and clinical biostatistics. The permanent members and the IDMC Chair are nominated by the EORTC Board for a term of three years which is renewable at the discretion of the EORTC Board. The terms will be staggered so that not more than half of the members will leave the committee during the same year.

The permanent EORTC IDMC members are part of the IDMC for all the studies presented for IDMC review during their term, except for safety reviews that require expedited review, for which not all permanent members may be called.

Permanent IDMC members must be free of conflicts of interest according to the terms set in section 5.2 and must agree with and sign the IDMC charter.

4.2 Study-specific IDMC members

Additional experts are appointed to be part of the IDMC for an individual study. They are selected for their relevant expertise.

Like the members of the permanent IDMC members they must be free of conflicts of interest and must agree with and sign the IDMC charter.

Names of potential independent study-specific IDMC members are proposed by the Study Coordinator and submitted to IDMC secretariat through the EORTC study statistician ahead of the first scheduled IDMC review of the study. The IDMC Chair and IDMC secretariat may also propose names of external reviewers. The IDMC Chair takes the final decision in the selection of the external IDMC members. The names of the external reviewers are then kept confidential.

4.2.1 For interim reviews involving the review of efficacy study data

A minimum of three (3) study specific external members are appointed to be part of the IDMC.

4.2.2 For interim reviews of safety data only

The EORTC IDMC Chair and at least one of the permanent IDMC members will be part of the review. A minimum of two (2) study specific external members are appointed to be part of the IDMC that review.

4.2.3 For requests to the IDMC that do not involve any data review

Usually, only the permanent IDMC members are involved in these kinds of reviews. However, the EORTC IDMC Chair may decide on a case by case basis to appoint up to three (3) external reviewers for such reviews.

5 CONFIDENTIALITY, CONFLICTS OF INTEREST AND FINANCING

5.1 Confidentiality

The IDMC members should not discuss issues relating to their involvement in the study at any time, and the content of IDMC meetings will remain confidential.

5.2 Conflicts of interest

All IDMC members function in accordance with the EORTC Policy on “Conflict of interest and Confidentiality” (ref: EORTC POL001).

Permanent IDMC members complete and sign the EORTC confidentiality agreement and interest disclosure form upon joining the committee.

In addition, all IDMC members complete and sign the EORTC confidentiality agreement and interest disclosure form for each meeting that they attend, where they specify the studies they review.

In addition to the terms of EORTC POL001, the following circumstances will be regarded as conflicts of interests for permanent and study-specific IDMC members which would require their exclusion from the IDMC for all or a specific study:

- Being a permanent member of other EORTC review committees such as the EORTC Protocol Review Committee or the EORTC Scientific Audit Committee,
- Having entered patients themselves or have been responsible for treatment of patients in the study being reviewed,
- Having served as officer in other bodies involved with the study such as but not limited to: be member of any drafting committee of the protocol, be member of an endpoint assessment committee of the study
- Serve as an officer of the EORTC Group responsible for the study at the time of the review.
- Be the principal investigator of a study that is competing with the one being reviewed.
- Have been on advisory boards either (a) for the same drug as the study drug, or (b) for the same Pharma company AND the same indication as in the study, if not the same drug.

Members who previously acted as external (occasional) reviewers (e.g. for EORTC Protocol Review Committee) for the study being reviewed should declare this as potential conflict of interest but this would not exclude them from the IDMC

Members who have served on advisory boards for the same company as the one involved in the study, if any, but for a different drug and a different indication should declare this on the conflict of interest but this would not justify their exclusion from the IDMC.

Whenever other potential conflicts of interest are declared on the form, the IDMC Support Unit will bring them to the attention of the EORTC Headquarters Institutional Review Board, who will decide on the appropriateness to replace the IDMC member. The IDMC Support Unit then informs the IDMC Chair of their decision regarding the possible conflicts of interest and the need to replace the member.

5.3 Financing of the IDMC

IDMC members will receive no financial remuneration for their time. Travel expenses will be reimbursed by the EORTC treasury. For fully supported studies, operating and administrative expenses will also be charged by the EORTC Headquarters in the contract with the pharmaceutical company.

6 ORGANIZATION OF THE IDMC MEETINGS

The EORTC IDMC meets approximately four times a year. It is recommended that at least one meeting should be face-to-face each year. Face-to-face meetings are preferred, with video-supported teleconference (e.g: Webex) as a second option, depending on the material to be reviewed. Review by email exchanges only is not normally recommended but it may be permitted in exceptional circumstances with the agreement of the IDMC Chair.

Safety reviews will be carried out according to need with no pre-established meeting schedule. As urgent decisions must be taken for safety concerns, the IDMC meetings for such reviews will be organized at short notice and will generally be held by (e.g.: Webex) teleconference. The time intervals for the preparation and distribution of safety reports may be shortened in order to expedite the review process. This will be decided on a case by case basis by the Head of EORTC IDMC Support Unit and the IDMC Chair.

For emergency issues, additional IDMC sessions may be organized at the discretion of the IDMC Chair.

6.1 Preparation of the IDMC Meeting

Before the IDMC, the IDMC Support Unit confirms to the Study Management Group that the study is scheduled for review. He also cross-verifies with them the questions that are addressed to the IDMC. In their communication with the IDMC, the Study Management Group is also asked to inform the IDMC Chair through the IDMC Support Unit of any additional information that they think is relevant to the IDMC review.

The members of the IDMC receive all study documentation ahead of the meeting. This includes: the study protocol, a copy of the case report forms and the most recent study status report the confidential interim analysis report and any other correspondence with the Study Management Group.

6.2 IDMC Meeting

An optional IDMC-only closed session initiates the meeting, restricted to the IDMC members, during which they may discuss their approach to the study at hand.

In an open session, the IDMC may seek information as appropriate from the Study Management Group. During this open session, no confidential information concerning treatment efficacy or other study endpoints may be presented.

The following confidential session is limited to the members of the IDMC and the statistician and clinical research physician who attend to present the confidential part of the interim analysis report, provide clarifications, and answer questions from the IDMC members. When un-blinded, interim results from a blinded study are to be reviewed, an independent un-blinded statistician and the un-blinded clinical research physician attend the confidential session in lieu of the study statistician and clinical research physician. In addition, in this instance, the Head of IDMC Support Unit and the IDMC Support Unit Officer will also not attend the session so that they too remain blind to the study data and results.

An IDMC-only closed session follows which is attended only by the IDMC members. During this session, the IDMC discusses in closed forum and formulates their recommendations regarding the future conduct of the study. The IDMC also decides whether, and if so, what information from the interim analysis report should be disclosed. Information about therapeutic efficacy or safety may only be disclosed in case of recommending study discontinuation, major study modifications or early publication.

Confidential minutes of the IDMC session are written by the EORTC Head of IDMC Support Unit and stored at the IDMC Support Unit after approval by all IDMC members and signature by the IDMC Chair.

6.3 Recommendations of the IDMC

The recommendations for each study are reviewed by all the IDMC members and distributed once approved and signed by the IDMC Chair.

The IDMC reports its recommendations in writing to Study Management Group who forwards it to the Study Steering Committee and other relevant parties (supporting bodies, collaborative groups).

Study modifications triggered by the advice of the IDMC may require protocol amendment. In this case, the IDMC recommendation will be included in the rationale of the study amendment.

6.4 Follow-up on the IDMC recommendations

The final decision to act on the recommendations is the responsibility of the Study Steering Committee (SSC) represented by the Study Coordinator.

The IDMC would generally expect that its recommendations would be endorsed by the SSC unless there is an exceptional reason to do otherwise. If the study steering committee disagrees with the recommendations of the IDMC, the study steering committee, voiced by the study coordinator should formulate a reply to the IDMC within 4 weeks of receipt of the IDMC recommendations and justify their reasons not to follow the recommendations.

The matter will be debated between the IDMC and the study steering committee. In the event that an agreement cannot be reached, the case will be escalated to the Director General and the Chairman of EORTC who will make a final decision.

7 COMMUNICATION WITH THE IDMC

All communication with the IDMC should be addressed in writing to the EORTC IDMC Support Unit (IDMC.sec(at)eortc.be)

Advices regarding the application of the present policy or IDMC processes may be addressed to the Head of IDMC Support Unit via the same email address.

8 REFERENCES

- DAMOCLES study group. A proposed charter for clinical trial Data Monitoring Committees: helping them to do their job well. The Lancet 2005; 365:711-722.
- European Medicines Agency. Guideline on Data Monitoring Committees. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003635.pdf. January 2006
- Food and Drug Administration. Guidance for Clinical Trial Sponsors Establishment and Operation of Clinical Trial Data Monitoring Committees . http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf . 2006.

9 DOCUMENT HISTORY

Version number	Brief description of change	Author	Date
1.0	Initial Release	Richard Sylvester	01 Apr 1999
1.1		Richard Sylvester	01 Jan 2001
1.2		Richard Sylvester	01 Mar 2001
1.3		Richard Sylvester	01 Oct 2002
1.4	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. The choice of external members for a given protocol should be suggested by the Study Coordinator. 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. 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.	Richard Sylvester	29 Oct 2003
1.5	Approval by the EORTC Executive Committee Addition of the IDMC Coordinator	Richard Sylvester	24 Feb 2004

	Agreement between the Group, Data Center and IDMC concerning the choice of external reviewers IDMC members should not review a protocol from a Group where they are an officer at the time of the review Addition of the reference to EORTC Policy 001 on Conflict of Interest IDMC Coordinator will prepare the first draft of the minutes of the meetings.		
2.0	Major revision to include safety review in the scope of the IDMC, remove the notion of DSMB, include the process for adaptive designs and simplify the whole document to reflect the smoother workflow adopted at the last IDMC changeover.	Laurence Collette	25 Mar 2013
2.1	Minor revision to change the terms (IDMC coordinator → head of IDMC), implement the IDMC charter if contractually agreed and the adaption of the process for double blind trial. Various clarifications	Laurence Collette	24 Oct 2013
2.2	Include a timeline of 4 weeks for reaction of the group if they disagree with the IDMC recommendations	Laurence Collette	26 Mar 2014
3.0	Adapt to new IDMC charter. Alignment of terminology "trial" becomes "study", "external expert" becomes "study-specific IDMC member", "Study Management Group" is defined, as well as Study Steering Committee, clarification of conflicts of interest, clarification of process if there is disagreement on the follow-up on the IDMC recommendations. General simplification of the text and organization of the policy. Removal of sections that belong to the SOP. Addition of the charter in appendix to the SOP. Renaming IDMC Unit to IDMC Support Unit	Laurence Collette	15 Jan 2016