

Protection of human subjects participating in medical research

POL002

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1. Objectives

The principal activity of the European Organisation for Research and Treatment of Cancer (EORTC) is to conduct clinical trials that involve human subjects.

This policy document, entitled “*Protection of human subjects participating in medical research*”, is to ensure the protection of the rights, safety and well-being of trial subjects. It provides guidance on how to ensure this protection which pertains to all EORTC activities within the European regulatory framework. Adequate information of each patient and efficient monitoring of drug/treatment safety through pharmacovigilance are a particular focus of this policy.

All research conducted under the auspices of EORTC is performed in compliance with the principles laid down in the Declaration of Helsinki (last amended by the 52nd World Medical Assembly, Edinburgh, Scotland, October 2000).

In addition to the guidelines of the Declaration of Helsinki, EORTC adheres to the principles expressed in ICH-GCP (International Conference on Harmonization - Good Clinical Practice, September 1997). ICH-GCP defines the standards of conduct for clinical research to be followed by EORTC and EORTC investigators. All, the CPMP/ICH/135/95 note from the European Medicines Agency (EMA) and Directives 2001/20/EC and 2005/28/EC, laying down principles and detailed guidelines for good clinical practice, apply.

Any other applicable national requirements are also binding to EORTC and EORTC investigators. This pertains in particular to any national laws, regulations and administrative provisions reflecting EU directives that govern or are applicable to research involving human subjects.

2. Definitions

Declaration of Helsinki: a statement of the World Medical Association that spells out the ethical principles for medical research involving human subjects.

International Conference on Harmonization – Good Clinical Practice (ICH-GCP): an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

European Directives: EU Directives are legislative acts which set minimum requirements that Member States of the European Union are obliged to reflect in national laws, regulations and administrative provisions.

EORTC Board: the steering and executive body of EORTC.

EORTC Data Center: the central trial management unit of EORTC. It provides scientific, logistic and administrative support for the conduct of EORTC trials.

EORTC Data Center Institutional Review Board: a panel responsible for safeguarding the rights and welfare of subjects participating in clinical trials conducted with the support of the EORTC Data Center. 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” (Ref.: POL001).

EORTC Independent Data Monitoring Committee: 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.

3. Core Principles and Procedures

3.1. Protocol approval

All protocols for clinical trials under the auspices of EORTC should state that all research has to be conducted in compliance with the principles of the Declaration of Helsinki.

All study protocols should be approved upfront by the EORTC Protocol Review Committee. The work of the EORTC Protocol Review Committee is governed by the EORTC Procedure Manual “Protocol review and approval” (Ref.: PM51).

All study protocols should be approved by competent authorities (when applicable) and by the leading and/or local ethics committee(s) (as specified by national regulations). Proof of protocol approval by the ethics committee(s) and competent authorities has to be provided to the EORTC Data Center prior to site authorization.

3.2. Adequate information of patients

3.2.1. Template documents for all EORTC trials

EORTC has developed informed consent templates in English language which are reviewed on a yearly basis by the EORTC Data Center Institutional Review Board. These templates ensure that EORTC documents for patient information comply at all times with existing and legally binding requirements. Both the CPMP/ICH/135/95 note from the European Medicines Agency (EMA) and Directive 2005/28/EC, laying down principles and detailed guidelines for good clinical practice, apply.

3.2.2. Master versions for a particular EORTC trial

Protocol-specific informed consent documents are referred to as the “Patient Information Sheet and Informed Consent (PIS/IC)”. The PIS/IC master version for a particular trial in English language is developed from the above-mentioned templates and should provide all necessary information to be communicated to the patient (please also refer to the “Guidelines for writing the informed consent document for an EORTC Trial” (Ref.: WP1107)). Please note that the master version of the PIS/IC in English language is an integral part of the protocol.

A copy of the translated and version-controlled PIS/IC in local language as approved by the ethics committee(s) and competent authorities as applicable has to be provided to the EORTC Data Center. Only after receipt of this document an institution can be authorized to enter patients in a particular trial.

3.2.3. Obtaining informed consent from each patient

Freely given informed consent should be obtained from and documented in writing, signed and dated personally by each patient (or by an individual or juridical or other body authorized under applicable law to consent on behalf of a prospective subject) before he/she is registered/randomized in a study. At registration/randomization the EORTC Data Center prospectively collects proof of each patient’s consent to participate in the trial and in any adjunct research project.

3.2.4. Measures to ensure compliance

The EORTC Board delegates to the Director of the EORTC Data Center all responsibility for monitoring the compliance of institutions with the above-mentioned procedures on patient information. The Director of the EORTC Data Center puts in place appropriate verification procedures.

The Director of the EORTC Data Center has full authority to take the appropriate corrective action (including temporary or permanent suspension of institutions from registration/randomization) whenever non-compliance with these procedures is suspected or proven. The same procedure as the one currently in use for suspected or proven misconduct and/or fraud will be followed. The EORTC Data Center Institutional Review Board will be informed directly about any corrective actions taken by the Director of the EORTC Data Center.

3.3. Enforcement of patients' rights

Patients' rights are enforced and protected by the following:

3.3.1. Protocol approval

All EORTC protocols including consent documents must be approved by ethics committees and competent authorities as applicable.

3.3.2. Adequate information of patients

EORTC protocols provide treating physicians/investigators with all information to ensure that a study is performed at the highest possible standard, with particular attention to the patients' rights and their protection.

In compliance with ICH-GCP, patients in EORTC trials are adequately informed prior to any trial participation. In particular, all patients are informed about the voluntary nature of his/her participation in any trial, confidentiality and protection of his/her data, insurance coverage and the possibility of withdrawal at any time. The principle of patient autonomy is clearly enforced.

3.3.3. Principles applying to translational research

Study protocols may foresee that the patient authorizes storage of and access to samples of his/her biological material for a defined research project. This can be requested as a mandatory or optional adjunct to the clinical trial. Thus, the patient is free to join any proposed research project fully or only in part, depending on the nature of each project. Specific mandatory wording is foreseen in the EORTC PIS/IC templates. In compliance with applicable legislation, approval from an ethics committee should be obtained before the actual start of any such research.

Storage of and access to biological material for future cancer research without a predefined research project also needs to be authorized by each patient. Specific mandatory wording is foreseen in the EORTC PIS/IC templates. Ethics committees, as appropriate (and/or other regulatory body if applicable), will be approached for review and approval prior to the start of any future research project on the patient's stored biological material. Whether or not the patient needs to be re-contacted in order to obtain his/her consent for a future research project will be determined individually, i.e. for each future research project, in compliance with applicable legislation.

3.3.4. Confidentiality and data protection

EORTC constantly checks all its procedures so that compliance with the EU Directive 95/46/EC on the protection of personal data is guaranteed. Personal data are defined as any information relating to an identified or identifiable natural person (data subject). EORTC obeys to the principles of this directive which are transparency, legitimate purpose and proportionality. In order to keep a patient's identity confidential, data collected by EORTC are coded, but not anonymized. Therefore, the individual patient retains all rights to access all data processed about him or her. The data are processed for the explicitly specified and legitimate purpose defined by the study protocol, i.e. that data are used only for the purpose for which they were collected. Data accuracy is ensured through the various EORTC Working Procedures that address data handling, "Data entry" (Ref.: WP1201), "Data management and validation procedures at the Data Center" (Ref.: WP1202), "Monitoring data timeliness" (Ref.: WP1301), "On site data monitoring" (Ref.: WP4801). The use of data is specified by the EORTC Procedure Manual (Ref.: PM13) that addresses the reporting of clinical trials.

3.4. Pharmacovigilance: drug/treatment safety

The protection of human subjects is also promoted by adequate monitoring of drug/treatment safety. In addition to collecting classical safety data, EORTC has created a Pharmacovigilance Unit (PVU). The PVU is a department within the EORTC Data Center in charge of recording and reporting all Serious Adverse Events (SAE or Serious Adverse Drug Reactions (SADR)) occurring in EORTC trials. In compliance with regulatory requirements, all SAEs are communicated within 24 hours to the study team at the EORTC Data Center, to the study coordinator/study principal investigator, to investigators at participating institutions and any other partners as applicable. SAE handling is governed by the “Management of Serious Adverse Events” (Ref.: WP1203).

In addition, all safety aspects of each on-going EORTC trial are constantly reviewed by a Data Safety Monitoring Board (DSMB), consisting of the Coordinating Physician at the EORTC Data Center and the Study Coordinator for the trial.

If specified by the study protocol (mainly for large phase III trials) or in case suspicious safety issues emerge, the support of EORTC’s Independent Data Monitoring Committee (IDMC) can be requested (please refer to EORTC (Ref.: POL004) and the “Practical implementation of EORTC Policy 004 for Independent Data Monitoring Committees” (Ref.: WP5201).

Given the above-mentioned safeguard procedures and structures, EORTC is confident that any exposure of patients to an unacceptable level of risk will be detected early on so that all appropriate action, including early termination of a trial, can be taken without undue delay.

3.5. Specific annotations

3.5.1. The EU Clinical Trials Directive 2001/20/EC

As of 2006, the EU Clinical Trials Directive 2001/20/EC and related guidances have been implemented into national laws, regulations and administrative provisions of the EU member states. The purpose of this directive is to design, conduct, record and report clinical trials according to internationally recognized principles of good Clinical Practice (GCP), to protect clinical trial participants and to generate accurate and verifiable data from trials. EORTC constantly checks all its procedures so that compliance with this directive is guaranteed, with particular attention to the protection of human subjects.

3.5.2. The EU Good Clinical Practice Directive 2005/28/EC

Practical aspects of the Directive 2005/28/EC are being addressed by related guidances in development. EORTC has however taken steps to ensure that the principles of Directive 2005/28/EC are being adhered to by its procedures. Specific modalities for non commercial trials are being addressed and will be implemented when released. EORTC follows the currently on going implementation process of this Directive and related documents into national laws.

3.5.3. EORTC collaboration with NCI cooperative groups

Within the scope of its guidelines for international trials, NCI-CTEP (Cancer Therapy Evaluation Program) requires that the EORTC Data Center comply with some requirements of the National Cancer Institute (NCI) and the US Office for Human Research Protection (OHRP), in addition to all applicable European and national legislation.

Among these requirements the need for the EORTC DC to hold an OHRP - approved assurance (currently called a Federal Wide Assurance-FWA). This assurance allows performance of trials for which EORTC exchange data with NCI supported cooperative groups or otherwise benefit from NCI resources.

Since 2000, the EORTC Data Center had been holding CPA T4631 which was replaced by a new registration (documented in Working Procedure “Collaboration with North America. Specific issues related to intergroup trials in collaboration with North-American groups” (Ref.: WP5106): FWA00004444 (which is linked to the EORTC Data Center Institutional Review Board: IRB00003305).

The EORTC Data Center Institutional Review Board meets at least annually to review all projects in collaboration with US groups as required by NCI-CTEP and OHRP.

4. List of abbreviations

Abbreviation	Full name
CTEP	Cancer Therapy Evaluation Program (of NCI)
CPA	Cooperative Project Assurance (of NCI)
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
FWA	Federal Wide Assurance (of NCI)
ICH-GCP	International Conference on Harmonisation – Good Clinical Practice
IDMC	Independent Data Monitoring Committee (of EORTC)
NCI	National Cancer Institute (United States of America)
NCI SCG	NCI Sponsored Cooperative Group
OHRP	Office for Human Research Protection (United States of America)
PIS/IC	Patient Information Sheet / Informed Consent
PM	Procedure Manual (of EORTC)
PVU	Pharmacovigilance Unit (of EORTC)
SAE	Serious Adverse Event
SADR	Serious Adverse Drug Reaction
WP	Working Procedure (of EORTC)

5. References

Document title	Reference
Directive 2001/20/EC (Clinical Trials Directive)	
Guideline for Good Clinical Practice (Note for Guidance on Good Clinical Practice CPMP/ICH/135/95)	via the EMEA home page www.emea.eu.int/Inspections/GCPgeneral.html or
Directive 2005/28/EC laying down principles and detailed guidelines for good clinical practice	www.eortc.be/Investigators/default.htm
Declaration of Helsinki	www.wma.net/e/policy/b3.htm
EORTC Policies	<i>All EORTC policies are available online at:</i> www.eortc.be/Services/Doc/policies/default.htm
EORTC Working Procedures	<i>All EORTC Working Procedures are available via the EORTC intranet.</i>
EORTC Procedure Manuals	<i>All EORTC procedure manuals are available via the EORTC intranet.</i>
EORTC templates for PIS/IC	<i>All EORTC templates for PIS/IC are available via the EORTC intranet.</i>