INVESTIGATORS' HANDBOOK

4th edition

Version 4.0

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Foreword

For almost half a century, thanks to its network of institutions, the EORTC has performed clinical research towards improving the survival of the cancer patient. To reinforce its position as a leading independent cancer research organisation and to include sophisticated translational research, genetic tests, targeted therapies, imaging technologies and innovative treatment strategies, the EORTC has undergone substantial reorganisation. This has included transforming the Data Centre into EORTC Headquarters with the aim of providing an optimal infrastructure for the support of the EORTC Groups. The creation of EPOD (Early Project Optimisation Department), the Project and Budget Development Department and NOCI (Network of Core Institutions) can be seen as very good examples of the new way forward.

Without the deep involvement of all of the EORTC Groups and their Investigators, and of EORTC Headquarters, the EORTC as an organisation would not exist, and neither would it be able to implement EORTC strategy and innovative approaches.

To reinforce the collaboration between EORTC Headquarters and the EORTC Investigators, this 4th edition of the Investigators' Handbook has been prepared. In this Handbook we have tried to provide a full, but concise, description of the new organisation that is the EORTC, while also describing the procedures to be followed to obtain optimal quality data.

In a nutshell, we want to simultaneously reduce unnecessary bureaucracy and collaborate fruitfully with all EORTC Investigators to reach rapid patient enrolment in a Good Clinical Practice environment.

We hope that you will find this Handbook 'user friendly', and that it covers enough information about the processes that need to be taken into consideration when developing future clinical studies with us.

We look forward to much new and renewed collaboration and take this opportunity to thank you in advance for your dedication and commitment.

Remy von Frenckell, Director of Methodology and Operations
Denis Lacombe, Scientific Director
Françoise Meunier, Director General

Acknowledgments

Through the earlier Editions to this 4th Edition, the EORTC Investigators' Handbook is the result of a joint effort, and we owe a great debt to a large number of people, including:

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1. What is the EORTC?

The European Organisation for Research and Treatment of Cancer (EORTC) was created in 1962 as an international cancer research organisation under Belgian law.

1.1. The EORTC Mission

"To develop, conduct, coordinate and stimulate translational and clinical research to improve the standards of care by increasing survival and patient quality of life."

The ultimate goal of the EORTC is to improve the standard of cancer treatment. This is to be achieved through the testing of more effective therapeutic strategies based on drugs, surgery and/or radiotherapy that are already in use, and also through the development of new drugs and other innovative approaches.

This is accomplished mainly through large, multicentre, prospective, randomised, phase III clinical trials. In this way, the EORTC facilitates the passage of experimental discoveries into state-of-the-art treatments.

The EORTC is based in Brussels, Belgium, at the EORTC Headquarters, from where its various activities are coordinated and run. However, the EORTC is both multinational and multidisciplinary, and the present EORTC Network comprises over 300 cancer centres in over 30 countries, which include:

- some 2,500 collaborators, from all disciplines involved in cancer treatment and research;
- some 5,000 new patients who are enrolled each year;
- some 50 trials that are permanently open to patient entry;
- some 50,000 patients who are in follow-up;
- a database of more than 150,000 patients.

Through translational and clinical research, the EORTC offers an integrated approach to drug development, drug evaluation programmes and medical practices. These cover a whole range of studies from early drug development to large-scale phase III clinical trials and quality of life evaluation.

The EORTC is a research organisation that links a network of qualified pre-clinical scientists and oncologists through voluntary collaborations of approximately 20 multidisciplinary groups.

1.2. Clinical trials and the EORTC

Clinical trials conducted by the EORTC have a known label of independency from any commercial conflict.

Clinical trials will be allowed to carry the EORTC Clinical Trial label and will be allocated EORTC resources only if they fulfil the following conditions:

- The clinical trial has undergone extensive scientific peer review and has been approved by the EORTC Protocol Review Committee (PRC);
- The full clinical trial database and associated data are held by and maintained at EORTC Headquarters or by an independent group;
- The statistical analysis for the full clinical trial dataset is performed by EORTC Biostatisticians or by an independent research group;
- The publication is prepared through the EORTC;
- EORTC or other independent group should organise the Independent Data Monitoring Committee (IDMC);
- Biological material collected alongside EORTC Clinical Trials is managed by an independent Steering Committee.

1.3. EORTC scientific strategy and priorities

Although development of new and innovative therapies is critical for improving cancer care, the primary interests of the EORTC remain with clinical trials that investigate strategic therapeutic questions that will influence medical practice or will fundamentally improve the understanding of a disease.

The EORTC has built an important part of its success on the multidisciplinary approach to cancer treatment, and this remains the principal strength of the EORTC. However, the present-day multidisciplinary approach to research into cancers and their treatment in the clinic also encompasses pathologists and laboratory scientists through translational research programmes that must be integrated into clinical trials. Hence translational research is an essential component of the EORTC Scientific Strategy, and it contributes to the ability to distinguish between a 'simple' trial and high quality academically driven studies.

The **EORTC Scientific Strategy** is defined by the EORTC Board and encompasses the following types of clinical trials:

- **Large phase III academic trials aimed at changing the standard of care;**
- **Clinical trials with a strong and methodologically sound translational research component;**
- **Prospective clinico-genomic trials;**
- **Clinical trials addressing rare tumor types.**

For the EORTC Executive Committee to determine the level of importance of each new trial proposal within the global strategy of the EORTC, for the EORTC Board to assign priorities when there is a competitive process for resources and/or funding, and for the EORTC Scientific Audit Committee (SAC) to review the global performance of each EORTC Group, three main trial categories have been defined within the priorities of the EORTC. With category 1A representing the highest priority for EORTC involvement and category 3C the lowest, these three categories can be summarised as follows:

Category 1:

- **A:** Randomised phase III trials that are designed to answer a question that directly contributes to defining a new standard of care as well as other trials with a strong multidisciplinary component and including trials prepared and run jointly by different EORTC Groups;
- **B:** Randomised phase III trials with a strong targeted translational research component that could provide a fundamental advance in the understanding of a particular disease;
- **C:** Intergroup randomised phase III trials not led by an EORTC Group but corresponding to the criteria listed under categories 1A and 1B.

Category 2:

- **A:** Randomised phase II trials clearly designed as a preparatory step for a subsequent phase III trial. Registration trials with a clinically relevant question and a translational research component;
- **B:** Phase I and phase II trials involving drugs with novel mechanisms of action and with commitment from a company for vertical drug development within the EORTC (including combination studies with radiotherapy and biological agents).

Category 3:

- **A:** Randomised phase III trials that do not meet the requirements of the above categories;
- **B:** Randomised phase II trials with a weak or no translational research component. Phase I and single-arm phase II trials using drugs with truly new mechanisms of action, but for which a plan for subsequent development within the EORTC is lacking;
- **C:** Other phase I and single-arm phase II trials.

1.4. EORTC cooperation with the pharmaceutical industry

Improving treatment strategies for cancer patients involves the development of new drugs, and the development of new drugs within the EORTC often involves cooperation with the pharmaceutical industry as an industrial partner/ sponsor.

This cooperation can range from full sponsoring of a trial by a pharmaceutical company to educational grant(s) and/or limited logistic support in the form of the supply of the drug(s) under investigation.

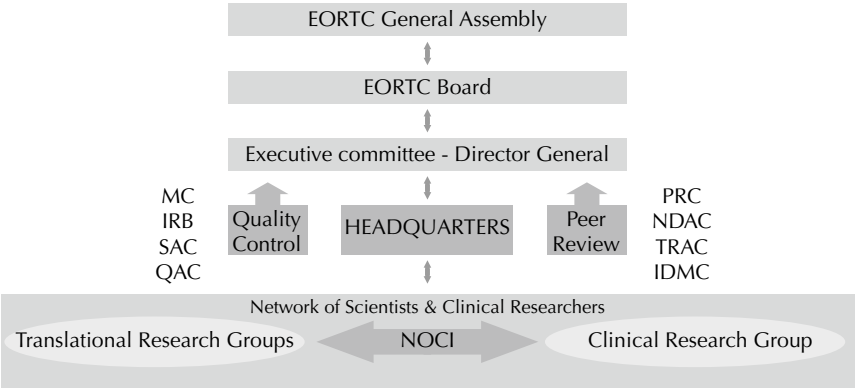
In all cases, all of the EORTC independency label requirements are fully applicable (see 1.2 Clinical trials and the EORTC).

For such trials, the EORTC Group, EORTC Headquarters and the industrial partner will together define the exact responsibilities of all of the parties concerned, which will then be formalised into a contract that needs to be approved and signed by the EORTC Group Chair and by one of the Directors of EORTC Headquarters.

Basic EORTC requirements :

- Peer review process / approval (PRC)
- Database control by EORTC
- Analysis of primary endpoints / IDMC
- Publication of primary analysis
- Control of biosamples

2. EORTC structure and organisation



Definitions:

PRC: Protocol Review Committee: ensures independence of EORTC studies.

NDAC: New Drug Advisory Committee: evaluates new agents for the EORTC portfolio.

TRAC: Translational Research Advisory Committee: ensures relevance and quality of translational research programmes.

IDMC: Independent Data Monitoring Committee: ensures methodological and ethical validity of on-going protocols.

MC: Membership Committee: verifies the qualifications of EORTC applicants.

IRB: Institution Review Board: verifies the ethical functioning of EORTC Headquarters.

SAC: Scientific Audit Committee: ensures the quality of scientific and medical contributions that EORTC Groups make to the scientific community.

QAC: Quality Assurance Committee: ensures the adequate functioning of the EORTC Network and promotes quality assurance research.

NOCI: Network of Core Institutions

3. Who are the EORTC Investigators?

All EORTC Investigators are members of one or several EORTC Groups or task forces.

EORTC CLINICAL RESEARCH DIVISION

Tumor-specific groups:

- Brain Tumor
- Breast Cancer
- Children's Leukemia
- Lung Cancer
- Leukemia
- Lymphoma
- Melanoma
- Soft Tissue and Bone Sarcoma
- Gastro-Intestinal Tract Cancer
- Genito-Urinary Tract Cancer
- Gynaecological Cancer
- Head and Neck Cancer

Other clinical groups

- Infectious Diseases
- Quality of Life
- Radiation Oncology

Task Forces

- Elderly
- Cutaneous Lymphoma

EORTC TRANSLATIONAL RESEARCH DIVISION

Comprises three groups:

- Pharmacology and Molecular Mechanisms
- Functional Imaging
- Pathobiology

How to recognize studies from an EORTC Group

All EORTC groups are assigned a two-digit number at their creation. This number is used to identify the studies carried out by these groups.

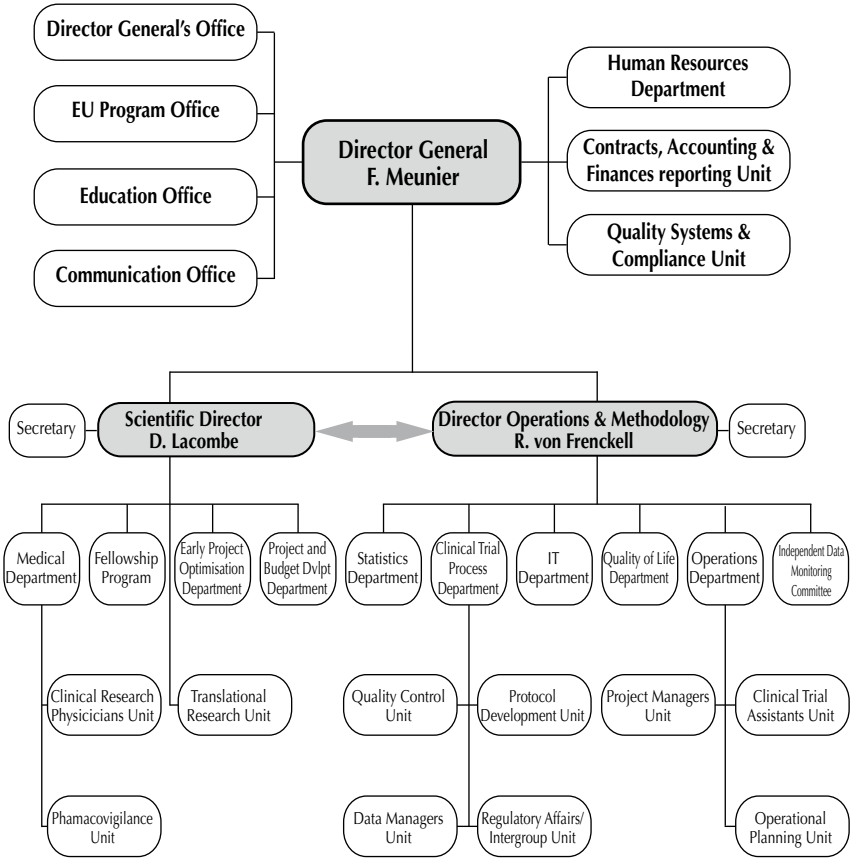
06 EORTC Leukemia Group
08 EORTC Lung Cancer Group
10 EORTC Breast Cancer Group
18 EORTC Melanoma Group
20 EORTC Lymphoma Group
21 EORTC Cutaneous Lymphoma Task Force
22 EORTC Radiation Oncology Group
24 EORTC Head & Neck Cancer Group
26 EORTC Brain Tumor Group
30 EORTC Genito-Urinary Tract Cancer Group
40 EORTC Gastro-Intestinal Tract Cancer Group
55 EORTC Gynaecological Cancer Group
58 EORTC Children's Leukemia Group
62 EORTC Soft Tissue Bone Sarcoma Group
65 EORTC Infectious Diseases Group
75 EORTC Elderly Task Force
90 EORTC NOCI

Each study has a five-digit study number that starts with these first two digits that identify the EORTC Group, followed by the last two digits of the year that the study was submitted to the EORTC Executive Committee, followed by the sequential number of the project for the year of application

4. Who is EORTC Headquarters?

EORTC Headquarters is a unique central facility that provides scientific, methodological, legal and operational support to the EORTC network of investigators. EORTC Headquarters offers a comprehensive approach to translational research and clinical research, and acts as a guardian with regards to the principles of independence and standar ds of quality for conducting cancer clinical trials.

EORTC Headquarters
Organistational / reporting chart



5. What are the strengths of the EORTC?

5.1 The EORTC Network

Through the full organisation that is the EORTC, it can be seen that the main EORTC strength lies in what has here been referred to on occasions as the 'EORTC Network'. This forms the basis of a network of oncology specialists; it also forms the basis of something much larger than its individual elements:

A network of scientists:

- Experienced EORTC Investigators and Study Coordinators;
- Experienced translational research and laboratory scientists

A network of Institutions:

- A network of excellence, including the EORTC Groups, and more recently, the Network of Core Institutions (NOCI);
- Access to high patient accrual;
- Access to rare cancer subpopulations;
- Access to multi-tumour studies.

A growing wealth of continued multidisciplinary knowledge generating new hypotheses from trial to trial, and pushing forward the standards of care

5.2 EORTC Headquarters

EORTC Headquarters provides the EORTC Groups with a comprehensive approach to cancer research and to the management of clinical trials for cancers. EORTC Headquarters also includes experts in all of the disciplines that are required, including not only oncology, but also biostatistics, regulatory affairs and methodologies.

Finally, EORTC Headquarters ensures the highest possible quality of EORTC Clinical Trials from the independent, objective and academic points of view, and from their design to their final analysis, and to the publication of the final results.

Project development:

- A focused port of entry into all EORTC projects through the Early Project Optimisation Department (EPOD);
- The backing of the EORTC EPOD and EORTC Headquarters in the strategic development of EORTC Clinical Trials;
- Provision of an integrated approach to any interface with industry.

Study conduct:

- A dedicated team provided through EORTC Headquarters;
- A high quality platform for the coordination of clinical trials in collaboration with industry;
- Validated tools for data management activities and statistical analyses.

5.3 The EORTC Board and Committees

The Board and Committees of the EORTC consist of leading experts in oncology who define the EORTC policies and strategies, and who provide the peer review process for all projects conducted with the EORTC label.

- EORTC New Drug Advisory Committee (NDAC)
- EORTC Translational Research Advisory Committee (TRAC)
- EORTC Protocol Review Committee (PRC)
- EORTC Scientific Audit Committee (SAC)
- EORTC Quality Assurance Committee (QAC)
- EORTC Independent Data Monitoring Committee (IDMC)
- EORTC Membership Committee (MC)
- EORTC Headquarters Institutional Review Board (IRB)

5.4 The NOCI Consortium

Within the EORTC, a recent initiative has seen the setting-up of the Network of Core Institutions, or NOCI. NOCI is a network of institutions that offers an integrated infrastructure that can assure clinical trials with complex designs that have a more specific focus on translational research.

The NOCI mission is to optimise the development of new treatments for cancers, through:

- an understanding of the biology of a disease;
- an understanding of the mechanisms of action of tested treatments;
- the determination of host/ tumour-related molecular discriminants that are predictive of toxicity or activity.

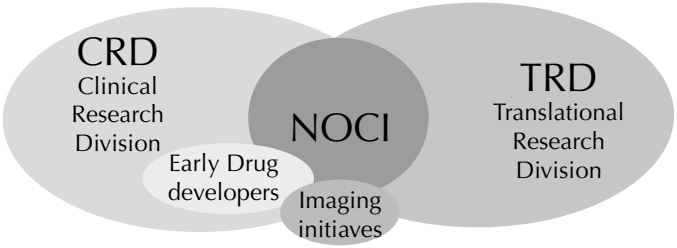
Purpose of the NOCI Consortium Agreement

> Defines the general rules for performing NOCI projects, including intellectual property, access rights and publication.

> Defines the rules for allowing the systematic comprehensive centralised collection of bio-samples from selected EORTC Trials.

> Defines the rules for making these high quality bio-sample collections and the attached clinical dataset available to the NOCI Consortium to answer challenging scientific questions.

A Network of Excellence



From early phase exploratory studies
- multi-tumor, multi-target, combinations, subpopulations ...

To large phase III confirmatory clinical trials
- closing schedule, multi-modality, multi-drug ...

NOCI is open to EORTC Institutions upon invitation from the NOCI Steering Committee or application of the EORTC Institution itself to be a part of NOCI. For an EORTC Institution to become a part of NOCI, they need to satisfy the NOCI standards of either a good clinical research track record with the EORTC, or laboratory research that has a good translational research infrastructure with recognized specific expertise. They also need to sign the NOCI Consortium Agreement, and it is desirable that they have a high patient accrual capacity that covers several disease indications. With participation in any specific NOCI project, a NOCI Institution also needs to sign a NOCI Project Agreement.

At present, the NOCI Consortium includes 23 centres across 12 countries in Europe. Of particular note, NOCI has been set-up in such a way as to cut across the boundaries of the EORTC Groups while complementing the EORTC Group structure. This has thus allowed the development of specific technical expertise that is now being further integrated into the pro-active project development plans of the Early Project Optimisation Department (EPOD) and the Project and Budget Development Department at EORTC Headquarters.

6. How are multidisciplinary expertise and international cooperation organised?

6.1 Cooperation within the EORTC

Within the EORTC, the cooperation between the different groups is known as "Intra-Group" collaborations.

In most of cases, these collaborations are between a disease-oriented EORTC Group, e.g. Breast Cancer Group, and a treatment-oriented EORTC Group, e.g. Radiation Oncology Group. At the start of the study, two collaborating EORTC Groups will agree on which will be the leading group in the collaboration.

Any "Intra-Group" study carries a double study number, where the first number indicates the leading group (eg. 22043-30043: lead group, Radiation Oncology Group; collaborating group, Genito-Urinary Tract Cancer Group).

6.2 EORTC cooperation with other clinical research groups

Cooperation with other clinical cooperative groups, both within and outside of Europe, can be an efficient way of achieving research objectives. In such cases, the EORTC will support the participation of the EORTC Groups in joint clinical trials with other organisations that have similar objectives and standards of quality according to the criteria defined by the EORTC General Assembly.

The EORTC policy entitled, 'Intergroup Trials Involving Non-EORTC Groups' (Policy POL005; see EORTC website) outlines the three main principles that have been adopted by the EORTC Board concerning such cooperation with the most important points being the following:

- There can only be one official clinical trial protocol, which must be used by all of the participating clinical groups;
- There can only be one set of Case Report Forms (CRFs), which must be used by all of the participating clinical groups;
- The CRFs from all of the participating clinical groups must be collected into one coordinating Data Centre (e.g. EORTC Headquarters) for entry into the database.

These rules aim to maintain the identities of all of the partners and to credit all of the efforts involved. They are recognized as international standards for intergroup collaborations by many major cooperative groups throughout Europe, the US and other parts of the World.

EORTC Policy also describes a framework for the development and conduct of intergroup trials according to these principles. The EORTC Policy entitled, 'Accrual Accounting in Intergroup Trials' (POL010; see EORTC website) describes how patient accrual within intergroup trials involving an EORTC Group will be counted for EORTC membership. This EORTC Policy specifically addresses the situation of investigators who are members of several groups cooperating in the same clinical trial.

7. Why should you join the EORTC?

To actively contribute and benefit from a network of multidisciplinary scientists at the cutting edge of cancer clinical trial methodology and at the forefront of new standards of care

With the backing and support of the EORTC, the EORTC Groups undertake clinical trials and/or translational research in all types of cancer and through multidisciplinary approaches respecting the EORTC Scientific Strategy and Policies. Of note, these trials need to be approved by the EORTC Executive Committee and the EORTC Protocol Review Committee.

Each EORTC Group has its own statutes, and each Group's Chair and Officers are elected through the EORTC Group meetings for a three-year period. The Chair represents the EORTC Group within the EORTC General Assembly (further details regarding their tasks and responsibilities can be found through the EORTC website "Summary of EORTC Group Chairmen Tasks and Responsibilities").

7.1 Access to EORTC Group meetings

The meetings of EORTC Groups are the principal communication tool between EORTC members. Each EORTC Group organises a plenary meeting of its members at least twice a year. It is during these meetings that the Group members have the opportunity to discuss the research strategy of any given EORTC Group, to set up new projects, and to follow the on-going clinical trials and projects run through the EORTC Group and EORTC Headquarters.

This is also where the Group members will be kept informed of decisions made by the EORTC Board and Committees as communicated via the EORTC Group Chair. Members are invited to attend all of the meetings of the EORTC Groups that they have joined, and some Groups will also have open sessions that can be attended by non-members.

Information regarding these EORTC Group meetings is available from the relevant Group Chair or Secretary, and their dates and locations are listed on the EORTC website.

There is also the EORTC Groups Annual Meeting (EGAM), which provides the opportunity for members of different EORTC Groups to exchange ideas and experience and to define common strategies for cancer research. EGAM includes open sessions where the activities of the different EORTC Groups can be presented, and a plenary session where the general EORTC strategies and achievements are discussed.

7.2 Participation in EORTC Group activities

Once you become an EORTC member, it is expected that you contribute to the projects within your chosen EORTC Groups, which should also involve attendance at the Group meetings. Most importantly, an EORTC Investigator is expected to enter patients in the EORTC Clinical Trials conducted by these EORTC Groups. Furthermore, to enable the smooth running of the EORTC Groups and their EORTC Clinical Trials, an EORTC Investigator is also expected to respond to inquiries made by the EORTC Groups and/or EORTC Headquarters within the required timeframe.

All EORTC Clinical Trials are multidisciplinary and EORTC Investigators should be supported at each site by a multidisciplinary team.

7.3 EORTC Courses and Conferences

Although they are available to EORTC members and non-members alike, the EORTC organises regular EORTC Courses on clinical trial methodology (e.g. 'One-Day Introduction to EORTC Trials', Statistics for Non-Statisticians) and Scientific Conferences, either alone, or in cooperation with other organisations (e.g. EORTC-NCI-AACR, EORTC-NCI-ASCO Annual Symposia). The lists for these are available through the EORTC website.

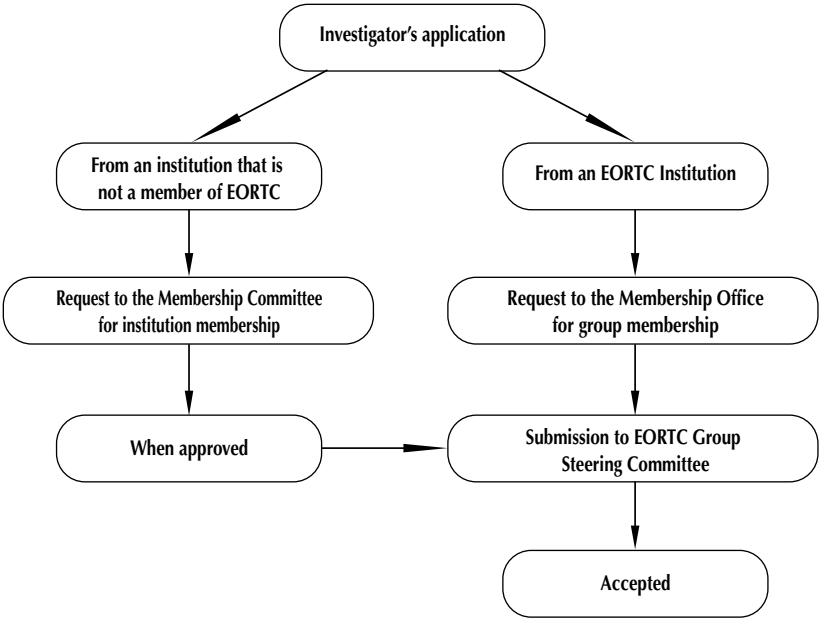
8. How do you join the EORTC?

Any new Applicant needs to submit a membership application to the EORTC Membership Committee. To become a member of an EORTC Group, a general prerequisite is Institutional approval. If a new investigator belongs to an EORTC Institution, the process is simplified and the request can proceed following a recommendation from the Membership Committee to the Steering Committee of the group.

If the Applicant is not an EORTC member, then the applicant must complete a questionnaire concerning his/her Institution and professional interests in the fields of cancer research.

Once the EORTC Membership Committee approves the qualification of an Institution, an individual becomes an associate member to the EORTC. Applicants from new Institutions should apply for participation in at least two EORTC Groups.

After evaluation by the EORTC Membership Committee, their recommendations will be forwarded to the relevant EORTC Groups, the Group Steering Committee will also need to agree on the group membership.



9. EORTC Affiliated Institutions

The EORTC can also grant recognition of Affiliation to Institutions or Departments that are actively participating in EORTC Clinical Trials. The criteria applied for Affiliation Institution are: participation in at least three EORTC Groups, with recruitment of 75 patients over a period of three years, with a minimum of 15 patients entered in EORTC Clinical Trials per year.

Institutions that reach these qualifications on recruitment through only two EORTC Groups are granted the Affiliated Department status.

10. What is expected from an EORTC Investigator?

10.1 Qualifications of EORTC Investigators

The International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) Guidelines (1997) requires that:

"All investigators (participating in a trial) should be qualified by education, training and experience to assume responsibility for the proper conduct of the trial. They should provide evidence of such qualifications by means of an up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the Institutional Review Board/ Independent Ethics Committee (IRB/IEC), and/or the Regulatory Authority(ies)."

10.2 Standards of conduct for EORTC Investigators

All EORTC Investigators should comply with the EORTC Standards of Conduct for Principal Investigators described in this section. This provides an overview of the responsibilities that an EORTC Principal Investigator (PI) accepts when they enter a patient in an EORTC Clinical Trial. The main points are as indicated here, and further details can be obtained through the EORTC website.

The EORTC Investigator/ PI:

- agrees to work according to the principles of Good Clinical Practice (GCP), as listed in the ICH-GCP Guidelines;
- will provide EORTC Headquarters and the relevant EORTC Groups with any documentation that is required prior to the activation of their institution as an EORTC Institution;
- accepts and respects the conflict of interest/ confidentiality policy/ principles (see section 1.2) of the EORTC. The PI will thus need to be a signatory to this policy, and also to sign the Protocol Commitment Statement that accepts that they will follow and respect the procedures set up as part of any particular EORTC Protocol;
- accepts responsibility for the conduct of an EORTC Clinical Trial at their trial site, as the leader responsible for the EORTC Clinical Trial team. The PI keeps all of their units involved in an EORTC Clinical Trial informed and takes responsibility for any initiatives undertaken by the local research staff, including all co-Investigators;
- ensures that adequate Informed Consent documents are obtained for each patient according to the ICH-GCP Guidelines. The Informed Consent documentation must be filed and made available on request for verification at any time by authorised personnel. The PI also ensures that the patient and/or their legal representative receive a copy of the Patient Information Sheet and the Informed Consent (PIS/IC) documentation after it has been signed by all parties;

- ensures that accurate clinical data and answers to respective queries from the EORTC Data Management and Pharmacovigilance Units are provided to EORTC Headquarters following the schedule defined in any EORTC Protocol in which they are involved;
- ensures that patient safety is protected, and promptly reports any safety issues according to protocol;
- accepts the provision of unrestricted access for EORTC Headquarters representatives to the clinical files of patients entered in EORTC Clinical Trials for the purposes of the monitoring/ auditing of these EORTC Clinical Trials;
- ensures that there is appropriate follow-up of all patients who have been entered in any EORTC Clinical Trial, and that this will be organised until patient progression/ death (or any other event, as defined by the EORTC Protocol);
- ensures that an adequate transfer of responsibility is arranged should they move to another hospital or retire. The PI also ensures that EORTC Headquarters and the relevant EORTC Groups will be informed should such a transfer of responsibility be necessary.

10.3 Participation in an EORTC Clinical Trial

When an EORTC Investigator agrees to participate in an EORTC Clinical Trial, the EORTC Investigator becomes the person responsible for this EORTC Clinical Trial for his/her Institution.

In the same way as the EORTC Investigator acts as the contact person for their Institution, a contact person is also appointed at EORTC Headquarters to deal with all communications concerning an EORTC Investigator and any specific EORTC Clinical Trial; this person is the EORTC Project Manager.

The EORTC Headquarters team will contact the EORTC Group members to determine their interest at the time of the production of the outline submission to the EORTC PRC.

The EORTC Headquarters team will guide interested EORTC Group members through their application for participation to an EORTC Clinical trial.

10.4 Protocol adherence in an EORTC Clinical Trial

As indicated in the ICH-GCP Guidelines, an EORTC Investigator should carry out an EORTC Clinical Trial in full compliance with the EORTC Protocol as agreed upon with the sponsor, and approved by the relevant Ethics Committee and the national Regulatory Authorities. Indeed, in signing the Study Acknowledgement/ Commitment Statement form, an EORTC Investigator agrees to comply with the EORTC Protocol and to carry it out according to the ICH-GCP Guidelines or their national regulations, whichever provides greater protection for the patient.

No deviation from, or change in an EORTC Protocol can be implemented by the EORTC Investigator without the prior informing of and agreement from EORTC Headquarters and the approval of the relevant Ethics Committee. Any deviation from an EORTC Protocol should be documented and explained by the EORTC Investigator, or by a person designated by the EORTC Investigator.

Only under exceptional circumstances can an EORTC Investigator implement a deviation from, or change in, an EORTC Protocol: where it becomes necessary to remove an immediate hazard or harm to the participating patient. As soon as reasonably possible, the EORTC Investigator should inform both EORTC Headquarters and the local Ethics Committee, whereupon an agreement on an amendment to the EORTC Protocol can be provided through EORTC Headquarters, if applicable.

Any such amendment to an EORTC Protocol (see also section 11.4) will be submitted by EORTC Headquarters as soon as reasonably possible to:

- The EORTC PRC for approval;
- The relevant Ethics Committee for approval/ favourable opinion;
- The national Regulatory Authorities.

An EORTC Investigator can be excluded from further participation in an EORTC Clinical Trial (and in further EORTC Clinical Trials) if they do not follow the EORTC Protocol.

10.5 Documentation in an EORTC Clinical Trial

According to the ICH-GCP Guidelines, the essential documents in any clinical trial are those that individually and collectively allow the evaluation of the conduct of the clinical trial and the quality of the data produced.

Therefore, the documentation of all actions and decisions during an EORTC Clinical Trial should be the most important task of the EORTC Investigator. For example, the information provided in the patient Case Report Forms (CRFs) should be correctly documented in the medical and/or nursing file(s) of the patient (the source documents), and retained at the local EORTC Institution for the duration required by ICH-GCP Guidelines.

Furthermore, it is well recognized that the availability of written procedures for different activities performed in any organisation improves its efficiency. Indeed, in the field of clinical research, GCP guidelines indicate that management and analysis of clinical trials should be carried out according to predefined standard procedures.

10.6 The use of the EORTC Case Report Form

The EORTC CRFs are specifically designed for each and every EORTC Protocol, to facilitate the collection of all of the required information, so as to obtain a valid answer to each protocol question

The EORTC Investigator should ensure the accuracy, completeness, legibility and timeliness of the data reported to the sponsor (i.e. EORTC Headquarters) in the CRFs, and in all of the required reports. The full schedule for the submission of the various forms is clearly outlined in the EORTC Protocol.

EORTC Headquarters monitors the situation and regularly requests that any missing forms from any given EORTC Investigators/ Institutions are completed and sent in according to schedule.

Increasingly, electronic CRFs are being used in EORTC Clinical Trials, where patient data can be submitted electronically via the internet though the Visual Information System for Trial Analysis (VISTA)/ Remote Data Capture (RDC) website.

As of March 2009, all new EORTC studies will use remote date capture.

10.7 Patient safety in an EORTC Clinical Trial

In all clinical trials, the monitoring of incidence and seriousness of adverse events during and after protocol treatment is a requirement of the ICH-GCP Guidelines. Furthermore, the conduct of all clinical trials is subject to the EU Clinical Trial Directive (2001/20/EC), which indicates that the Competent Authorities must be informed of any Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring in a clinical trial. Each European country must respect this EU Clinical Trial Directive, although the way that it is implemented into national laws differs from country to country. Furthermore, all clinical trials need to work according to the principles and detailed guidelines of Good Clinical Practice set out in the EU GCP Directive (2005/28/EC).

Therefore, to ensure patient safety and in accordance with ICH-GCP Guidelines and these EU Directives, there is the need to monitor all adverse events that occur in the patient physical and biological status during an EORTC Clinical Trial (and, indeed, during any clinical trial).

There are five levels of 'adverse events' that can occur during patient treatment, and these can be defined as follows:

- **Adverse Events** (AEs): Any unfavourable and unintended diagnosis, symptom, sign (including laboratory findings) or disease that occurs during a study (if absent at baseline) or appears to worsen (if present at baseline). These may or may not be related to the treatment or procedure.

- **Adverse Drug Reactions** (ADRs): AEs that imply a relationship to a treatment, and thus specifically related to toxicity of the treatment.

- **Serious Adverse Events** (SAEs): AEs that may or may not be related to the treatment or procedure, but that are considered as serious as they result in:
  - death;
  - a life-threatening event;
  - a permanently disabling event;
  - inpatient hospitalisation or prolongation of existing hospitalisation;
  - a congenital anomaly/ birth defect;
  - other medically important conditions.

- **Serious Adverse Drug Reactions** (SADRs): SAEs that imply a relationship to a treatment, and are thus specifically related to toxicity of the treatment.

- **Suspected Unexpected Serious Adverse Reactions** (SUSARs): SAEs that are suspected to be caused by the investigational medicinal product and that are not expected according to the reference document (Investigators' Brochure [IB] or Summary of Product Characteristics [SmPC]) used for the clinical trial protocol.

Within an EORTC Clinical Trial, AE reporting is the responsibility of the EORTC Investigator at each EORTC Institution that has patients enrolled in an EORTC Clinical Trial. There is thus the need to gather the supporting evidence of any AEs and to complete the appropriate AE form.

With respect to SAEs, the full responsibilities of EORTC Investigators/ Data Managers on sites and EORTC Institutions that have patients enrolled in an EORTC Clinical Trial are detailed in every EORTC Protocol.

To satisfy the specifications of the EU Directives, SAEs must be reported within 24 hours of the initial observation of the event, and hence by fax to the EORTC Pharmacovigilance Unit (PVU), with the completed SAE forms returned to the EORTC PVU within seven calendar days.

These SAEs should be recorded from patient registration to 30 days after the last treatment administration, and subsequently only study-related SAEs must be reported to the trial sponsor.

11. The Genesis of an EORTC Trial

11.1 The origins of an EORTC Clinical Trial

The usual avenues for the origins of a proposal that can lead to an EORTC Clinical Trial include:

- EORTC Group(s)
- EORTC partners
- The EORTC Early Project Optimisation Department
- Pharmaceutical company

11.2 EPOD and the development of the study outline

Strategic endorsement by the EORTC Executive Committee

Study proposals can be submitted directly to the EORTC Executive Committee (ExCo) by EORTC Groups, with the proviso that they are first processed through and considered by the EORTC Early Project Optimisation Department (EPOD) as a 'gate keeper'. However, for optimal advice on the strategic development and optimisation of any study proposal, the full involvement of EPOD is highly recommended during development and prior to submission of any proposal to the EORTC ExCo.

The optimal route for a project outline or proposal intended for development into an EORTC Clinical Trial is for it to be initially submitted for scientific evaluation, feasibility assessment and trial proposal development to EPOD. This is carried out through the collaboration of the Study Coordinator and the EORTC Clinical Research Physician (CRP) nominated through EORTC Headquarters, along with the others who make up the full EORTC Headquarters team (e.g. EORTC Biostatistician). The CRP will review the scientific plan and content of the proposal with the Study Coordinator

The next stage in this decision-making process is the presentation to and defence of the proposal with ExCo, which is carried through by the Study Coordinator and the CRP. While the ExCo decision can be for straight project endorsement or rejection, there is also provision for the resubmission of a proposal to ExCo. This can take the form of a written response or a second project presentation to ExCo, both of which need to take into account the major comments of ExCo that are provided with the invitation for resubmission.

Project development and PRC outline submission

Following this strategic review stage, the proposal and the draft budget are developed further to provide the study outline for submission to the scientific peer-reviewing stage of the EORTC Project Review Committee (PRC), the Translational Research Advisory Committee (TRAC), and the New Drugs Advisory Committee (NDAC). At about this stage, the project is 'formally' handed over from EPOD to the EORTC Headquarters Project Manager (PM), who continues with the submission in collaboration with the Study Coordinator and the CRP.

EORTC Headquarters will ensure that the major elements that drive the feasibility of a project (e.g., intergroup setting, budget conditions) are in place or are well enough enough advanced before the study outline is sent to the EORTC PRC.

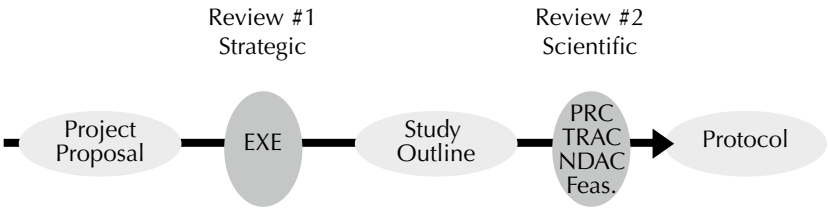
The PM will then take the proposal through this stage to the PRC presentation and decision. Should the study outline receive a 'green light' from the PRC, the PM will continue their management through to the full EORTC Protocol development and release, and throughout the lifetime of the EORTC Clinical Trial.

The main role of the PRC, supported by the TRAC and the NDAC, is thus for the evaluation of whether:

- a project adheres to the EORTC Scientific Strategy;
- the scientific value of a project is sufficient to justify involvement of the EORTC;
- the proposed methodology is appropriate to answer the objectives of the trial;
- the project is scientifically feasible.

The PRC decision and the possible comments, questions and suggestions of the PRC will be sent to the Study Coordinator by the PRC Chair. The EORTC Headquarters team will continue to help to address statistical, methodological and logistic issues.

Steps driving EORTC Protocol development

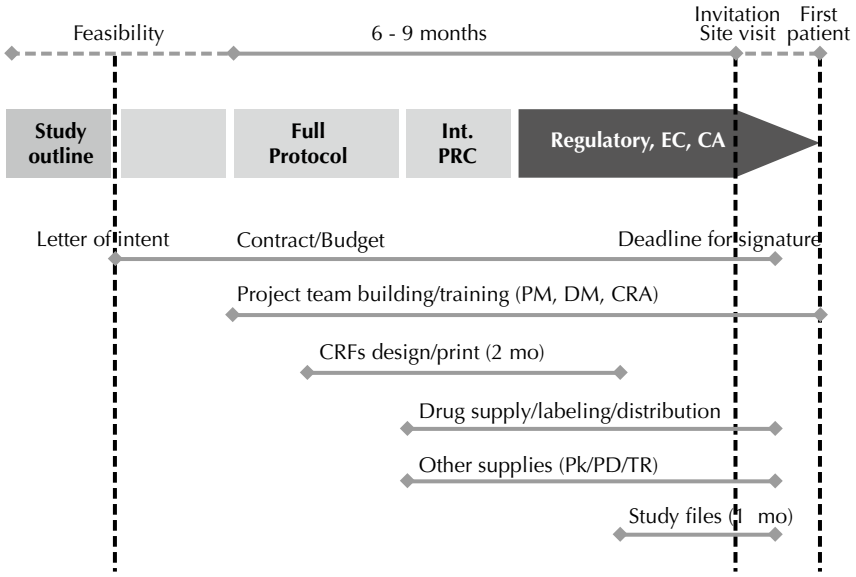


11.3 From study outline to EORTC Protocol

Once the study outline has been approved by the PRC, the Study Coordinator will continue to be supported by the EORTC Headquarters team which, in addition to the CRP and the PM, will include a Data Manager.

This full EORTC Headquarters team will continue in the development of the EORTC Protocol, possibly also with the assistance of a writing committee appointed by the EORTC Group. Preferably, the full EORTC Protocol should be available within six months of the approval of the study outline by the PRC.

The EORTC Headquarters team will coordinate the development of the final EORTC Protocol through the distribution of the models and guidelines to the selected authors of each written section and the collation of the completed sections. When all of the sections are complete, the Protocol Help Desk assembles the first version of the full EORTC Protocol and circulates it as necessary for review and modification. Then, the Study Coordinator will give their authorisation for its submission for final review within EORTC Headquarters (internal review). The aim of this final review is to be certain that the full EORTC Protocol has been built according to the model that was approved by the PRC, that it includes all of the suggestions made by the PRC when the outline was reviewed, and that it remains compatible with EORTC Procedures and Policies.



11.4 The EORTC Protocol

All aspects of a clinical trial are prospectively described in a written document that is known as the **'clinical trial protocol**', or here, the **EORTC Protocol**. In contrast to 'treatment protocols' that are available in most clinical institutions, a clinical trial protocol is only applicable to a selected population of patients (as defined in the eligibility criteria), and it addresses more than strictly medical questions.

According to ICH-GCP Guidelines, a clinical trial protocol is, "**a document that describes the objective(s), design, methodology, statistical considerations and organisation of a trial.**"

The clinical trial protocol is the principal working tool for investigators and all other people involved in a clinical study. It also serves as a reference for the Scientific and Ethics Committees that need to review and approve any given study and for publication of the study results.

Each Protocol contains the information necessary to perform a given study and is compatible with the requirements of the ICH-GCP Guidelines. The PI must ensure compliance with all aspects of the EORTC Protocol in their Institution.

Should an EORTC Protocol need to be amended after its final acceptance by the PRC, the EORTC Headquarters team will detail the proposed changes and submit these to the PRC. Following their review of the proposed amendments, the PRC can approve, request changes to, or reject the amendments. Upon approval of any proposed amendments, the Protocol Help Desk will implement the agreed changes and re-issue the newly amended new version of the EORTC Protocol.

12. Conducting an EORTC Clinical Trial

How are patients registered and randomised in an EORTC Clinical Trial?

Patients are registered/ randomised in an EORTC Clinical Trial through central procedures either through the internet or by telephone. Patient inclusion through the internet is encouraged as it is available at all times, and hence also outside office hours. Details for inclusion procedures are described in each EORTC Protocol. Only EORTC Investigators with their membership in good standing are allowed to enter patients in EORTC Clinical Trials after protocol-specific ethical and regulatory procedures have been completed.

Why does the EORTC verify all of the selection criteria for each patient at the time of registration / randomisation?

The EORTC places a lot of emphasis on, and takes great efforts to maintain, data quality as far as possible, with this occurring from very early on and remotely at the source of information. To decrease the patient ineligibility rate, all of the selection criteria are verified for each patient who is being registered to enter an EORTC Clinical Trial. This EORTC registration/ randomisation system thus provides for automatic verification with actual patient data values where possible, instead of relying on simple Yes/No questions.

Why is it so important to accurately fill in all of the registration / randomisation criteria?

As indicated above, in its continued efforts to maintain and improve data quality, the EORTC has established these measures to minimise the patient ineligibility rate. Also, the applied stratification and randomisation processes will take into account the patient data values provided at the time of patient registration/ entry. Therefore, when incorrect values are entered, an inappropriate balance between the treatment arms can result, which will affect the overall quality of the study. The EORTC always verifies the inclusion criteria, which also need to be entered on CRFs, for which cross-checks are performed. Finally, the selection criteria are source-verified during on-site monitoring, quality assurance and/or audit visits, as applicable.

Why and how queries are issued and what is the importance of replying rapidly?

Similarly to the CRFs which have to be submitted in a timely fashion during an EORTC Clinical Trial, queries issued by EORTC Headquarters must be handled swiftly by EORTC Investigators. This enables the EORTC Headquarters team in charge of the EORTC Clinical Trial to carry out quality verification on recently entered data, and to implement efficient corrective measures. Central monitoring is a major element of the EORTC quality criteria. This allows EORTC Headquarters to issue up-to-date trial status reports. These trial status reports are produced at least twice a year, and they describe the status and the progress of a given EORTC Clinical Trial. Thus, the status reports provide an efficient monitoring and decision-making process for any given EORTC Clinical Trial, and hence the need for these to be assembled based on the most recent data available.

Queries may reach an EORTC Investigator either by e-mail attachments, by the remote data entry system, or by a monitor/CRA visit to a participating site.

Why must sites be organised in a multidisciplinary setting?

In line with the principles of the EORTC scientific strategy, the vast majority of EORTC Clinical Trials address therapeutic strategies. Therefore it is of the utmost importance that investigators joining EORTC studies have the benefit of a multidisciplinary support team comprised of all of the locally involved professions. Because of this, EORTC Headquarters advises that studies be discussed with multidisciplinary boards, and that all investigators involved be informed of the specific EORTC requirements such as the Quality Assurance Programme for radiation oncology.

Today, clinical trials are based on a strong translational research component or are even built on bio-banking. Local pathologists should therefore be involved early on in the trial planning, so that they understand the need for access to tissue. EORTC Headquarters is setting up procedures to prospectively ensure that collected biological material is traceable and, preferably, centrally stored. The procedures are trial specific, but the use of tissue microarrays is preferred when an EORTC Institution or EORTC Investigator is allowed to retain material from their patients. Specific site requests or approaches can be discussed with EORTC Headquarters.

13. Publication policies for an EORTC Clinical Trial

The general rules for authorship of manuscripts arising from EORTC Clinical Trials are defined in the EORTC Publication Policy (POL009). The EORTC Group rules on authorship for participating EORTC Institutions are further defined in the statutes of each EORTC Group. Protocol-specific criteria are also detailed in the 'Publication' section of each EORTC Protocol.

14. What does it mean to be an EORTC Study Coordinator?

The role of an EORTC Study Coordinator is to take on the leadership in the development, conduct and publication of an EORTC Clinical Trial on behalf of the EORTC Group conducting the study. The Study Coordinator for any EORTC Clinical Trial is appointed by the Chair(s) of the EORTC Group(s) involved, and they assume their role early on in the submission of a project proposal to the EORTC Headquarters Early Project Optimization Department (EPOD) (see section 11).

The Study Coordinator will seek endorsement from the Group Steering Committee and EORTC Headquarters for any additional/ subsequent studies planned on the data/ biological materials collected in the EORTC Clinical Trial to which they were assigned.

The Study Coordinator needs to be aware of EORTC Policies, and to ensure that the EORTC Clinical Trial that they are coordinating is designed, conducted and published according to these policies. The Study Coordinator also needs to participate in 'their' EORTC Clinical Trial as an active EORTC Investigator, which in the case of an EORTC Clinical Trial, also involves their active accrual of patients.

Tasks and responsibilities of EORTC Study Coordinators

The responsibilities of Study Coordinators have been defined by the EORTC Board, and they are available on the EORTC website. As a summary, they include the following:

- Identify an original research question that can be answered by an EORTC Clinical Trial. As such, it needs to be relevant to the EORTC Scientific Strategy so as to obtain the support of the EORTC New Drug Advisory Committee and Translational Research Advisory Committee.

- Collaborate with EPOD through the Coordinating Research Physician (CRP) and the EORTC Headquarters team.

- Discuss the project with potential EORTC Investigators and other eventual partners (other EORTC Groups, other non-EORTC groups, potential industrial sponsors), and with the CRP and the EORTC Headquarters team, to ensure that the study is feasible.

- Present the project proposal to the EORTC Executive Committee (ExCo) for strategic assessment, in close collaboration with the CRP and the EORTC Headquarters team.

- Further develop the project proposal with the CRP and the EORTC Headquarters team, for presentation of the study outline to the EORTC Protocol Review Committee (PRC) and the EORTC advisory committees (TRAC, NDAC).

- Develop the study outline into a full EORTC Protocol according to EORTC methodology, in close collaboration with the EORTC Headquarters team.

- Review and approve the final version of the complete EORTC Protocol prior to resubmission to the PRC. The final PRC-approved version of the EORTC Protocol should in all cases be ready within 12 months of the original study outline approval.

- Review the contents of the Case Report Forms (CRFs) proposed by the EORTC Headquarters team, and approve the final PRC-approved version of the EORTC Protocol.

- Answer all medical questions from EORTC Investigators (and others) and from the EORTC Headquarters team, in a timely fashion.

- Review the Serious Adverse Event (SAE) reports forwarded by the EORTC Headquarters Pharmacovigilance Unit, on a timely basis (as detailed in the EORTC Protocol).

- Participate regularly in study team meetings or in teleconferences initiated by the Project Manager.

- Review patient files and relevant evaluation forms in collaboration with the CRP.

- Discuss and comment on EORTC Headquarters reports during EORTC Investigator and EORTC Group meetings.

- Discuss eventual protocol amendments with the full EORTC Headquarters team, who will then submit them to the PRC for approval.

- Discuss the final analyses of the results of the EORTC Clinical Trial with the EORTC Headquarters team.

- Draft a manuscript within six months of receipt of the final statistical report (or earlier if previously agreed), circulate the draft manuscript to all of the co-authors and to the EORTC Headquarters team, and submit the manuscript for publication after approval by the co-authors, the full EORTC Headquarters team.

- Review and approve all subsequent publications that make use of 'their' EORTC Clinical Trial data, in accordance with the 'publication' section of the EORTC Protocol.

15. How is quality assurance organised within the EORTC?

By accepting participation in an EORTC Clinical Trial, all EORTC Investigators (including EORTC PIs) also agree to cooperate fully with any quality assurance and control visits (audit, monitoring) that might be undertaken by third parties, including representatives of EORTC Headquarters, national and/or foreign Regulatory Authorities, or an industrial partner/ sponsor, if applicable. All EORTC Investigators also agree to allow direct access to documentation pertaining to the EORTC Clinical Trial (including CRFs, source documents, patient hospital charts, and other study files) to these authorised individuals.

EORTC Headquarters also agrees to provide support to all EORTC Investigators and their clinical research teams should they be notified of an audit by an industrial partner/ sponsor, or an inspection by their Regulatory Authorities (e.g. national, European, US FDA). A visit will be scheduled to help the EORTC Institute site and all the EORTC Investigators to prepare for the audit/ inspection, and, if relevant, a representative of EORTC Headquarters can also attend the actual inspection to facilitate the process.

The EORTC Investigator needs to inform EORTC Headquarters (via the EORTC Headquarters team, and including the Quality Systems and Compliance Department) immediately upon being notified of a regulatory inspection.

EORTC Headquarters makes every effort to comply with the ICH-GCP Guidelines, the EU Directives and all other national regulations that are applicable to international clinical research. The development of Standard Operating Procedures (SOPs) within the EORTC Headquarters also guarantees that all EORTC Clinical Trials are handled according to the highest standards of clinical trial development, management and analysis.

To guarantee that EORTC Investigators do comply with all of the necessary requirements, some EORTC Clinical Trials (and especially pivotal/ registration studies) are audited/ monitored with local EORTC Institution site visits.

The objectives of these EORTC Institution site audits is to provide quality assurance for EORTC Clinical Trials. The audits are performed by a team of individuals who are knowledgeable of the discipline covered by the EORTC Protocol.

These audits can cover multiple aspects of quality assurance, with the main purposes being to:

- ensure that data reported on CRFs accurately reflect what happened to the patient and what is recorded in the patient hospital file (source document);
- evaluate local facilities, organisation of clinical research, and data management structures in an EORTC Institution;
- check on the ethics and informed consent procedures and on regulatory compliance (Ethics Committee);
- check on patient eligibility in EORTC Protocols;
- assess the overall quality of treatments, with a special focus on protocol-specific treatment parameters;
- evaluate EORTC Protocol compliance and ensure validity of response evaluations;
- make sure the safety of the EORTC Clinical Trial patients is being protected, and that the relevant safety information (e.g. site AEs, SAEs, SUSARs) have been properly reported, distributed, read and filed (e.g. SUSAR notification from other studies, safety alerts);
- verify EORTC Institute site compliance with the relevant international/ national guidelines and regulations;
- review storage and accountability of investigational drugs, and their related documentation.

On-site monitoring is also performed for selected EORTC Clinical Trials or selected sites on a case-by-case basis.

Depending on the EORTC Clinical Trial set-up, the monitoring might be carried out by EORTC Clinical Research Associates (CRAs) from EORTC Headquarters, or by a Monitoring Clinical Research Officer under the supervision of the EORTC.

The aims of such EORTC Clinical Trial monitoring are to:

- verify that the rights and well-being of the human subjects are protected;
- verify the accuracy, completion and validity of reported EORTC Clinical Trial data through access to the source documents;
- evaluate the conduct of an EORTC Clinical Trial within the EORTC Institution with regard to compliance with EORTC Protocol, ICH-GCP Guidelines, EU Directives, and the relevant regulatory requirements.

16. Conclusion

The present EORTC Investigators' Handbook is intended to be a practical guide to the EORTC and EORTC Clinical Trials, and it is addressed to all scientists and clinicians who have been, are, and, in particular, will be dedicated to EORTC clinical research, and to their local co-workers who support them in the various related activities.

We hope that this EORTC Investigators' Handbook has been able to answer the following specific set of questions:

- How are the EORTC and EORTC Headquarters structured?
- What are the strengths of the EORTC as an organisation?
- Who does EORTC cooperate with?
- How do you become a member of the EORTC Network, as an EORTC Investigator?
- How can EORTC Investigators contribute to the EORTC Group activities in an optimal way?
- How do EORTC Investigators become involved in EORTC Clinical Trials?
- What are the responsibilities of an EORTC Investigator within an EORTC Clinical Trial, from the generation of ideas to the publication of the results?
- What are the responsibilities of an EORTC Study Coordinator in the process from the concept of a clinical study to the final publication of the results of an EORTC Clinical Trial?

Of final note, this EORTC Investigators' Handbook is a complement to the EORTC annual report booklet entitled "EORTC Organisation, Current Research and Strategies", or alternatively, come and have a look around the EORTC website at: www.eortc.be

We thank you in advance for your collaboration.