Facing the Challenges of the European Clinical Trials Directive – The European Organisation for Research and Treatment of Cancer Perspective

a report by

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The European Organisation for Research and Treatment of Cancer (EORTC) is a pan-European, non-profit, independent research organisation that develops, conducts, co-ordinates and stimulates high-quality translational and clinical research aimed at improving the standards of treatment for cancer patients in Europe.[1] This mission is achieved through collaboration in the development of new drugs and other innovative approaches, and through the evaluation of more effective therapeutic strategies testing currently approved drugs, surgery and/or radiotherapy in clinical studies. Driving international cancer clinical trials in Europe constitutes the daily work of the EORTC and has always posed multiple challenges. These challenges have become magnified and more complex since enactment of the EU Clinical Trials Directive 2001/20/EC (EU CTD) due to the multinational nature of EORTC clinical trials. Issued in May 2001 and enshrined into the national legislation of all EU Member States as of May 2004, the overall intent of this Directive was to create a clinical research environment across Europe conducive to the discovery of much-needed innovative medicines while simultaneously ensuring the protection of all clinical trial participants. Four years after coming into legal force, many believe that the original goals of the Directive have yet to be fully achieved.[2–6]

Aim and Scope of the EU Clinical Trials Directive

The EU issues directives, a mechanism by which decisions made centrally are implemented at the Member State level. The aim of any directive is the harmonisation of fundamental principles and core procedures. However, a directive itself does not specify the means or methods for accomplishing this goal. The EU CTD 2001/20/EC is a directive on the approximation of the laws, regulations and administrative provisions of the Member States relating to implementation of good clinical practice (GCP) in the conduct of clinical trials on medicinal products for human use.[7] It endorses the 1996 International Conference on Harmonisation (ICH) recommendations for GCP, the foundation for the Directive and its provisions.

The fundamental aims of the EU CTD are:

- to protect the rights, safety and wellbeing of clinical trial participants;
- to simplify and harmonise the administrative provisions governing clinical trials; and
- to establish a transparent procedure to harmonise the conduct of clinical trials in Europe and ensure the credibility of research results.

These are sound fundamentals. However, the Directive does not distinguish between commercial and non-commercial clinical trials – that is, between trials conducted by the pharmaceutical industry to register a new compound and trials carried out primarily by academic researchers. Under the EU CTD, all interventional clinical trials that involve medicinal products must meet new legal obligations. To the detriment of independent researchers, the Directive failed to take into consideration the unique nature of non-industry-sponsored clinical trials. Reprieve was found in recital 14 to the Directive, which specifically recognised non-commercial trials conducted by researchers without pharmaceutical industry support. However, application of the Directive remains fraught, with time-consuming, costly bureaucratic requirements.

Since implementation of the EU CTD into the legislation of the Member States, intense debate has ensued. Stakeholders have voiced their concerns over the impact of the Directive on clinical research in Europe. The European Medicines Agency (EMEA) organised a conference for all stakeholders in late 2007 to examine the consequences of the Directive. The benefits and drawbacks of this legislation were highlighted and recommendations proposed for future action. The EORTC has used its pivotal role to weigh in on the EU CTD and its impact on the future of European clinical research.[8] In an ongoing effort, the EORTC collects metrics, figures and precise data on the effects of the Directive through its partnership in the European Commission 7th Framework Programme (FP7), 'Impact on Clinical Research of European Legislation', also known as the ICREL project. The EORTC co-organised a workshop on biomedical research in Europe in May 2008 that provided an additional opportunity to evaluate the impact of the EU CTD. The members of the ICREL, Connective Tissue Cancer Network (CONTICANET) and European Clinical Research Infrastructures Network (ECRIN) projects, funded by the European

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Commission 6th and 7th Framework Programmes, will assess whether the current Directive can be amended or if new legislation is required.

Application of the EU Clinical Trials Directive – Benefit or Burden?

Major bottlenecks and obstacles have emerged for academic researchers when applying the EU CTD. First, due to its legal nature, transposition of the Directive imposed a complex new legal landscape consisting of 27 frameworks at the EU national level. Gaining access to domestic legislation, corresponding updates and maintaining familiarity with each new regulation, decree or ordinance is a challenge in itself. An overview of the current European legal framework, legislation, regulations and guidelines related to the conduct of clinical trials with medicinal products is shown in *Figure 1*. The amount of information that one needs to consider when planning and conducting clinical trials in Europe is immediately striking and reflects the diversity of national implementations of the Directive. Although the Directive set out to introduce a single set of principles and procedures, EU Member States have implemented it in different ways. Countries differ notably in their interpretation of the sponsorship rules, the complexity of the procedures for ethics approval and the level of detail required for drug safety reporting. Harmonisation is still a distant reality.

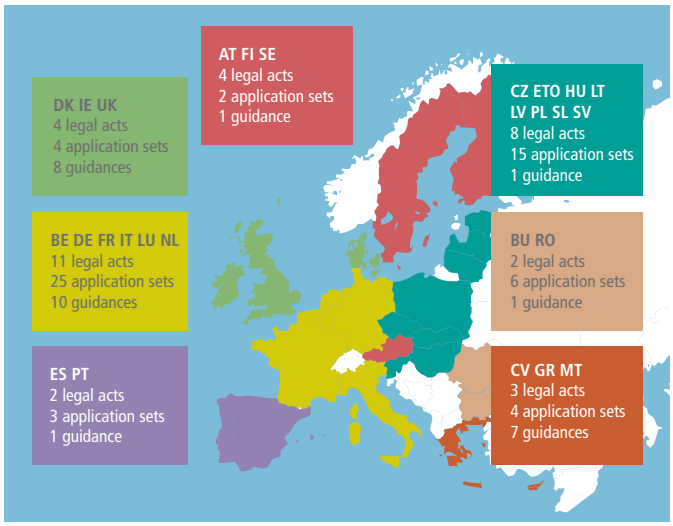
Second, the Clinical Trials Directive applies to "the conduct of clinical trials, including multicentre trials, on human subjects involving medicinal products".[9] The EU CTD, issued by the Directorate Enterprise, was written in the context of interventional trials testing investigational medicinal products (IMPs) largely intended for inclusion in registration dossiers compiled by the pharmaceutical industry. It failed to define the legal system that would apply to non-interventional trials, interventional trials not testing a drug or trials using a standard drug treatment but focusing on other therapeutic modalities such as radiation therapy or surgery. Further difficulties arise when considering complex research projects that evaluate multimodality treatments involving radiotherapy, surgery or combination surgery–radiotherapy. An unintended consequence of the EU CTD was the indiscriminate application of these rules to other types of clinical study.[10]

Third, the overall costs of conducting cancer clinical trials have increased substantially under the EU CTD. The global cost of EORTC insurance coverage multiplied approximately five-fold between 1996 and 2006, with increases ranging from 22 up to 128% (see *Figure 2*). Prior to the EU CTD, the EORTC insured its clinical trials with an annual global policy covering all participating countries. Today, national variability in the type of policy required (i.e. fault or no-fault) and the ceiling of costs and/or duration of coverage force the EORTC to hold different insurance policies to comply with all territories and regulations.[11] The annual insurance policy covers a said territory under which a given number of patients are insured per year for a specific Member State regardless of the number of clinical trials activated. To date, the EORTC has contracted only six annual policies. The second is the individual insurance policy, which is protocol-based for a given country. Thirteen countries were insured under this type of policy in 2006.

Fees paid to Competent Authorities and/or Ethics Committees for submitting a Clinical Trials Application also contribute to the rising costs of academic clinical research under the Directive. National differences in fees levied on non-commercial sponsors range from €0 to €2,500 for an initial ethics committee application and from €0 to €1,000 when submitting a substantial trial amendment. A number of Member States agreed to a waiver for non-commercial sponsors through the 'legal recognition' of academic research.[12] Likewise, fees paid to Competent Authorities range from €0 to €4,000 for an initial application and from €0 to €1,500 for a substantial amendment with waivers for non-commercial sponsors.[13] Some Ethics Committees, as in the case of Germany, also charge for the review of suspected unexpected serious adverse reactions (SUSARs).

The so-called 'free-of-charge' supply of IMPs, as defined in Article 2(d) of the Directive, pushes costs even higher. National divergences exist in the interpretation of this concept. The classification of a medicinal product as an IMP has important financial implications for the Sponsor. Article 19 of the Directive stipulates that unless Member States have established precise conditions for exceptional circumstances, the Sponsor must provide, free of charge, IMPs and any device(s) used for their administration. This disposition does not apply to non-IMPs and

Figure 1: EU Member States' National Legislation Implementing the European Clinical Trials Directive 2001/20/EC



AT = Austria; BE = Belgium; BU = Bulgaria; CZ = Czech Republic; CY = Cyprus; DE = Germany; DK = Denmark; ES = Spain; ETO = Estonia; FI = Finland; FR = France; GR = Greece; HU = Hungary; IE = Ireland; IT = Italy; LT = Lithuania; LU = Luxemburg; LV = Latvia; NL = The Netherlands; PL = Poland; MT = Malta; PT = Portugal; RO = Romania; SE = Sweden; SL = Slovenia; SV = Slovakia; UK = The United Kingdom.

Figure 2: European Organisation for Research and Treatment of Cancer Global Insurance Costs 1996–2006

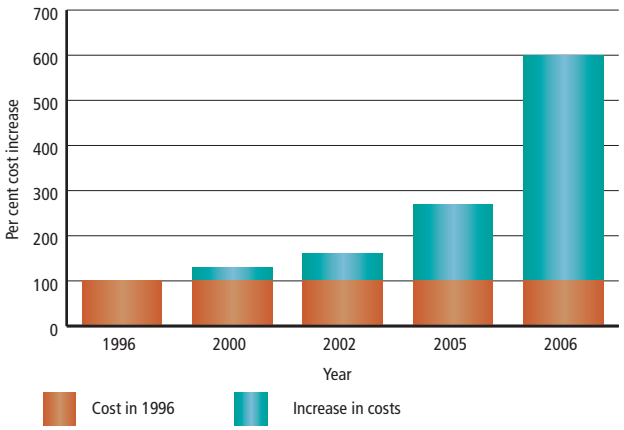
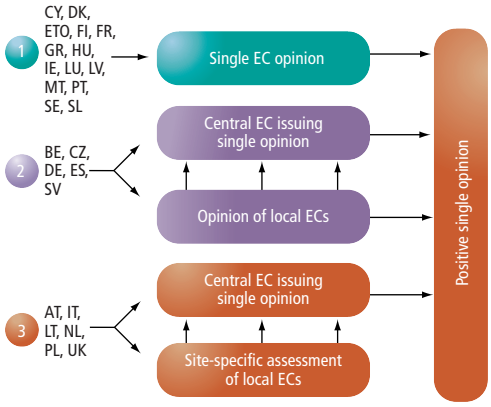


Figure 3: Ethics Committee Single-opinion Procedure



EC = Ethics Committee; for country abbreviations see Figure 1.

Sponsors are therefore under no obligation to provide them free of charge. The possibility of waivers remains an open debate. Some European regulatory authorities have adopted a very broad interpretation of the IMP concept, resulting in enormous additional costs to the sponsor. In Austria and Hungary, for example, every medication specified in the protocol must be supplied free of charge, whether a standard or experimental medication, control arm or supportive treatment.[14] In Denmark, non-IMPs are also provided for free.[15] In Germany, an IMP is any product used to initiate specific reactions in human beings.[16]

The single 'sponsorship' model of the Directive poses another hurdle. This requirement fails to reflect the nature of non-commercial sponsorship for pan-European multinational clinical trials and is not feasible given the previously discussed differences in Member States legislation. A 'multi-sponsorship' model would be more appropriate, with the responsibilities and duties of each sponsor defined by contract according to the discretionary power of the parties. This solution provides increased flexibility, which is particularly important for collaborative clinical trials conducted between research groups (i.e. intergroup trials).

The 'single opinion' ethics committee procedure remains one of the major challenges of the Directive due to the variety of national models currently in use. Article 7 of the EU CTD holds that for multicentre clinical trials conducted simultaneously in Member States, a single opinion shall be given for each Member State concerned. This procedure must be established "notwithstanding the number of Ethics Committees". The most recent provisions allow Member States to involve various Ethics Committees in this single-opinion process. Furthermore, some countries may also require the opinion of local Ethics Committees. For practical purposes, the EORTC Regulatory Affairs Unit has classified these various national single-opinion procedures into three possible scenarios (see *Figure 3*). Scenario I represents the 'authentic single opinion' in which one opinion per county is issued. Scenario II involves both central and local Ethics Committees with the central body issuing a single opinion. However, each local site evaluates and provides an opinion on the proposed trial. In the event of a local negative opinion, trial initiation may be delayed at that specific site. Scenario III falls between scenarios I and II in that a central Ethics Committee issues the single opinion while the local bodies only assess trial feasibility.

According to article 10(a) of the EU CTD, a clinical trial may be amended after its commencement. However, only "substantial" amendments, such as those that affect the safety or physical or mental integrity of the subjects, the scientific value or the conduct and management of a trial or the quality or safety of any IMP used in the trial, require submission to the Competent Authorities and Ethics Committees.[17] Attachment 5 of the detailed guidance on Competent Authorities provides a non-exhaustive list of what constitutes a substantial trial amendment.[17] A change in principal or co-ordinating investigator or the addition or deletion of a study site are considered substantial amendments, as are revisions to the study protocol including, for example, modifications to the inclusion or exclusion criteria. The number of amendments has increased significantly and further application to Competent Authorities and Ethics Committees is required prior to implementation. Each proposed amendment requires a substantial amount of documentation, adding further to the red tape and extra workload brought about by the EU CTD.

Two final contentious issues of the EU CTD are data monitoring and safety reporting. Due to a broad interpretation of the binding character of some principles of GCP, Competent Authorities increasingly request on-site monitoring. One could question the rationale of systematically monitoring all participating institutions in large-scale strategic trials such as those conducted by non-commercial academic sponsors. Ensuring data quality should not be limited to on-site monitoring procedures. Alternative methods such as limited or risk-driven monitoring and central data review can provide the same data quality when coupled with an appropriate quality assurance audit programmme, such as that employed at the EORTC Headquarters. Others suggest using tailored approaches to data monitoring according to the level of risk a trial presents.[18] The existing safety reporting system under the EU CTD is unnecessarily complex in terms of definitions and reporting requirements, resulting from the way in which the rules were transposed into national law. Further complicating this is the fact that electronic reporting via the EudraVigilance database is not a legal requirement in all Member States and the administrative red tape is excessively time-consuming. These obstacles blur the original intention of the Directive, namely to improve the safety of clinical trial patients.

Despite the previously discussed challenges, the EU CTD has brought benefits to the conduct of clinical trials, along with partial harmonisation. Timelines for obtaining ethics committee and competent authority approvals are defined and mostly respected. Each clinical trial is now registered in the EudraCT database under a unique single identifier. EudraVigliance is a first step towards enhanced safety reporting. Funding and financing of clinical trials are more transparent. GCP awareness and compliance have improved and enforced good manufacturing practices now govern the manufacturing of IMPs. Due to the EU CTD, scientifically weak clinical trials and duplication of studies that address similar end-points are now less frequent. This will eventually lead to a higher quality of research with more investigators collaborating to address important therapeutic questions by pooling their research expertise, infrastructure resources and research funding.

However, these positive effects are outweighed by the negative impact of the EU CTD on non-commercial research. An increasingly complex new legal framework, expanding administrative workloads, rising

20th EORTC - NCI - AACR Symposium on "Molecular Targets and Cancer Therapeutics"

Geneva, Switzerland, 21 - 24 October 2008

Dear Colleagues,

We cordially invite you to Geneva, Switzerland, to participate in the 20th EORTC-NCI-AACR Symposium on "Molecular Targets and Cancer Therapeutics" from 21 to 24 October 2008.

This symposium, hosted by the EORTC, NCI and AACR, will bring together academics and scientists and representatives from the pharmaceutical industry to discuss innovation in drug development, target selection and the impact of new discoveries in molecular and cell biology.

Understanding the pathways and mechanisms which cause cancer and regulate the biological behaviour of tumor cells has lead to the development of numerous new agents and innovative targets for clinical trials. This conference has been organised to reflect the many recent advances in the early development of promising new compounds, which are at different stages of preclinical and clinical development. It will bring together delegates from all over the world igniting an enormous exchange of information, as well as promoting and developing global partnerships in translational research.

The conference has been developed to ensure the maximum amount of interaction and discussion. We hope that the plenary sessions and the workshops will be informative and lively with extensive discussions.

We are all looking forward to seeing you in Geneva!

Patrick Schöffski
Scientific Chairman

Martine Piccart
Conference Chair

Registration:
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Further information is available on the EORTC website: www.eortc.be/ENA2008.htm

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American Association for Cancer Research

Figure 4: European Organisation for Research and Treatment of Cancer Headquarters Budget 1997–2007

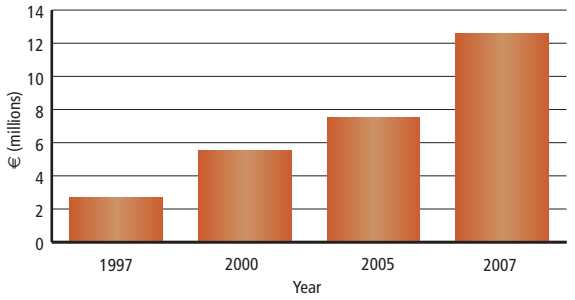
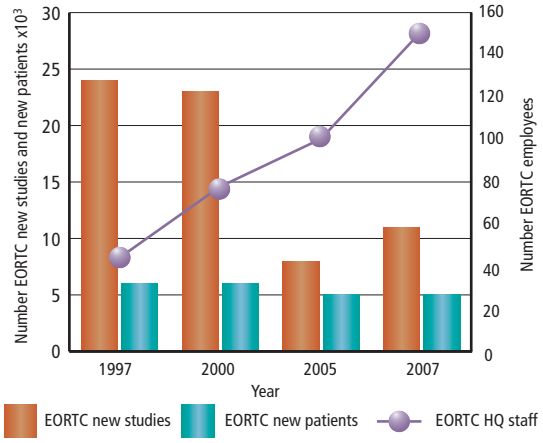


Figure 5: European Organisation for Research and Treatment of Cancer Study Activation, Recruited Patients and Headquarters Staff 1997–2007



costs and increasing demands on resources are encountered daily. The EORTC Headquarters budget has increased six-fold over recent years (see *Figure 4*) and the staff has tripled despite a drop in the number of newly activated clinical trials and number of treated patients (see *Figure 5*). This is largely related to national legislation and implementation of the EU CTD. Less interest in academic research means important scientific questions are left unanswered, fewer and fewer clinical trials are initiated and patients are denied access to potentially beneficial therapies. In order to guarantee the survival of academic clinical research in Europe, urgent steps are needed to reverse this downward spiral.

The Next Step – EU Clinical Trials Directive Amendment or New Legislation?

The EORTC and numerous research groups outside the field of oncology recommend revision of the current Directive. Formal recognition of the non-commercial sponsor is a major first step. Second, a risk-based approach is needed. The US Food and Drug Administration (FDA) allows certain regulatory exemptions for non-interventional trials and trials that study life-threatening diseases or diseases that lack good therapeutic alternatives, such as cancers. To maintain a high level of quality, the same GCP standards should apply to both commercial and non-commercial sponsors. Support mechanisms such as fee waivers as well as public funding and sponsorship would assist academic sponsors in meeting these standards. Funding remains a central issue and although industry and academic clinical trials may address different but complementary scientific questions, collaboration is essential. Partnerships between industry and non-commercial academic research organisations can only lead to a win–win situation.[19] These measures will ensure early access to innovative agents and novel therapeutic modalities, increase the competitiveness of European research and, most importantly, provide patients with the best available therapy.

In spite of the challenges presented by the EU CTD, the EORTC is actively seeking concrete solutions to remain at the forefront of cancer research while working to improve the Directive. A current EORTC priority is research that will identify individual cancer gene signatures that clinicians will use one day to 'tailor' patient treatment using 'targeted' therapies. Another priority is the study of rare types of cancers in small 'niche' patient populations. Both initiatives demand scientific expertise but also significantly large patient numbers, which in turn requires a pan-European, multinational, harmonised approach to co-ordinate and conduct such trials. If Europe is to remain competitive and expand its capacity for medical research excellence, innovative solutions, novel research approaches, successful industry–academia partnerships and, above all, a new EU CTD are clearly needed. ■

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