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Target groups for whom the report could be relevant: all stakeholders implied in clinical research in the European Union, e.g. medical academic institutions, investigators, pharmaceutical companies, pharmaceutical industry associations, European regulatory authorities, European Commission, ethics committees, patients and patient organisations, insurance companies, medical press, politicians.

Impact on Clinical Research of European Legislation (ICREL)

Final Report – Second Version
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Executive Summary

Introduction and Rationale

European legislation on the clinical research environment was harmonised in 2001 with the implementation of Directive 2001/20/EC, the "Clinical Trial Directive" (CTD). Its main objectives were:

- protection of human subjects in clinical research,
- implementation of the Good Clinical Practice (GCP) standard in all clinical trials with medicinal products,
- harmonised procedures for clinical trial authorisation from competent authorities and ethics committees,
- central collection of information on clinical trial activities and safety results.

The Directive came into force on May 1, 2004. Directive 2005/28/EC, the "GCP Directive" and a number of guidance documents, today presented in the Directorate Entreprise and Industry's "EudraLex" database under "Notice to Applicants, Volume 10", completed the legislative environment for the preparation, approval, performance and reporting of clinical trials.

Implementation of Directive 2001/20/EC into national legislation of all 27 EU member states was completed in 2006. Principles like Clinical Trial Authorisation by the competent authority and favourable opinion of a single ethics committee within defined maximum timelines led to significant harmonisation of the clinical trial approval process. However, differences in interpretation of the modalities for this and other processes harmonised by the CTD, led to even higher complexity levels – especially in the performance of multi-national clinical trials. Today, a sponsor of a clinical trial needs to have very detailed knowledge about every country's national requirements for clinical trial authorisations from competent authorities and ethics committees and has to integrate the different requirements to the protocol and IMPD resulting from parallel submission in multi-national trials.

The Heads of Agencies have initiated a "Clinical Trial Facilitation Group" to work on better harmonisation of the requirements, but there is no structured attempt towards aligning the ethics committee systems and approval procedures in the different countries. While the Clinical Trials Directive was able to harmonise the understanding of the quality requirements for clinical trials, safety data reporting is also handled differently by the different member states. Thus, at least one main aim of the Clinical Trial Directive – the reduction of administrative burden in preparing and performing clinical trials – has not been achieved. Concerns were raised that this administrative complexity is not only hindering clinical research in Europe but even leads to a decrease of the clinical trial activity in Europe, especially in the non-commercial sponsor sector.

As stated in the Clinical Trial Directive, a review of its impact on clinical research in Europe was scheduled 5 years after its implementation along with exploration of potential revisions of the legislation. This FP7-funded ICREL project aimed at objectively measuring the impact of the clinical trials legislation on the key stakeholder groups "commercial and non-commercial sponsors", "competent authorities" and "ethics committees" in the European Union by providing:

- objective information on positive and negative impact factors on clinical trials with medicinal products and on other types of clinical research,

- reliable figures on the impact of the legislation on the clinical research activity of big Pharma Industry -, SME- and academia-sponsored trials,
- evaluation of the resource, cost and effectiveness implication of the EU CTD implementation for all stakeholders,
- comparison of the success of national CTD implementation,
- consolidated conclusions on the findings amongst the stakeholders,
- dissemination of the conclusions to the public at large.

Methodology

The first step was a comprehensive collection, review and presentation of reports on research performed by other groups on a pan-European and national basis, for different stakeholders and for a comparable timeframe.

Anonymised data from the EudraCT database was received and compared with the ICREL survey findings for the period 2004 to 2007 as far as the data structure allowed.

The ICREL study was a longitudinal, retrospective, observational and comparative study (survey) carried out in four stakeholder groups [Commercial Sponsor (CS), Non-Commercial Sponsor (NCS), Ethics Committee (EC) and Competent Authority (CA)] to assess the impact of the CTD on the number, size and nature of clinical trials, on workload, required resources, costs and performance. Mean differences between 2003 and 2007 were estimated to verify whether a marked change occurred in the investigational indicators further to the CTD implementation.

The project was subdivided in 7 Work Packages covering management and coordination of the overall project, the performance and management of the 4 different surveys, the compilation of information on non IMP-research from the 4 surveys, as well as the organisation of a conference to discuss the results and receive public input before finalisation of the final report.

The surveys intended to compile comprehensive information from all 27 competent authorities (plus 2 non-EU countries) and representative information from size-related strata of the three other stakeholder groups. Due to lack of response after the launch of the surveys the request for survey completion was extended to the complete, extensive list of institutions identified.

Results

Competent Authorities

1. The vast majority (25 out of 28) of EU CAs participated in the survey. Two non-EU CAs from countries integrated within the EU regulatory system accepted to participate and provided responses.
2. Content and quality of the responses varied greatly and were obviously dependent on the time, resources and systems the CAs had available to compile the information.
3. An impact on clinical research activity in the EU derived from the CTD implementation was apparent, though could not be readily confirmed from the available data.
4. No negative impact of the CTD on commercial sponsors could be detected. The number of CTAs submitted by commercial sponsors increased slightly (+11%) between 2003 and 2007.

5. Overall, a slight potential negative impact of the CTD on non-commercial sponsors was detected represented by a relative change of -25% of CTAs between 2003 and 2007, however, while some countries faced strong or even dramatic decreases other countries experienced an increase of non-commercial CTAs.
6. The number of substantial amendments and SUSAR reports increased strongly after CTD implementation.
7. Average CTA timelines decreased after CTD implementation and were, in 2007, with 49 days clearly below the 60-day limit.
8. The indisputably increased administrative burden imposed by the CTD on the evaluation process and supervision of CTAs was reflected by an increase in workforces and related costs which was paralleled by a raise in fees.

Ethics Committees

1. Despite multiple contacts, the number of responding ECs was quite low.
2. The overall number of positive opinions increased by 23% between 2003 and 2007, with especially strong increases in CTs with medical devices and radiotherapy as well as non-interventional/observational studies.
3. A huge increase in workload for ECs was observed since the implementation of the CTD, evidenced by not only the increase of opinions but also higher numbers of substantial amendments and SUSAR reports to ECs.
4. The number of negative opinions issued by lead or central ECs increased between 2003 and 2007 in line with the overall increase of reviews. More than 25% of responding ECs did not have an appeal system in place in 2007, but in countries where an appeal system was in place, it was significantly more frequently used than in 2003.
5. An increase in FTEs per EC was reported, however, the absolute numbers of employees per EC were still very low and often no clear differentiation was made between unpaid EC members and employees.
6. More than half of the ECs did not involve external reviewers in assessing applications despite the increasing complexity of the CTAs.
7. No differences could be detected in number of EC meetings and duration of review time per protocol between 2003 and 2007. However, the duration of the meetings increased slightly, but significantly.
8. Fees charged by lead or central ECs to commercial sponsors, SMEs and orphan drug trial sponsors for review of protocol and substantial amendments increased significantly from 2003 to 2007, but the fee level was different for these categories. The fee for academic trials was much lower and increased only slightly. Non-lead ECs did not charge significantly lower fees than lead or central ECs.
9. The annual budget of ECs increased by 50% between 2003 and 2007.
10. In 2007 ECs received final report summaries for less than 20% of the reviewed protocols.
11. 60% of responding ECs had no patient representative in their membership.
12. Especially non-lead/central ECs considered the procedure to generate a single opinion to be difficult.

Commercial Sponsors

1. The overall number of commercially-sponsored clinical trials increased by about 30%, driven by increases seen in large and medium-sized companies.
2. SMEs did not experience an increase but faced higher staff needs and related costs due to an increase in trial complexity.
3. Areas of relatively stronger increases were clinical trials with biotechnology products and with orphan indications.
4. Clinical trials were increasingly organized in more countries and more sites than before implementation of the CTD, however, the number of recruited patients increased only slightly.
5. There was no shift detectable in the responding companies in the type of trial phases performed in 2003 and 2007. However, generic companies did not participate in the survey because they reportedly do not perform their bioequivalence trials in Europe anymore.
6. Time lines for the overall protocol and substantial amendment approval process were extended by approximately 30%.
7. Need for staff increase for preparation and management of clinical trials as well as for pharmacovigilance tasks, need for investment required to adapt IT systems to the new safety reporting requirements, and an increase of subject indemnity insurance fees added to an overall increase in resources required for the performance of clinical trials in the new regulatory environment without a demonstrable impact on improving patient safety.
8. In the opinion of commercial sponsors, the CTD has created a certain level of harmonisation of the clinical trials infrastructure in the EU, but as this harmonisation has not been sufficiently far-reaching, the complexity of clinical trials has increased.

Non-Commercial Sponsors

1. According to this survey's data, the major impact of the CTD on the NCS activities was reflected in a significant increase of the workload and timelines, i.e., an increase in the time period before the entry of the 1st patient. The CA data did not show significant changes in the overall number of clinical trials conducted by NCSs. Overall, the CTD was perceived as having introduced a partial harmonisation of procedures, but this positive effect was heavily counterbalanced by the general lack of harmonisation, the increase of the administrative burden and related costs. NCSs called for simplified and harmonised requirements and sound risk based-approach.
2. A great heterogeneity was observed in the responses rates, the number of missing values, and the trends arising from the data collected from NCSs. These reflected the great heterogeneity of the NCS organisations, reaching from large research organisations and well-organised structures to small structures with a lower level of cooperative and dedicated resources. The capacity of NCSs to log critical information needs to be improved.
3. This survey was not designed for qualitative assessment of the impact of the CTD on the performance of future studies. The following questions need to be addressed: has the CTD improved patient protection and safety? What is the impact of the CTD on the quality of science: do we guarantee progress for patients in a timely manner? Can the nature of investigator-driven trials be preserved when independence from industry is threatened by the increasing burden of conducting such kinds of activities?

4. A re-evaluation of the situation with respect to the implementation of the CTD and its impact would need to be performed over a 3-year time frame in order to take advantage of a more complete EudraCT database. The systematic comparison with the situation in non-EU territories, e.g. US, Canada and Japan, should also be included.

Overall Conclusion and Recommendation

Through extensive collection of data from different stakeholders, from different countries, and for various categories of clinical research, ICREL provided metrics on the changes in clinical research activity in Europe observed in the period before and after implementation of the Directive 2001/20/EC. These data will provide a major contribution to the debate on the need for a possible revision of the current European legislative and regulatory framework for clinical research. ICREL provided strong arguments supporting some of the recommendations proposed by various stakeholders in scientific journals, at the EC-EMEA conference on the Directive (2007) and in the ESF "Forward Looks on investigator-driven clinical trials" (2009). For instance, a risk-based approach to regulation would result in a substantial reduction in workload and cost, particularly for academic institutions that run a number of low-risk studies using marketed drugs. Simplification of the Clinical Trial Authorisation process by the competent authorities through a single CTA for multi-national trials would reduce duplication of efforts and also save time, costs, and expertise. Harmonised practice in ethics committee requirements would facilitate and reduce the administrative burden of dossier submission, and changes in expedited SUSAR reporting to the ethics committees would alleviate their workload. Insurance coverage for clinical trials should be reconsidered at the EU level and adequate funding should be provided to institutions performing clinical trials to ensure capacity and expertise for all trial-related activities.

The legislative and regulatory framework for clinical research is one of the major determinants for the attractiveness of a given region for clinical research. Clinical research is a critical activity for science and for developing knowledge on diseases and their treatments. It is also critical for health, allowing development and optimal use of preventive, diagnostic and therapeutic strategies. It is a central activity for the health industry, allowing development of innovation and subsequent economic growth. It is also a source of employment and of revenue for investigational sites. From this perspective, ICREL may be regarded as a model for monitoring the attractiveness of the European Union for clinical research. For this reason, ICREL should now be extended over time for the monitoring of the EU legislation. This could be achieved through a similar survey proposed every 2nd year, in an updated and focused version, including metrics on the impact on the quality of studies and the protection of participants.

Abbreviations

CA	Competent Authority
CHMP	Committee for Human Use Medicinal Products
CI	Clinical Investigation
CO	Confidential
CPS	Clinical Pharmacology Service
CRO	Contract Research Organisation
CS	Commercial Sponsor
CS-CTs	Commercially Sponsored Clinical Trials
CT	Clinical Trial
CTA	Clinical Trial Authorisation
CTD	Clinical Trials Directive
CTFG	Clinical Trials Facilitation Group
CTU	Clinical Trials Unit
DG RTD	Directorate General for Research
DG SANCO	Directorate General for Health and Consumer Affairs
EC	Ethics Committee
ECRIN	European Clinical Research Infrastructures Network
EDCTP	European and Developing Countries Clinical Trials Partnership
EFGCP	European Forum for Good Clinical Practice
EFPIA	European Federation of Pharmaceutical Industries Associations
EMEA	European Medicines Agency
EMRC	European Medical Research Council
EORTC	European Organisation for the Research and Treatment of Cancer
ESF	European Science Foundation
EU	European Union
EudraCT	European Clinical Trials Database
FP7	Seventh Framework Programme
GMP	Good Manufacturing Practice
HCPB	Hospital Clinic i Provincial Barcelona
HIV	Human Immunodeficiency Virus
ICH-GCP	International Conference on Harmonisation – Good Clinical Practice (Guideline)
ICREL	Impact on Clinical Research of European Legislation
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IIT	Investigator-initiated trial
IMI	Innovative Medicines Initiative
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug
INSERM	French Institute of Health and Medical Research
ISO	International Standards Organization
IT	Information Technology
M	Month
MD	Medical Doctor
MedDRa	Medical Dictionary for Drug Regulatory Activities
MUW	Medizinische Universität Wien
NCA	National Competent Authority
NCS	Non-commercial Sponsor

OECD	Organisation for Economic Co-operation and Development
PhD	Philosophical Doctor
PP	Restricted to other programme participants
PU	Public
QA	Quality Assurance
Q&A	Questions & Answers
R&D	Research & Development
SA	Substantial Amendment
SME	Small and Medium-size Enterprise
Supp	Support Activities
SUSAR	Suspected Unexpected Serious Adverse Reaction
UKCRC	United Kingdom Clinical Research Collaboration
US	United States of America
VISEAR	Vienna Initiative to Save European Academic Research
WP	Work Package

Glossary

The present definitions are used in the ICREL project.

- **Adverse event**

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Source: Directive 2001/20/EC, article 2 (m)

- **Adverse reaction**

All untoward and unintended responses to an investigational medicinal product related to any dose administered.
Source: Directive 2001/20/EC, article 2 (n)

- **Big pharmaceutical companies**

Pharmaceutical companies which are not classified as SME and not amongst the top 50 companies ranked by their revenue in 2006.

- **Biotechnological products**

See Biotechnology.

- **Biotechnology**

Any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use.
Source: United Nations, Convention on Biological Diversity adopted in Rio de Janeiro 1992. Article 2: Use of terms

- **Clinical trial**

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy.
This includes clinical trials carried out in either one site or multiple sites, whether in one or more than one Member State. Source: Directive 2001/20/EC, article 2 (a)

- **Competent authority (CA)**

In the context of this survey, the CA is the national authority which provides clinical trial authorisations for trials with investigational medicinal products.

- **Ethics committee (EC)**

An independent body in a Member State, consisting of healthcare professionals and nonmedical members, whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent.
Source: Directive 2001/20/EC, article 2 (k)

- **Full-time equivalent (FTE)**

Tool to measure the workforce required in a project.
One FTE is one full-time position or two half-time positions, etc.
If a task requires 2.5 days per week to be realised, it will require one half-time employee or half the time of one full-time employee; this is 0.5 FTE.
If a task requires three full-time people or six half-time people we talk about 3 FTEs.

- **Informed consent**

Decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation.
Source: Directive 2001/20/EC, article 2 (j)

- **Inspection**

The act by a competent authority of conducting an official review of documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the competent authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organisation's facilities, or at other establishments which the competent authority sees fit to inspect.
Source: Directive 2001/20/EC, article 2 (l)

- **Investigational medicinal product**

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.
Source: Directive 2001/20/EC, article 2 (d)

- **Investigator**

A doctor or a person following a profession agreed in the Member State for investigations because of the scientific background and the experience in patient care it requires. The investigator is responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of

individuals at a trial site, the investigator is the leader responsible for the team and may be called the principal investigator.
Source: Directive 2001/20/EC, article 2 (f)

- **Investigator's brochure**

A compilation of the clinical and non-clinical data on the investigational medicinal product or products which are relevant to the study of the product or products in human subjects.
Source: Directive 2001/20/EC, article 2 (g)

- **Medicinal product**

As the EU CTD refers in its article 1 to article 1 of the Directive 65/65/EEC:
Medicinal product: any substance or combination of substances presented for treating or preventing disease in human beings or animals.
Any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings or in animals is likewise considered a medicinal product.
Source: Directive 65/65/EEC, article 1.2

- **Medicinal product with orphan designation**

A medicinal product that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment;
and
there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.
Source: Regulation (EC) No 141/2000, article 3.1

- **Multi-centre clinical trial**

A clinical trial conducted according to a single protocol but at more than one site, and therefore by more than one investigator, in which the trial sites may be located in a single Member State, in a number of Member States and/or in Member States and third countries.
Source: Directive 2001/20/EC, article 2 (b)

- **Non-commercial sponsor**

A non- commercial sponsor of a clinical trial is a either an individual researcher or a public institution/organization like a university, a hospital, a public scientific organisation, a non profit institution, or a patient organisation.

- **Non-interventional trial**

A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation.
The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data.
Source: Directive 2001/20/EC, article 2 (c)

- **Orphan drugs - Orphan medicinal product**

See medicinal product with orphan designation

- **Protocol**

A document that describes the objective(s), design, methodology, statistical considerations and organisation of a trial. The term protocol refers to the protocol, successive versions of the protocol and protocol amendments.
Source: Directive 2001/20/EC, article 2 (h)

- **Serious adverse event or serious adverse reaction**

Any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.
Source: Directive 2001/20/EC, article 2 (o)

- **Small and medium-size enterprises (SME)**

At European Community level, small and medium-sized enterprises (SMEs) are defined by a set of criteria concerning the workforce, turnover and independence of the business. A SME is an enterprise engaged in economic activity; has fewer than 250 employees; has an annual turnover smaller than 50 million Euros and/or an annual balance sheet total smaller than 43 million Euros and is an autonomous legal entity.
Source: Commission Recommendation 2003/361/EC
Also refer to: http://ec.europa.eu/research/sme-techweb/index_en.cfm

- **Sponsor**

An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.
Source: Directive 2001/20/EC, article 2 (e)

- **Subject**

An individual who participates in a clinical trial as either a recipient of the investigational medicinal product or a control.
Source: Directive 2001/20/EC, article 2 (i)

- **Substance**

Any matter irrespective of origin which may be:
- human, e.g. human blood and human blood products;
- animal, e.g. micro-organisms, whole animals, parts of organs, animal secretions, toxins, extracts, blood products, etc.;
- vegetable, e.g. micro-organisms, plants, parts of plants, vegetable secretions, extracts, etc.;
- chemical, e.g. elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis.

Source: Directive 65/65/EEC, article 1.3.

- **Unexpected adverse reaction**

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product).
Source: Directive 2001/20/EC, article 2 (p)

Introduction

Historical context

One of the consequences of the Nuremberg trial (1947) was a statement on the need to collect informed consent prior to the participation of human beings in biomedical research experiments[1]. This principle was enlarged and refined in the Declaration of Helsinki (1964) and its various revisions, and adopted as a standard for clinical trials on medicinal products run by drug manufacturers for registration and post-marketing purposes. Based on a harmonisation agreement covering the three main geographic areas where clinical development was prominent (European Union, United States of America and Japan), the International Conference on Harmonisation's[2] good clinical practice guideline (ICH-GCP-E6) from 1996 defined the standard for all type of clinical research (*"The principles established in this guideline may also be applied to other investigations that may have an impact on the safety and well-being of human subjects"*)[3] but only adopted by industry as a standard for commercial trials. But whereas drug regulatory agencies required compliance to ICH-GCP in trials intended for submission to competent authorities, there was no mechanism of enforcement for compliance to ICH-GCP in non-commercial trials. The ICH-GCP guideline was implemented in the context of clinical trials for marketing authorisation of medicinal products. Clinical trials on medical devices for registration purposes have to follow the technical requirements provided in ISO14155 and Directive 2007/47/EC, amending Council Directive 90/385/EEC. However, no requirement existed to enforce the implementation of the Helsinki principles and to ensure appropriate protection of participants in medical device and non-commercial clinical research.

Development of national legislation

During the 80's and 90's, some countries developed national legislation to enforce protection of participants in all categories of clinical research. For instance the pioneering Huriet Law[4] in France (1988) covered the participation of patients and healthy volunteers in any 'interventional' clinical research (defined as therapeutic interventions, but also as any invasive investigation), requiring a sponsor responsible for the study, an insurance coverage, an approval by the ethics committee, a collection of informed consent, a notification to the competent authority, and a mechanism for adverse event reporting. Other laws in other countries also resulted in an improvement in the protection of participants; however the type of clinical research covered by these laws and the nature of the protection widely varied between countries. Some countries developed legislation centred on the patients, with an equivalent level of protection in any type of biomedical research, whereas other countries adopted legislation centred on the product, focusing on the credibility of data used for registration purposes, and in which the protection of participants is restricted to clinical trials on medicinal products (and often on medical devices)[5]. This resulted in major challenges for drug manufacturers involved in multinational studies in the EU, and also for

[1] Lemaire F: The Nuremberg doctors' trial: the 60th anniversary. Intensive Care Med. 2006, 32:2049-52.
[2] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. www.ich.org.
[3] ICH Good Clinical Practice Guideline E6 (R1), 10 June 1996.
[4] Jaillon P, Demarez JP, History of the Huriet-Sérusclat's law genesis (December, 1988): protection of patients in biomedical research. Med Sci (Paris). 2008, 24:323-7.
[5] Hartmann M, Hartmann-Vareilles F, The clinical trials directive: how is it affecting Europe's non-commercial research? PLOS Clinical Trials, June 2006, e13.

academic institutions conducting clinical trials: for instance, a randomised surgery trial will require in some countries a sponsor, a liability insurance for trial-related harm to study participants, a submission to ethics committees and to a competent authority, and the reporting of adverse events, and nothing in some other countries. The situation is similar for radiotherapy (with for instance a specific legislation steered by the Ministry of Environment in Germany), and for non-therapeutic clinical research.

The EU Clinical Trials Directive (CTD)

This emphasised the need for harmonisation of the legislative framework for clinical research in the European Union, with the objective of harmonising the regulatory systems, of improving the protection of participants, of optimising the use of safety information, and of ensuring the quality of studies and the credibility of data.

As a consequence, the Directive 2001/20/EC[6] was prepared and adopted on 4 April, 2001 and was to be implemented by all Member States on 1 May, 2004. This new EU legislation led to a strengthening of the responsibility of the sponsors and of the EU Member States in clinical trials, sharing some responsibilities of the ethics committees with the competent authorities, reducing the investigators' responsibility, and improving the patients' protection[7]. A single sponsor in the EU, covered by liability insurance for study-related harm to study participants, has now to submit a clinical trial authorisation application to the national competent authority, and in parallel a request for a single favourable opinion to Ethics Committee(s). With the CTD, an EMEA-based database for study identification (EudraCT) was implemented and a section for clinical trials added to the EudraVigilance database.

However the strength of this new concept was dampened by four major weaknesses:

1. The fact that the clinical trials legislation was established as a Directive required transposition of its principles into national legislation. Since most of the EU countries already had their own legislation and practice before the adoption of the Directive, their interpretation of the Directive and the changes brought to the national legislation were highly dependent on this pre-existing framework. As a result, the harmonisation target was partly missed for clinical trials on medicinal products.
2. Due to the structural singularities of the European Commission it was in the remit of the Directorate Enterprise and Industry to implement clinical trials legislation, and thus the scope of the CTD centred on the product, failing to protect participants in clinical research other than clinical trials on medicinal products. However, several EU Member States choose to implement the CTD in their new clinical research legislation with a wider scope than the Directive's. And as the revision of the national legislations covering other types of clinical research was performed without any EU coordination this process resulted in totally divergent systems.
3. In an attempt to achieve the same quality standards for all types of clinical trials with medicinal products almost similar requirements for all types of clinical trials with medicinal products were introduced. The Directive does not consider the different categories of clinical

[6] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. OJEC 1.5.2001, L 121/34-44.
[7] Editorial: Who's afraid of the European clinical trials Directive? Lancet 361:2167, 2003.

research performed by the commercial (registration studies on new treatments) vs. the non-commercial sponsors (mostly studies comparing treatment strategies and combinations using marketed drugs, or exploring the potential for new indications). Using similar rules and requirements for all types of studies reportedly leads to major obstacles to academic research[8], whereas it was discussed that case-by-case, risk-based strategies taking into account the hazard to the patients and the hazard to public health would probably help ensure quality and protection with less administrative burden and lower costs. Anecdotal and early structured feedback revealed that the increase in sponsor's responsibilities and tasks was not a major obstacle for big pharmaceutical companies. However, SMEs, including small biotechnology companies, face major difficulties in acting as a single sponsor on the EU level for their commercial trials, mostly early proof-of-concept trials, often in rare diseases. Also multi-national non-commercial trials are difficult to organise in an efficient way because a sponsor based at an academic institution in one EU Member State has not the institutional coverage to take over legal responsibility for clinical trial activities performed at an academic institution in another EU Member State. In addition, in different EU Member States academic investigators do not have at all the legal coverage to play the role and endorse the responsibilities of a sponsor according to the requirements of the Clinical Trial Directive.

4. Several of the CTD-related requirements were reported to have led to an increase in administrative tasks for all stakeholders leading to a need for increased resources with the related cost generation, delays in study preparation and performance and the danger of reduced protection of the trial participants as ethics committees reported to have reduced capacities to cover their patient protection responsibilities due to overwhelming administrative tasks, especially in the area of expedited safety reporting.

In addition to these general weaknesses - and despite the release of some guidance documents - the implementation of the CTD suffers from lack of unambiguously clear definitions and processes. These are in particular

- The definition of "Sponsor"
- The definition of "Substantial amendment"
- The definition of "IMP"
- GMP related issues – import rules, manufacturing license, particularly relevant for active biological ingredients
- Free access to marketed drugs in clinical trials
- Liability insurance in multi-national trials

The CTD had a major impact on the structure, procedures and activity of most of the national competent authorities, leading to the need of additional resources and the charging of a fee to the sponsor for clinical trial applications and substantial amendments.
Varying practice in competent authorities and in the dialogue with the ethics committee resulted in significant differences in clinical trial application procedures (for instance, whereas the parallel submission by the sponsor is the rule in most countries, Hungary uses a one-stop shop approach in which the competent authority, not the sponsor, interacts with the central ethics committee).

[8] Meunier F, Lacombe D: European Organisation for research and Treatment of cancer's point of view. Lancet 362:663, 2003.
Meunier F, Dubois N, Negrouk A, Rea LA, Saghatchian M, Turz T, Sullivan R, Law K, Tiner R, Throwing a wrench in the works ? Lancet Oncol. 4:717-9, 2003.
Moulton B, Save European research campaign. BMJ 328:286, 2004.

As the staff and budget capacities vary in the different competent authorities, the management of SUSARs notified to the competent authorities, their practices to support MedDRA coding and to send electronic notifications to the EudraVigilance database differ. In addition, the EU Member States' requirements for dissemination of SUSAR information varies.

There is an indirect impact of the CTD as some countries developed strategies for cost-effective, risk-based monitoring in non-commercial trials, and some provide logistic and financial support to this monitoring activity for investigator-initiated studies. Some went further and fostered the development of a national infrastructure for clinical research: clinical research centres, clinical trials units[9], national networks[10], and EU-wide infrastructures networks[11] or disease-oriented scientific networks[12]. In addition, initiatives were developed to facilitate the conduct of industry-sponsored trials in some countries (the UK Clinical Research Collaboration, the CeNGEPS in France).
The impact of the Directive on the ethics committee was major as it requires delivering a single opinion in each EU country. However, this was implemented in very different ways in the EU Member States, and often the single opinion still requires multiple submissions of information and review as well as extended delays[13]. Differences in the interaction between ethics committees and competent authorities, in processes, composition, training, fees, number and activity of ethics committees, in their independence, and in the cultural context of ethical review result in major discrepancies between countries in protocol and patient information requirements, review timeframes, costs and acceptability for a single protocol[14] in a multinational study. Moreover, ethics committees and sponsors complain about the workload due to the useless notification of SUSARs.

This disharmony in the national implementation of the CTD, the disagreement on definitions and the varying support and initiatives provided by different governments raise concerns on the competitiveness of the clinical research in the European Union and on its attractiveness as a place for clinical trials, in the context of globalisation of these activities with emerging investigation sites in Eastern Europe and in Asia-Pacific.

[9] Bell J. Resuscitating clinical research in the United Kingdom. BMJ 2003; 327: 1041-43.
[10] Demotes-Mainard J, Chêne G, Libersa C, Pignon JP. Clinical research infrastructures and networks in France: report on the French ECRIN workshop. Thérapie, 60:183-199, 2005.
[11] Demotes-Mainard J, Ohmann C. European Clinical Research Infrastructures Network: promoting harmonisation and quality in European clinical research. Lancet 2005; 365, 107-108.
[12] Bassand JP, Martin J, Ryden L, Simoons M: The need for resources for clinical research: the European Society of Cardiology calls for European, international collaboration. Lancet 2002; 360: 1866-69.
and Clumeck N, Katlama C. Call for network of Centres of Excellence in clinical research in Europe. Lancet 2004; 363: 901-02
[13] Druml C, Singer EA, Wolzt M, Report of the 1st meeting of the "Vienna Initiative to Save Academic Research (VISEAR)", Wiener Klinische Wochenschrift 118/5-6 (Suppl)1-12, Apr. 2006.
[14] EFGCP Ethics Working Party, Subgroup on Ethics Committees Reviewing Investigational Medicinal Products within the European Union. The procedure for the ethical review of protocols for clinical research projects in the European Union. Int J. Pharm. Med, 2007, 21:1-113.

Rationale

To ensure the achievement of the Clinical Trials Directive's aims it may be necessary to reconsider certain aspects of the current legislation and to adapt or revise the legislative framework. Such decision requires,

- objective information on positive and negative impact factors on clinical trials with medicinal products and on other types of clinical research,
- reliable figures on the impact of the legislation on the clinical research activity of big Pharma Industry -, SME- and academia-sponsored trials,
- evaluation of the resource, cost and effectiveness implication of the EU CTD implementation for all stakeholders,
- comparison of the success of national CTD implementation,
- consolidated conclusions on the findings amongst the stakeholders,
- dissemination of the conclusions to the public at large.

Data from individual countries, based on different methodologies, suggest that the impact of the Directive may vary from one country to another. Therefore, collection of data throughout the European Union, with the same methodology and compared to existing partial information will certainly help further describe and interpret this impact.

Objectives

This work is expected to help improving Europe's attractiveness and competitiveness for clinical research by delivering the facts for proposing pathways for improvement of the clinical trial environment in the EU, allowing better balance of high level patient protection, optimal use of safety information, high quality and credibility of data with acceptable cost and workload for investigators, sponsors, ethics committees and competent authorities, for both national and multinational studies in the EU. Together these improvements should increase the competitiveness of the academic EU clinical research and its attractiveness as a place for commercial clinical trials compared with emerging investigation sites in Eastern Europe and in Asia-Pacific[15].

[15] Thiers FA, Sinskey AJ, Berndt ER, Trends in the globalization of clinical trials. Nature Reviews Drug Discovery, 7:13-14, 2008.

Review of other assessments, reports, analyses and case studies

A large amount of information has been collected and reported in an attempt to describe the current situation of clinical research in Europe and world-wide. Primary focus and methodology, broadness and reliability of results vary considerably and thus the relevance for this project differs. However, it is worthwhile to create an overview to identify patterns.

Multi-stakeholder-related

International aspects

Is the randomized controlled drug trial in Europe lagging behind the USA?

Hiddo J. Lambers Heerspink, Mirjam J. Knol, Robert J.W. Tijssen, Thed N. Van Leeuwen, Diederick E. Grobbee & Dick de Zeeuw; British Journal of Clinical Pharmacology, DOI:10.1111/j.1365-2125.2008.03296.x.

Research Topic and Methodology

The authors investigated the number of publications on randomised clinical trials with drugs in the US, Europe and Australia/Japan between 1995 and 2004, considered as a proxy measure for the quantitative output of this kind of trials. They evaluated the number per originator country and adjusted the number with the population size of these countries. In addition they explored the national health-related R&D expenditures by governments as a proxy measure for the country's investment in clinical research. And they evaluated the number of headquarters of pharmaceutical companies in a country and the companies' R&D expenditure.

Results

Europe produced the largest number of publications in that period, followed by the US and Australia/Japan. However, after adjustment for the average population size, Europe ranked lower than the US but higher than Australia/Japan. The increase of publications during that period was lowest in Europe (29.1%), followed by the US with 40.1% and Australia/Japan with 63.4%. Also the citation rate was lower in Europe than in Australia/Japan and the US. The statistical evaluation revealed that the smaller number of Pharma company headquarters in Europe and their R&D expenditures in Europe and in a more modest way the lower national governmental R&D expenditure in Europe compared to the US were the responsible factors for the lower publication output in Europe.

When they compared the publication output of the different EU countries they found that UK, Germany and Italy produced the highest numbers of publications, after adjustment with the population size, the top countries, however, were Denmark, Finland and Sweden, all countries with a relatively high number of Pharma companies. As also other recent bibliometric research of Europe's top 10 Pharma companies revealed a distinctive "home advantage" where these companies tend to prefer local research partners, the authors recommend a closer collaboration between researchers and national Pharma companies in order to attract pharmaceutical research investment and retain their role in conducting randomized clinical trials with drugs. But also an increase in national governmental R&D investment should be encouraged.

The authors also described the potential weaknesses of their scientific approach: they feared a weakening impact of a publication bias as it is known that 30-60% of the trials performed in Europe are never published. And they could not find quantitative data to compare other potentially influencing factors like academic promotion policies, number of researchers in medical sciences and the amount of research funding provided by private organisations.

Comments

The data stem from the period before implementation of the CTD, but they reveal important factors influencing clinical trial publication activities in different countries. It would be important to compare the publication activity in Europe after 2004 with the results generated in this publication.

Trends in the globalization of clinical trials

Thiers FA, Sinskey AJ, Berndt ER. Nature reviews. January 2008 volume 7

Research Topic and Methodology

To quantify trends of the globalisation of biopharmaceutical clinical trials based on publicly accessible data (www.clinicaltrials.gov), the authors discussed the recent shift in clinical trials sponsored by the industry towards emerging regions like Eastern European, Latin American and Asian countries.

Results

The US dominates by a large margin, more than eight times the number of trials sites than Germany, the second in place.
The top five countries are all in traditional regions (North America, Western Europe and Oceania) and together host 66% of all trial sites.
Countries in emerging regions (Eastern Europe, Latin America, Asia Middle East and Africa) are mostly small players when analysed individually (each with less than 2% global share), but as a group they host 17% of actively recruiting sites.
In terms of growth rates, 24 of the fastest growing 25 countries are from emerging regions, while 18 of the 25 slowest growing top 50 countries are from traditional regions.

Comments

Country trends in participation in biopharmaceutical clinical trials are valuable information when applied to ICREL and the different European countries, for the country sampling categorisation.

Pan-European aspects

Vienna Initiative to Save European Academic Research (VISEAR)

Druml C, Singer EA, Wolzt M, Report of the 1st meeting of the VISEAR, Wiener Klinische Wochenschrift 118/5-6 (Suppl)1-12, Apr. 2006.

Research and methodology

The Vienna Initiative to Save European Academic Research (VISEAR) brought together leading stakeholders from academic research groups and interested parties from industry, international organisations and regulatory authorities to focus on the issues of concern regarding the

organisational and funding of academic clinical research in order to improve the development and use of medicines in Europe. The first step of the initiative was a meeting held on May 30, 2005 in Vienna. This report summarized the results of the first meeting of VISEAR.

Results

According to the experience of the 40 invited experts in this meeting, some areas were of particular concern: trial sponsorship, the ethical review process, the participation of patients who are temporarily not able to consent in clinical trials, in particular the informed consent process, an accepted European registry for all clinical trials, insurance and pharmacovigilance. They agreed that especially the bureaucratic burden for academic investigators had tremendously increased without representing any contribution to patients' safety or the scientific value of research. Furthermore, some large European academic trials could not be conducted due to the new legislation, resulting in an overall decrease in number of trials and number of patients enrolled in trials.
In particular, the following request for clarification and consistency, respectively recommendations were made:

- Acceptability of allocation of sponsor legal responsibilities among a group of academic researchers.
- Aspects of study management and pharmacovigilance should be adapted to the type of trial and the level of involved risks for the patient.
- Clarification of details of GCP which may be guaranteed by other means and taking due cognizance of measures normally implemented in national health care systems or in overlapping patient care structures.
- When access to marketed IMP on the same basis as routine treatment may be acceptable and when not?
- Establishment of an information centre on ethical review standards and procedures in each Member State.
- The development of education programmes for ethics committees across Member States
- Coordination and interaction between ethics committees at the EU-level.
- Evaluation of existing experience and establishing guidance to assist researchers and ethics committees with the involvement of incapacitated patients into all types of clinical trials
- Access to the EudraCT database for the public.
- Definition of minimal data requirements to be entered in a clinical trial registry, avoidance of multiple entries in different databases (one-stop-shop principle), establishment of a separate database for non-IMP trials.

Comments

The VISEAR initiative was aimed to make suggestions and improvements to the clinical trials directive, by involving different stakeholders of clinical research.

Clinical research in Europe: national differences in legislative and regulatory frameworks

ECRIN-TWG Deliverable 4, 2008, see www.ecrin.org

Research and methodology

The ECRIN-TWG Working Group on regulation provided an in-depth description of the regulatory framework for clinical research and how to interact with competent authorities in ten countries (Austria, Denmark, France, Germany, Hungary, Ireland, Italy, Spain, Sweden, United Kingdom).

Designing the survey required to reach an agreement on common definitions for categories of clinical research. Seven main categories were considered, each split into sub-categories.

1. Clinical trials on medicinal products.
2. Clinical trials on medical devices.
3. Other therapeutic trials (including radiotherapy, surgery, transplantation, transfusion, cell therapy, physical therapy, psychotherapy trials).
4. Diagnostic studies.
5. Clinical research on nutrition.
6. Other interventional clinical research (including complementary and alternative medicines, biobanks, physiology, physiopathology and psychology trials).
7. Epidemiology (observational studies).

The survey on national requirements for each category of research covered the following items:

- is a submission to an ethics committee required (specify the name of the committee and who is responsible for the submission)?
- is a submission to competent authority required (specify the name of the competent authority and who is responsible for the submission)?
- is there a specific procedure for substantial amendments?
- is there a requirement for a sponsor and is co-sponsorship allowed?
- is insurance required (specify who is covered; sponsor, investigator, participant)?
- adverse event reporting (specify which adverse events have to be reported by the sponsor, when, and to whom)?
- is a safety report requested?

Results

The main outcomes of this survey are that:

- The extent of the legislation on clinical research varies from one country to another: some national legislation focus on clinical trials on medicinal products, whereas other legislation considers the protection of participants in all the categories of clinical research.
- There is partial harmonisation in the legislation for clinical research on medicinal products. As a consequence of divergent transposition of the Directive 2001/20/EC into national laws substantial differences in the regulatory framework make planning and execution of multinational clinical studies still very difficult. The main differences concern the number and role of competent authorities, the number and role of ethics committees, the process leading to the single ethical opinion, the interaction between competent authorities and ethics committees, the requirement for submission to a personal data protection board (or boards). Some countries allow multiple sponsorship, most do not. Insurance for academic research is covered by the public health system in some countries, and in others the union of pharmaceutical companies has contracted a national insurance package covering all the industry-sponsored trials. There are differences in the interpretation of the definition of investigational medicinal product (IMP), especially regarding the baseline treatment, with major consequences for SUSAR reporting, labelling, and provision by the sponsor. Under some circumstances and in some countries cell therapy products are considered as IMP and in other countries as non-IMP (and in this latter case the trials is not covered by the Directive 2001/20/EC). Finally some countries, and not

others, have a definition for non-commercial sponsors or for non-commercial trials, with related adaptations and waivers.

- There are major discrepancies in the regulatory framework for other categories of clinical research, not covered by the Directive 2001/20/EC, especially regarding the requirements for a submission to competent authorities (often distinct from the medicines agencies, depending on the nature of the health product, and in some countries there is a need to submit to a competent authority even in the absence of a health product). There are also major differences in the requirements for a sponsor (required only in some countries, or for particular categories of research), and for adverse event reporting. Some countries have extended the concept of SUSAR to trials on medical devices, or even to all interventional research. There are major discrepancies regarding insurance, which may or may not be required depending on the country for the same protocol. In some countries the ethics committee decides on the need for insurance. There is a need to clarify the definition of categories of research and their interpretation (for instance the border between interventional and observational studies may differ between countries).
- In turn, protection of participants is achieved through submission of protocol applications to the ethics committee in every country, at least for all the categories of interventional research. These ethics committees may, or may not, be the same for every category of research. In some countries observational studies do not require submission to a research ethics committee.

Comments

This was an in depth and comprehensive (more than 100 pages) comparative analysis between 10 national regulatory requirement for all the categories of clinical research, with recommendations for improvement, but without metrics on its impact.

Further details on the ECRIN Project's methodology, findings, conclusions and recommendations can be found in Annex V.

Who's afraid of the European Clinical Trials Directive?

Editorial, Lancet 361:2167 (2003)

Research and methodology

This editorial describes the objectives of the Directive 2001/20/EC and the concerns about its implementation.

Results

The fears expressed by academic institutions, by the UK pharma industry (ABPI) as early as in 2003 are a poor harmonising effect and increase in administrative burden.

Comments

Even before the implementation of the Directive 2001/20/EC into national legislation, academic and industry sponsors anticipated a negative impact.

Outcome of the Clinical Trials Directive on clinical cancer research in Europe: a 3-years'-follow-up analysis

Hartmann M, Hartmann-Vareilles F, Poster. Eur J Cancer Supplements (2007) 5(4):107(abstract 700)

Research Topic and Methodology

Analysis of Clinical Trial Application (CTA) charts covering the period 2001-2006 published by the EMEA and national authorities in six EU countries. Whenever possible, data for commercial and non-commercial trials, oncology and paediatric oncology were tracked separately

Results

The implementation of the European Clinical Trials Directive has resulted in a drop of around 7% of the proportion of non-commercial clinical trials in oncology.

Comments

This paper provides preliminary data on the impact of the Clinical Trials Directive on non-commercial clinical research in oncology according to the activity reports published by the EMEA and several Competent Authorities.

Does the European Clinical Trials Directive really improve clinical trial approval time?

Hiddo J. Lambers Heerspink, Daniela Dobre, Hans L. Hillege, 1 Diederick E. Grobbee2 & Dick de Zeeuw; for the Collaborative Study Group, British Journal of Clinical Pharmacology, DOI:10.1111/j.1365-2125.2008.03246.x.

Research Topic and Methodology

The authors compared the clinical trial approval times in a multi-national clinical trial approved in 2005 in different countries: Austria, Belgium, Denmark, Hungary, Italy, Poland, Portugal, Spain, Sweden, United Kingdom, France and the Netherlands (these two countries had at that time not yet implemented the CTD), as well as Israel, Switzerland, USA and Australia representing non-EU-CTD countries.

Results

The median approval duration was significantly longer in sites following the CTD when compared with EU sites following national legislation (75 vs. 59 days). However, further analysis revealed that 5 of the 10 EU-CTD countries did not follow their legal requirements at that time: they applied sequential instead of parallel submission of CTA applications to regulatory authorities and central ethics committee and/or their local ethics committees performed procedures which should have been limited to the central ethics committee. When these countries were excluded from the evaluation, the approval times were similar for countries which had implemented the CTD into their national legislation and countries following a non-revised national legislation (59 vs. 61 days). And the variation of approval times was smaller in EU-CTD countries (43-67 days) compared with the European non EU-CTD countries (10-119 days). However, the overall approval time in Europe was significantly longer than in the US (67 vs. 15 days), especially when compared with US sites following a central ethics committee procedure (9 days). In comparison with Australia the European approval times were comparable (67 vs. 68 days) but longer in EU-CTD countries (68 vs. 75 days).

Comments

This investigation represents a snapshot of the situation in 2005 in the EU and the implementation of the CTD has further developed, but it is of persistent relevance for the comparison with the US and Australian approval times as the magnitude of these has not changed since 2005.

The Clinical Trials Directive: 3 years on

Hoey R., Lancet 369:1777-8 (2007)

Research and methodology

This paper describes the concerns raised by various stakeholders following the implementation of the Directive 2001/20/EC.

Results

This paper comments various analyses regarding the impact of the Directive 2001/20/EC: effects on harmonisation, effect on administrative burden, effect on costs, effects on sponsor responsibility, effect on the number of trials as deduced from scattered data. It claims for an in depth re-engineering of the Directive (Directive-2), and announces the EMEA conference on October 2007.

Comments

Some quantitative data on the number of clinical trials are quoted in the text, but there is no systematic collection of data on metrics regarding the impact of the Directive.

Data from the EudraCT database

Following the implementation of the Directive 2001/20/EC, an EMEA-based database for study identification (EudraCT) was created on the 1 May 2004. The information stored in EudraCT are the total of clinical trials applications (CTA) with subtotals for the type of sponsor (commercial or non-commercial) and the type of trial (single site, multiple site, multi-member states or third countries).
All data presented in Annex 4 show the number of total clinical trials applications and since one trial may involve more than one Member State, the actual number of distinct trials is less than the number of CTAs.
Provision of data from the EudraCT data base for this report was only possible in an anonymous way. Thus the individual curves can not be allocated to particular countries. However, the messages provided are very relevant for the understanding of clinical trial activities in Europe since 2004.

National Aspects: Denmark

Effect of European Clinical Trials Directive on academic drug trials in Denmark: retrospective study of applications to the Danish Medicines Agency 1993-2006

Louise Berendt, Cecilia Hakansson, Karin Friis Bach, Kim Dalhoff, Per Buch Andreasen, Lene Grejs Petersen, Elin Andersen and Henrik Enghusen Poulsen. BMJ published online 6 Dec 2007; doi: 101136/bmj.39401.470648.BE

Research Topic and Methodology

To determine the impact of the European Union's Clinical Trials Directive on the number of academic drug trials carried out in Denmark, compared with data from Sweden and Norway.
Retrospective review of applications for drug trials to the Danish Medicines Agency (DMA) from 1993 to 2006.

Results

Applications for clinical trials to the DMA from 1993 to 2006 showed a continual decline, from 417 in 1993 to 260 in 2005 and an increase to 336 in 2006. A similar trend was found in Norway but not in Sweden where the number of applications remained nearly unchanged. Applications from the commercial sector in Denmark decreased from 262 in 1993 to 174 in 2005, increasing to 229 in 2006 and those from academic researchers decreased from 147 in 1993 to 86 in 2005, increasing to 107 in 2006. Investigator initiated applications in Norway showed the same trend as in Denmark while the rate in Sweden practically constantly increased since 1996.

In contrast to other country reports no decline was shown in the number of Danish drug trials by academic researchers or the commercial sector after 1 May 2004 when the European Clinical Trials Directive came into force. Since 1993, however, a steady decreasing trend has been observed in numbers of clinical trials. The increase in clinical trials in 2006 was unexplained and needs to be followed up to determine whether this is the start of a trend or coincidence. The authors concluded that the establishment of university- and university hospital-based GCP units already in 2000, providing free assistance to academic researchers, has helped to avoid a decline of clinical trials after 2004 as seen e.g. in Austria.

Comments

The results are based on solid data and the authors provide an interesting recommendation for best practices.

Competent Authority-related

National Aspects: Germany

CTA applications at BfArM and PEI

www.bfarm.de/cln_012/nn_1198732/DE/Arzneimittel/1__vorDerZul/klinPr/news/5000__Genehmigungsantraege.html__nnn=trueUpdate 17.02.2009
http://www.pei.de/cln_108/nn_161972/DE/infos/pu/02-klinische-pruefung/klin-pruef-statistik/klin-pruef-statistik-node.html?__nnn=true&__nnn=true#doc158036bodyText2. Update 05.02.2009

Research Topic and Methodology

On 6 August 2004, the Clinical Trials Directive was implemented in the German national legislation, requiring a CTA and a single favourable ethics committee opinion as a pre-requisite for starting a clinical trial with an IMP. Before that date both German competent authorities, the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) and the Paul-Ehrlich-Institut (PEI) received and confirmed receipt of notifications only. On 26.02.2008 the BfArM published results on their clinical trials activities between 2001 and 2007 on their webpage, presenting the monthly number of notifications/CTA applications as well as the representation of the different clinical trial

phases per year. On 17.02.2009 the overall number of applications between 06.08.2004 and 31.12.2008, the involved product groups and clinical trial phases were published.

Results

In 2001 to 2003 BfArM received between 1300 and 1400 notifications for clinical trials per year. In 2004, a lot of sponsors submitted a notification before the new legislation came into force, after that the submission of CTAs started only slowly. Nevertheless, the overall number of notifications/CTAs in 2004 amounted to 1735. Since 2005 the number of CTA applications remained stable around 1200/year. In total, BfArM had received 4911 CTA applications between 06.08.2004 and 31.12.2008. While in 2004 the percentage of trials from non-commercial sponsors had a historic low of 7.5%, this percentage increased to 15.6%, 19.7%, 19.4%, and 16.6% in the years 2005, 2006, 2007, and 2008, respectively. The distribution between the phases 1 to 3 remained stable at approximately one third over the complete observation period, however, after 2004 the percentage of Phase IV trials increased from in the average 4% to 10%.
With 20.29% the most frequent product category was anti-neoplastic and immune-modulating products, followed by CNS (17.78%) and alimentary system/metabolism (12.71%) products.

For the PEI no figures on notifications could be retrieved from their webpage. However, detailed statistics for CTA applications between 06.02.2004 and 31.12.2008 are provided for the biomedical products the PEI is responsible for:
Only 25 CTAs were submitted in 2004, but then the number steadily increased to 155, 183, 210, and 214 CTAs in 2005, 2006, 2007 and 2008, respectively, in total 787. The percentage of non-commercial trials remained constant around 20%, the most frequently submitted CTAs concerned monoclonal antibodies followed by vaccines. Over the years the phases shifted from a majority in phase 3 towards phase 2.

Comments

The data provided by BfArM show a small overall decrease of clinical trial activity in Germany after implementation of the CTD with stable numbers between 2005 and 2008 and a consistent percentage of non-commercial trials between 16 and 20%. The data provided by PEI do not allow a comparison with before CTD implementation.

National Aspects: Italy

Bulletin Clinical Trials of Drugs in Italy

Agenzia Italiana del Farmaco, Osservatorio Nazionale Sperimentazone Clinica, 2008.
http://oss-sper-clin.agenziafarmaco.it/pubblicazioni/boll_ing_2008.pdf

Research Topic and Methodology

This Bulletin contains data collected by the National Monitoring Centre, entered by sponsors and ethics committees as well as Phase 1 trials evaluated by the Italian Institute of Health from 1 January 2000 to 31 December 2007 in Italy. The Italian database – Observatorio - is a mandatory step for each sponsor willing to perform a clinical trial on medicinal products in Italy. Based on all those data, the Italian Medicines Agency publishes on a yearly basis Italian figures on clinical trial data.

Results

Since 2000, 5122 clinical studies have received positive EC approval. The most active year was 2006 with a number of 769 clinical studies whereas there has been an increase of approximately 29.5% from 2003 (579 clinical studies) to 2007 (750 clinical studies). Phase I trials have increased from 11 CTs in 2003 to 32 CTs in 2007 and Phase II have increased from 202 CTs to 287 CTs for the same years. Phase III trials remained stable over years whereas Phase IV trials increased from 47 CTs in 2003 to 92 CTs in 2007.

In 2003, 123 CTs were mono-centre trials and 456 multi-centre CTs whereas in 2007, 152 CTs were mono-centre trials and 594 multi-centre ones. As per national versus international multi-centre clinical trials, a small increase was observed in both categories: national multi-centre CTs raised from 135 in 2003 to 147 in 2007 whereas international multi-centre CTs increased from 320 in 2003 to 447 in 2007.

Over the years (2000-2007), 70.5% were CTs performed by commercial sponsors and 29.5% by non-profit sponsors (Phase I trials excluded).

Most represented therapeutic category was oncology with 27.8%; then cardiology/vascular diseases with 11% and immunology and infectious diseases with 9.4% (Phase I trials excluded).

Comments

Useful data on the situation in the period considered for the project in Italy with breakdown per type of sponsor and areas of activity.

Ethics Committee-related

Pan-European aspects

The Procedure for the Ethical Review of Protocols for Clinical research Projects in the European Union

The European Forum for Good Clinical Practice (EFGCP) Ethics Working Party, Subgroup on Ethics Committees Reviewing Investigational Medicinal products within the European Union. International Journal of Pharmaceutical Medicine vol.21, No. 1 (pp. 1-113) 2007. Annual Update on www.efgcp.be

Research Topic and Methodology

EFGCP prepared a questionnaire with 35 questions asking for specifics of the national implementation of the Clinical Trials Directive in all EU Member States impacting the ethics committee systems and the ethical review procedures. The questionnaire was sent to national ethics committee experts who had been involved in the implementation of the new systems and who had an overview over the outcome of the implementation in the different countries.

Results

In this way it was possible to receive comparable information from all EU Member States. The result is listed in this Final Report and provides a striking impression of the diversity and complexity of the ethical committee systems and the ethical review procedures in Europe.

Comments

Very useful data on the diversity of ethics committee systems and procedures in the EU, updated on an annual basis.

National Aspects: The Netherlands

Nefarma Clinical Trial Database (NCTD) Monitor

August 2008, http://www.nefarma.nl/cms/publish/content/showpage.asp?pageid=1967

Research Topic and Methodology

This database contains data from 1 March 2007 to 29 February 2008 where 83 clinical trials and 150 local assessments were registered (numbers are larger than previous years). The aim of this bulletin is to provide trends on the ethical review process in the Netherlands. This database contains information on time lines for central Ethics Committee (METC) approvals and local feasibility assessment by local Ethics Committees.

Results

While the Dutch legislation requires a limitation of the review period for the central ethics committee of 60 days and for the local ethics committees of 30 days, the overall review period is in approximately 30% over-run be the central ethics committee and in 70% by the local ECs in 20% of those by even more than 70 days.

Comments

Useful data on the ethics committee approval timelines in 2007 in the Netherlands.

Commercial sponsor-related

Pan-European aspects

Promoting Consistency of Implementation and Interpretation of the Clinical Trials Directive across EU Member States

BIA and EuropaBio "White Paper", October 2006, adapted in "EuropaBio Submission", September 2007

Research Topic and Methodology

EuropaBio and BIA, the BioIndustry Association released a White Paper in October 2006 and adapted its content in their submission to the European Commission and EMEA in preparation for the 3 October Meeting 2007 in London: "Conference on the Operation of the Clinical Trials Directive (Directive 2001/20/EC) and Perspectives for the Future."

Results

EuropaBio and BIA are representing especially medium-size companies and SMEs. These companies are particularly hampered by increased bureaucracy and related costs. The organisations detected from their members the following difficulties:

- Lack of harmonisation for applications for CTAs, increased bureaucracy and proliferation of Member State- specific requirements, e.g. for the IMPD, and differences in definition of "substantial amendment"
- Multiple, complex ethics committee structure, undefined review procedure and overlap with the competent authority review
- Different interpretation of the definition of IMP and requirements disproportionate with the objective of safeguarding clinical trial subjects in the guidance on IMP definition.
- GMP requirements of IMPs such as the scope of Manufacturing Authorisation requirements, different IMP labelling requirements or Import Licence requests for products from other EU Member States by some National Agencies.
- Enhanced quality data requirements for biopharmaceuticals from some National Agencies
- Differences in requirements for safety reporting and the Annual Safety Report

The following suggestions for improvement were provided in the "EuropaBio Submission, September 2007:"

- **Transparency in documentation and data requirements for CTA applications** through updated Commission guidance, National Agency websites clarifying national CTA requirements and guidance on data requirements for CTAs for Phase I, II, and III trials.
- **Harmonisation of scientific assessment** by providing pan-European training for assessors.
- **Guidance on substantial amendments** by providing clarity on what constitutes a substantial amendment and the approval/notification process with National Authorities and Ethics Committees.
- **Transparency of approval time lines** by publishing approval metrics to allow better planning
- **Improving communication between Ethics Committees and National Competent Authorities** by better coordination of their activities.
- **Update of Directive 2001/20/EC** by modifying the language in the provisions which are open to misinterpretation and misapplication by Member States.
- **Clear provisions and definitions in the body of the Directive** especially in definition of IMP, substantial amendment as well as format, content and submission of a CTA.
- **Streamlining the review processes** through mutual recognition of assessment by National Competent Authorities and strengthening the role of the Clinical Trials Facilitation Group.
- **A single point of entry for submission of CTA applications into EudraCT**.
- **Harmonisation of safety reporting requirements** with harmonised electronic reporting to all concerned Member States, only periodic reporting of SUSARs in form of line listings to ethics committees and in form of SUSAR summaries to investigators.
- **Promoting Europe's competitiveness for clinical development of innovative medicines** through collaboration on inspections between EU and US FDA as well as through harmonisation of approval time lines on both Continents.
- **Promoting innovation: Industry and academia relationships** by fostering collaboration between industry and academia, developing guidance on how industry can support academia without affecting the scientific, technical and procedural autonomy of the investigators and by a more homogenous and consistent definition of the modalities for non-commercial trials.

Comments

These observations and recommendations are very important for a comparison with the SME observations in the ICREL project.

Results of the Joint EFPIA-PhARMA Survey on the Implementation of the Clinical Trial Directive in Europe

February 2006

Research Topic and Methodology

EFPIA/PhARMA Member Companies conducted a follow-up survey on experiences collected within the framework of the Clinical Trials Directive focusing on the year 2005. The survey aimed at reassessing the validity and relevance of clinical trial issues identified in a 2004 survey. Time lines for Clinical Trial Authorisation applications and Substantial Amendments were reported as well. Twenty five (25) companies participated in the survey.

Results

The main findings were:

- Critical issues identified in the 2004 survey were mostly still considered valid by the participating companies.
- The issues with the highest occurrence and impact on the performance of clinical trials were:
  - Diversity of national requirements and lack of harmonisation for Clinical Trial Authorisation (CTA) applications;
  - Different requirements from Member States in Safety Reporting to Competent Authorities, Ethics Committees and Investigators;
  - Differing review outcomes by Competent Authorities and Ethics Committees.
- Other areas which will require further clarification include:
  - Differing interpretations of the definition of Investigational Medicinal Products in multiple background therapy trials In particular the areas of HIV, oncology, rheumatology and organ transplantation were highlighted;
  - GMP issues in some Member States;
  - Requirements for Annual Safety Reports;
  - Classification of substantial amendments.

In general, it was appreciated that the Clinical Trials Directive sets a framework for requirements and time lines in Europe. When asked, however, whether the environment for performing clinical trials in the European Union has improved, 72% of the respondents indicated that the environment has either stayed neutral or has become more negative. Most critical points that were highlighted included the lack of harmonisation and the increased bureaucracy.

The remaining 20% of respondents indicated that the environment has become more positive. About 8% of the companies did not provide a response to this question. The areas of improvement specifically mentioned were the harmonised requirements for IMPDs and the defined maximum approval time lines for Competent Authority and Ethics Committee approval. Also, average approval time lines of Competent Authorities and Ethics Committees were mostly within the 60 days frame. This confirms the supportive effect of harmonisation.

Comments

EFPIA is in the process of releasing a position paper recommending a facilitated approach to CTA approval in multi-national clinical trials, but this position paper is not yet available for our report.

National Aspects: France

France, an attractive country for international clinical research: 2008 survey

assessed by Leem: Lassale C, Sibenaler C, Béhier JM, Plétan Y, Courcier S., Therapie 63: 345-57 (2008)

Research and methodology

This paper evaluated the attractiveness of France for conducting international clinical trials, through a survey performed every two years among pharmaceutical companies that are based in France or have affiliates in France. This survey provided performance indicators for France (recruitment, time to approval, costs, etc).

Results

Nineteen companies (61.9% of the French market) had participated in the current survey which included 385 international phase II and III clinical studies, 77 countries, 29,708 centres and 312,835 patients (included in 2006/2007). France (400 patients/million inhabitants) ranked among the best European recruiters in second position behind Scandinavia. Since 2006, France has improved administrative processes and reduced deadlines for hospital contracts. Protocols are now to be given the go-ahead by French Authorities (AFSSAPS and CPP) within 60 days, in accordance with the European Directive. Its performance in early phases, oncology/haematology and vaccines/anti-infectious contribute to the attractiveness of France in international clinical research.

Comments

This paper provided metrics on the performance of clinical research in France in 2006 and 2007.

National Aspects: Germany

Genehmigung klinischer Prüfungen in Deutschland

Birgit Wolf, Ferdinand Hundt, Pharm. Ind. 69, Nr. 12, 1421-1427 (2007)

Research Topic and Methodology

17 research-based pharmaceutical companies of the Verband forschender Pharmahersteller (VFA) participated in a survey on the current experience with the Clinical Trials Directive's implementation in Germany. They represented 244 CTAs and 182 substantial amendments between October 2005 and June 2006. A similar survey had been performed in 2005 and thus allowed a comparison and valuable insight of the performance of the regulatory approval procedure from the view point of commercial sponsors.

Results

According to German legislation the regulatory approval timeframe for most products is limited to 30 days. However, if the submission dossier is incomplete the competent authority has an additional 10 days to request completion of the dossier and the sponsor has then 14 days for the sponsor to achieve this. In case of request for additional information during the approval period the clock is stopped and the sponsor has 90 days to provide the additionally requested information. In the survey the average overall duration from arrival of an application to approval was 43.8 days for Phase I trials and 57.3 days for Phase II/III trials. The minimal duration was 12 days for Phase I trials and 29 days for Phase II/III trials. But there were also approval times of 111 days for Phase I and 141 days for Phase II/III trials which included formal and content objections. The average review time of a complete dossier by BfArM was 29 days for Phase I trials and 27.7 days for Phase II/III trials.

During the observation period sponsors reported of 2 rejections and 3 withdrawals of applications. The reported time lines were not different from those observed in 2005.

The relative frequency of formal objections in the dossier review period was 31% in Phase I trials and 38.6% in Phase II/III trials. This was a significant reduction in comparison to the 2005 survey where the frequencies were 56% and 67%, respectively.

Comments

The article provided in addition detailed information on the type of formal and content objections experienced during the survey period.

Non-commercial sponsor-related

International aspects

Investigator Initiated Clinical Trials Characteristics

Johan PE Karlberg, Clinical Trial Magnifier, Oct. 2008, Volume 1, Issue 10.

Research Topic and Methodology

The NIH clinical trials repository (clinicaltrials.gov) was analysed in order to characterise all CTs registered during a 3 year period (1 Oct. 2005- 29 Sept. 2008).

Results

24,931 new trials were registered. Industry was the prime sponsor in 49%, NIH in 15%, other non-industry sponsors in 37%.
Types of trials: Drugs or biological products: 83% (93% industry - 77% non-industry), devices 5.4% (non-industry: 10% - industry 1%), medical procedures 5.1% (1% industry- 7% non industry), behavioural 3.7%.
Setting: 26% of industry and only 4% of non-industry sponsored trials were multi-national. Therapeutic area of the non-industry sponsored trials: ca.36% oncology, 15% CNS, 10% cardiovascular and 9% infectious. The authors stated that the NIH CT repository is not globally representative for non-industry sponsored CTs: non-US academic sponsors seem to not register with this US CT repository.

Comments

Limited use for ICREL: EU and Non-EU trials were pooled together. No comparison before and after the CTD.

Pan-European aspects

FECS survey on the impact of the directive on academic research

Research Topic and Methodology

In 2005, the Federation of European Cancer Societies performed a qualitative survey to analyse the EU CTD provisions implemented in national laws to address the main concerns of academic research: sponsorship, IMP, free access to marketed drugs, IMPD and drug labelling provisions, serious adverse events, financial aspects (fee waivers, definition of IMP), pharmacovigilance, GCP

and monitoring, Clinical Trials scope, NCA and EC, additional national requirements and clinical trials insurance. A questionnaire was drafted with the EORTC and disseminated to all FECS members and to 25 NCAs. Replies were received from investigators and sponsors from 15 of the Member states, Switzerland and 11 NCAs.

Results

The survey concluded to:

1. Significant differences in the implementation of CTD across EU;
2. Different interpretation by experts concerning the national provisions and
3. Huge unanimity regarding the negative impact of the Directive on academic research:
   - Increase in costs, bureaucracy and human resources
   - Increase in time to activate the trial
   - Increase in dependence from pharmaceutical industry
   - Decrease in number of trials
   - Decrease in enthusiasm of investigator
   - Reluctance of institutions to become sponsor
   - Inability to get all data needed for IMPD and EudraCT
   - Threat for small trials and for investigator's trials
   - No place at EU level to ask for clarification of uncertain issues
   - In most cases no practical benefit perceived

Comments

As this survey was a qualitative one, its scope is very limited for the ICREL project. No metrics were collected. Nevertheless, it permits some comparisons with the ICREL conclusions and with the respondents' answers to ICREL's open questions.

"Facilitating International Prospective Clinical Trials in Stem Cell Transplantation" project

Data from the FP6 CLINT Project

The CLINT survey results in the field of clinical trials related to stem cell transplantation are being submitted for publication and therefore not available for this report.

The Clinical Trials Directive: How Is It Affecting Europe's Non-commercial Research?

Hartmann M, Hartmann-Vareilles F, PLOS Clin Trial 1(2): e13.doi:10.1371/journal.pctr.0010013

Research Topic and Methodology

The authors discussed the non-commercial sponsor situation two years after the implementation of the CTD.

Results

Major obstacles and unsolved issues are:

1. lack of harmonisation of legislations among Member States; particularly for complex and therapeutic trials (e.g. surgery, radiotherapy, combination of drugs and devices);
2. single sponsorship;
3. definition of IMP transposed differently into national legislations;
4. free supply of IMP (in Italy, Belgium, Sweden and The Netherlands, specific mechanisms have been set up for non-commercial trials: tested drug and standard treatment (support or

background medications) are publicly supported);
5. increased cost of insurance coverage;
6. increased cost of quality assurance systems;
7. increased cost of submission to EC, CA and fees for GCP inspections;
8. liability issues: agreements between investigator and sponsor, investigators and hospitals, hospitals and their public or private shareholders and between hospitals' owners and the state authorities.

Nevertheless, Good Manufacturing Practice, patients' protection, transparency, reduced poorly conducted clinical trials and better quality of research constitute major beneficial achievements according to the authors. Funding remains therefore the key issue for non-commercial sponsors to continue their clinical research activities. In addition, a risk-based approach together with a single European protocol assessment process is highly recommended to keep EU competitive.

Comments

Problems have been identified but no metrics were collected. References to some European figures were presented as well.

Two years later: the impact of the EU Directive. Why Research in Europe has declined since the implementation of the Clinical Trials Directive

Moulton B, Applied Clinical Trials, Aug 1, 2006

Research Topic and Methodology

The author evaluates the academic clinical trial situation two years after the CTD should have been implemented into national legislations.

Results

His observations were:
1. a reduced harmonisation,
2. different dates and national delays for transposing the EU CTD,
3. the free supply of study medications which varies from one country to the other,
4. the complexity of the EC approval process,
5. the drug safety reporting,
6. the single sponsorship model (having a negative impact on investigator-initiated studies),
7. the obligation to contract insurance.

Recent figures showed a clear drop in the clinical research activity in Europe. The number of CTAs was down by 25% in Sweden and by 40% in Ireland (by 60% for academia) whereas the Cancer Research UK (CRUK) noted a drop of approximately 50% of its study start-up rate. In Poland, the free-of-charge supply of all study medications (not only IMPs) caused a decrease of 90% of clinical trials led by NCS. On the commercial side, F. Hoffmann-La Roche recorded a decrease of 50% in patients' recruitment from 2003 to 2004 while Roche and GlaxoSmithKline decided to perform their research activity in Asia.

The author ended with two propositions:
1. to remove the obligation of insurance for academic organisations but to ensure they comply with basic conditions and
2. to put in place grant funding programmes for NCSs.

Comments

The article refered to data from 2005. Problems have been identified but the author didn't collect metrics.

European Organisation for Research and Treatment of Cancer (EORTC) experience

EORTC was created in 1962 as an international cancer research organisation with the objective to perform research on improvement of cancer treatment. This is accomplished mainly through large, multicentre phase 3 oncology trials. The implementation of the CTD had a major impact on this organisation's clinical trial activities, staffing and costs. An analysis of this impact is provided in Annex VI.

Forward Looks on Investigator-driven Clinical Trials

Jürgen Schölmerich, Håkan Billig, Roger Bouillon, Marja Makarow, Liselotte Højgaard, Carole Moquin-Pattey, ESF-EMRC, March 2009 ISBN: 2-912049-95-4.

Research Topic and Methodology

The European Medical Research Councils (EMRC) of the European Science Foundation (ESF) examined the situation of investigator-driven clinical trials (IDCT) in Europe. In five workshops with different themes and attended by different experts in their field, specific issues which needed to be addresses were identified and recommendations were elaborated. The themes of the 5 workshops were:

- Categories and design of IDCTs
- Regulatory and legal issues, intellectual property rights and data sharing
- Management of IDCTs
- Education, training and careers, and authorship
- Funding and models of partnership

A total of 88 recommendations emerged, were subsequently processed following the advice of the Forward Look Management Committee, resulting lastly in a list of 26 recommendations. In a consensus conference the recommendations were discussed and ultimately ranked according to their priority for the participating experts.
A panel of experts subsequently convened to develop a strategy for the sustainable implementation of the recommendations. The advices for developing an implementation plan were presented in this Forward Looking Report. In addition, a separate meeting was held to consider particular problems faced by IDCTs in CEE countries. It was concluded that these countries face broadly similar problems to those in Western Europe, but that the problems tend to be more acute and extreme.

Results

The recommendations elaborated in this project are presented in Annex VII.

United Kingdom

The impact of the 'Clinical Trials' directive on the cost and conduct of non-commercial cancer trials in the UK

Hearn J, Sullivan R. Eur. J. Cancer 43:8-13, 2007

Research Topic and Methodology

The authors investigated the impact of the CTD on 8 clinical trials units in the UK (around 2005-6?) with face-to-face interviews and questionnaires sent prior to the meeting. They didn't collect metrics but perception through rating scales e.g. ranging from "very good" to "very bad". Some costs data were collected in 2 CTUs only.

Results

Results showed that costs have doubled and the start of the trials is delayed. Overall starting, conducting trials is much more difficult than before. Strong concerns were expressed on the quality of the information and guidance delivered by the MHRA. The lack of harmonisation limited strongly the willingness to open trials in non-UK sites.

Comments

The investigation was based on a small population limited to UK. No metrics were collected.

The death of academic clinical trials

Morice AH., Lancet 361:1568 (2003)

Research and methodology

This paper expressed the opinion of a clinical investigator on the implementation of the Directive 2001/20/EC.

Results

This paper commented more specifically on the need to submit to competent authorities even studies using marketed drugs, and the need to consider them as IMP with the subsequent requirements in terms of adverse event reporting, handling and labelling.

Comments

Qualitative description of anticipated difficulties for academic researchers.

Conclusion

The level of concern about the impact of the CTD on clinical research activities is intense and wide-spread over all stakeholder groups. Opinions and quantitative survey results draw a picture of increased bureaucracy and costs, reduction of important research without creating benefits for patients. However, concrete, comprehensive figures about the clinical trial activities are only available from competent authorities. Figures on the CTD's impact on organisation, staffing, costs and processes of the different stakeholders are missing.

ICREL Methodology

Organisation of the Project

Project Design

ICREL was a **longitudinal**, **retrospective**, **observational** and **comparative** study (survey) carried out in four stakeholder groups [Commercial Sponsors (CS), Non-Commercial Sponsors (NCS), Ethic Committees (EC) and Competent Authorities (CA)] to assess the impact of the CTD on the number, size and nature of clinical trials, on workload, required resources, costs and performance. Mean differences between year 2007 and 2003 were estimated to verify whether a marked change occurred in the investigated indicators further to the CTD's enforcement.

The project was sub-divided in 7 Work Packages to enable the performance of the project within the given one-year time frame.

Work Packages

Work Package 1: Strategy, management and coordination of the project

The leader of this Work Package 1 was EFGCP, located in Brussels, Belgium, providing the required resources to complete the tasks within this Work Package in time and on budget.

Objectives

To effectively design the project, manage the preparation, performance and evaluation of the project and its budget, to coordinate the activities of the WPs, to organise the Project Committee meetings and to ensure timely release of deliverables.

Description of work and role of participants

Management and coordination of the project was be performed by a full-time position of Assistant Project Manager (Corinne Gaillard), supported by the Project Coordinator Dr. Ingrid Klingmann. An independent consultant, Mr. Bruno Scherrer, was responsible for the statistical aspects of the project. This management and coordination team was steered and supported by the ICREL Project Committee, composed of two representatives for Work Packages 3 to 6. The Project Committee met for a Kick-off meeting and then in bi-monthly face-to-face Project Committee meetings with interim teleconferences.

The management and coordination team was in charge of:

- organising and managing the different team meetings and tele-conferences;
- coordinating the development of the project strategy;
- coordinating the preparation of the surveys in order to develop synergies and avoid overlap between WPs 2 to 6;
- supporting the technical preparation and the dissemination of the questionnaires;
- supervising and supporting the collection of information and performance of the surveys by the WPs 2 to 6;
- coordinating the evaluation and validation process for the methodology;
- supervising and supporting the evaluation of the surveys by the WPs 2 to 6;
- performing the financial management of the project;

- preparing and releasing the financial report;
- physical compilation, quality control and dissemination of the Final Report.

Work Package 2: Impact on commercial sponsors and clinical trials

The leader of this Work Package 2 was EFGCP with the same team as in WP 1 but supported by EuropaBio and other industry organisations with sponsor information and contact support.

Objectives

To provide metrics on the impact of the new EU legislation on clinical trials sponsored by large, medium-sized and small pharmaceutical and biotechnology industry with special emphasis on the impact on SMEs.

Description of work and role of participants

The Coordinator of this Work Package was Dr. Ingrid Klingmann. She was supported by part-time Assistant Coordinator Corinne Gaillard in EFGCP and the statistician Bruno Scherrer who was responsible for the statistical methodology of the information collection, for the design of the survey, the handling of data, the programming of estimations and tests as well as the statistical evaluation of the results.

With the support of the relevant stakeholders (e.g. EuropaBio, EFPIA, national industry associations, EMEA, national competent authorities), this Work Package addressed the impact of the new EU legislation on clinical research sponsored by the pharmaceutical and biotechnology companies including the evaluation of the specific challenges for SMEs (as defined by the European Commission).

Efforts were made to receive non-confidential information from the EudraCT database for completion of and comparison with the data collected through the survey.

This WP collected and evaluated publicly available results and experiences from other research groups and performed a survey comparing data from 2003 and 2007.

The survey was particularly supposed to provide metrics for CT performance, time lines, workload and costs before and after implementation of the new legislation.

The literature review was supposed to cover commercial sponsor-relevant aspects related to differences in national requirements and conditions for clinical trial planning and execution.
Finally, the WP was compiling information on issues related to the definition of sponsor tasks in the EU and its impact on the capacity of pharmaceutical companies and of SMEs to act as a sponsor in national or in EU multi-national studies.

Statistical methodology of the commercial sponsor survey

The methodology of the survey allowed to estimate change over time (2007 with respect to 2003) in the indicators but not to address directly the question of the impact of the CTD. Imputation of change to the CTD is a matter of interpretation since many environmental and confounding factors (currency fluctuations, mergers and acquisitions, level of capitalisation, return on investment…) evolved as well.

Main indicators of CT performance were:

- Number of clinical trials notified in 2003 and 2007 regarding:
  - All types of clinical trials
  - Investigational Medicinal Products
    - phase 1
    - phase 2
    - phase 3
    - phase 4
  - Diagnostic products
  - Advanced therapies
  - Biotechnological products
  - Products with orphan designation
  - Non-interventional/observational studies
- Number of not approved protocols
  - by CAs
  - by central ECs
  - by local ECs
- Number of submitted multi-national trial protocols on IMPs
- Number of submitted national multi-centre trial protocols on IMPs
- Number of submitted mono-centre trial protocols on IMPs
- Number of centres involved in CTs
- Number of countries involved in CTs
- Number of participants involved in CTs

Main indicators of time lines were:

- Average time from protocol finalisation to inclusion of the first patient
- Average time from substantial amendment release to implementation at the first investigational site

Main indicators of workload were:

- Workload for CTA and IMPD preparation
- Workload for CT coordination and monitoring
- Workload for pharmacovigilance tasks
- Workload for quality assurance

Main indicators of costs were:

- Cost to adapt IT system
- Overall subject indemnity insurance cost

Besides data concerning quantitative indicators (or metrics), open questions regarding strengths, weaknesses and suggested changes to the CTD were collected during the survey.

Sampling of commercial sponsors

Target Population

The target population was composed of all *commercial organisations sponsoring any clinical investigations (C.I.) in the EU,* thus pharmaceutical companies. CROs were not approached as they perform CTs on behalf of pharmaceutical companies. It would have been difficult to exclude the

possibility of double-reporting of the same CT by the pharma company and the CRO working for the company.

Studied population

The studied population was expected to be a little different from the target population due to some unknown or newly created organisations at the time of the constitution of the sampling frame or due to mergers and acquisitions during the survey period. Organisations that disappeared further to mergers were not studied but the new entity combining the former ones was included in the sampling frame. The major difficulty to perfectly match the target population was the sponsoring of clinical investigations. Many organisations may have occasionally sponsored clinical investigations in the EU but it was not possible to know precisely which ones sponsored them in 2003 and 2007. Another difficulty was presented by groups that operate under a "constellation" of companies such as Abbott, Johnson & Johnson and many others.

Planned sample size

It was planned to have a total of at least 150 questionnaires completed with at least that total number of studies approved in 2003 and 2007. Such sample size allowed to detect (significant effect: $\alpha = 0.05$ two-sided) with 80% power a factor that explains 1% of the total variance. This sample size allows to detect ($\alpha = 0.05$ two-sided) with 85% power a standardized difference of 0.25 (a difference between means equal to 0.25 standard deviation). This good power of differentiation (sensibility) is based on the normal approximation. Unfortunately, most of the variables seemed to follow an over-dispersed distribution that is to say with a variance greater than the mean. In that case, 0.25 SD may be relatively large. A provision for non-respondents was applied assuming that the response rate would be approximately 50%.

Sampling frame

The sampling frame consisted of the list of all known commercial sponsors that probably carried out a clinical trial in the EU between 2003 and 2007. The list was mainly constituted from information provided by the NIH site (www.clinicaltrials.gov) and www.scrip100.com site as well as information provided by pharmaceutical industry associations and EFGCP. The list was revised to add known missing commercial sponsors or to remove companies that were probably not sponsoring any CT in the EU due to their stage of new drug development, their size or lack of European legal presence. The list was simplified by only contacting headquarters and only one company per Holding group. If the information was not available in the contacted company it was requested to forward the questionnaire to the appropriate service of the appropriate company (headquarters or other).
The sampling frame was composed of N = 668 companies at the end of the sampling scheme preparation (see Table CS 1 from the Statistical Report CS available on www.efgcp.be/ICREL > Report).

Planned sampling strategy

As for other stakeholders stratified random sampling was planned to increase the precision of estimation and for decreasing the bias due to non-respondents.

Stratification factor

Since drug development is often dependent upon sales (a percentage of the turnover), companies were sorted according to sales and divided into 4 strata:

- The top 15 (the largest companies): $N_{top} = 15$ companies.

- The top 100 (large companies 16 to 100): $N_{very\ large} = 82$ (82 instead of 85 due to mergers)
- The "beyond the top 100 companies" large companies: $N_{rank>100} = 222$ companies
- SMEs: $N_{SMEs} = 349$ companies

The top 100 was found in the www.scrip100.com site. The list of very large companies was composed of 82 companies due to mergers and acquisitions. Classification into SMEs and non-SMEs in the sampling frame was approximate.

Sales were not necessarily the best indicator of the level of clinical trial activity in EU. The number of clinical trials notified to NIH was used to check whether the mean number of CTs was linked to the sales and dependent upon the classification into the strata. We got the following results:

- Top 15: 695 CTs on average per company (variance = 131701, $N_{top} = 15$)
- Very large company: 47 CTs on average per company (variance = 6248, $N_{large} = 82$)
- Large companies: 9.3 CTs on average per company (variance = 307.5, $N_{medium} = 222$)
- Small companies (SMEs): 4.0 CTs on average per company (variance = 31.6, $N_{SME} = 349$)
- Overall: 25.57 trials on average (variance = 14099, N = 668).

Fortunately there was a major difference in the means of strata. As expected the variance was dependent upon the mean. Consequently, even if the number of clinical trials notified to NIH was not a perfect indicator of the number of clinical trials carried out in the EU we could expect that stratification would be efficient.

Planned sampling effort

The sampling fraction was planned to be dependent upon the level of clinical trial/investigation activity in each stratum. One of the best indicators of the activity level would have been the number of CTAs per company because this number is probably highly correlated with several other indicators such as the number of clinical trials actually carried out in the EU. Unfortunately, this information was not available at the time of sampling scheme preparation and therefore the number of clinical trials notified to NIH was used to allocate the planned sampling effort.

Optimal allocation of the sampling effort was performed according to the following general formula:

$$n_h = \frac{n.W_h.s_h / \sqrt{c_h}}{\sum_{h=1}^{k} W_h.s_h / \sqrt{c_h}}$$

where n_h is the number of CSs to sample in stratum h, n is the total number of CSs to draw from the sampling frame, W_h is the weight of stratum h: $W_h = N_h / N$, N_h is the total number of sponsors in stratum h, N is the total number of CSs within the EU, s_h is the standard deviation in stratum h and c_h is the cost of sampling in stratum h. We assumed that the cost of sampling is equal in all strata. We assumed that the standard deviation observed in each stratum (NIH notification) would be approximately proportional to the actual standard deviation of the number of CTs performed in EU. We assumed that 300 questionnaires must be sent in order to receive at least 150 questionnaires with at least non-missing responses in 2003 and 2007 for the number of initiated clinical studies. The application of the formulae led to the results presented in Table 1. Since the formula does not take into account the coefficient of exhaustivity (n_h / N_h), optimal sample size is larger than the size of the stratum for two strata. The planned sample size of these 2 strata was set at the stratum size ($n_h = N_h$) and units in excess were allocated to other strata in the optimal proportion.

Table 1: Planned sample size in the four planned CS strata

Strata	Number of CSs	Weight of strata	Mean nbr. of CTs (NIH)	Standard deviation of the nbr. of CTs	Optimal sample size	Planned sample size	Sampling fraction
Top 15	15	2.2455%	695	362.9	92	15	100%
Large Top 100	82	12.2754%	47	79.0	109	82	100%
Beyond top 100 large	222	33.2335%	9.3	17.5	66	135	60.8%
Beyond top 100: Small / medium	349	52.2455%	4.0	5.6	33	68	19.5%
Total	668	100%	25.6	118.7	300	300	44.9%

Source: Table CS1M in Appendix CS, available on www.efgcp.be/ICREL > Report

As a reminder, it was obvious that some assumptions would be violated. In that case the optimal sample size was no longer optimal but estimations were not biased by such violations.

Within substrata sampling method

CSs were sorted in alphabetic orders within strata. We assumed that the alphabetic order was equivalent to a random order and that the correlation between the response of i^e and $(i+k)^e$ CS in the list was null whatever i and k (absence of autocorrelation[16] whatever the lag). For facilitating the selection of CSs within strata, systematic sampling was used. The increment k_h in the h^{th} stratum is equal to N_h / n_h and the base j_h (first selected CS) is a random number between 1 and k_h. Selected CSs were the j_h^{th}, $(j_h + k_h)^{th}$, $(j_h + 2k_h)^{th}$, $(j_h + 3k_h)^{th}$, $(j_h + 4k_h)^{th}$,…, $(n_h - k_h + j_h)^{th}$. The same rule was applied for fractional increment.

Data collection and handling

The electronic invitation for the selected companies to complete the survey was accompanied by a link to the web-based survey form where data were directly entered into a database prepared by EORTC. In addition, it was offered to return the completed form by e-mail. The completed surveys were to be checked for completeness, consistency and cohesiveness by the WP team. Queries were to be raised and clarified with the respondents before the database could be locked.

Work Package 3: Impact on non-commercial sponsors and clinical trials

The leader of this Work Package 3 was EORTC, located in Brussels, Belgium, providing the required resources to complete the tasks within this Work Package in time and on budget.

Objectives

To provide metrics on the impact of the new EU legislation on non-commercial sponsors and clinical trials on medicinal products.

[16] Presence of positive autocorrelation leads to an **overestimation** of the standard error of the mean. So, in case of autocorrelation, confidence intervals of means will be conservative (Aubry 2000).

Description of work and role of participants

The coordinator of this Work Package was Dr. Denis Lacombe (supported by Ms. Diane van Vyve and Mr. Stéphane Lejeune). The statistician Bruno Scherrer was responsible for the same tasks as described in WP 2.

With the support of the relevant stakeholders (EU academic networks, national academic sponsors, national competent authorities), this Work Package addressed the impact of the new EU legislation on non-commercial, investigator-initiated clinical trials. These trials are usually sponsored by the investigator himself or by a public institution.

This WP collected publicly available information from other research groups and performed a survey providing, for individual countries and for multinational studies in the European Union, metrics before (2003) and after (2007) introduction of the new legislation on the same parameters as described in WP2. In addition this WP evaluated the cost of providing marketed IMPs for free.

Per literature review this WP was supposed to cover non-commercial sponsor-relevant issues related to differences in national requirements for CTA application, SUSAR reporting by the sponsor, the definition of IMP, to the GMP requirements and import rules, and to the interpretation of the definition of substantial amendments.

Finally, this WP compiled information regarding definition of the non-commercial sponsor and of sponsor's tasks in the EU and its impact on the capacity of public institutions to act as a sponsor in national or in EU multi-national studies. A special focus was given to advanced therapies (gene, cell therapy, tissue repair, regenerative medicine) and to biopharmaceuticals.

Work Package 4: Impact on clinical studies other than clinical trials on medicinal products

The leader of this Work Package 4 was INSERM-ECRIN, located in Paris, France, providing the required resources to complete the tasks within this Work Package in time and on budget.

Objectives

To assess the indirect impact of Directive 2001/20/EC on the national and EU regulatory framework for clinical research other than clinical trials on medicinal products.

Description of work and role of participants

The coordinator of this Work Package was Professor Jacques Demotes-Mainard, supported by Project Manager Christine Kubiak and the statistician Bruno Scherrer who was responsible for the same tasks as described in WP 2.

As the Directive on clinical trials on medicinal products had to be transposed into national legislation, national laws were released by national health authorities and implemented between 2003 and 2006. In many countries these laws not only cover clinical trials on medicinal products, but also clinical studies on other health products and research topics. Since no guidelines or Directives to cover these other types of clinical research were released at the EU level, major discrepancies in regulatory requirements for these other categories of clinical research hamper especially the organisation and performance of multi-national studies.

This WP collected publicly available information from other research groups and supported the development of the surveys prepared by WPs 2, 3 and 5 by adding questions or question elements to these surveys, depending on where/from which stakeholder that information could be best assembled.
Based on information collected by the ECRIN network which worked on the categorisation of clinical research in the various EU countries, the following other categories of research were evaluated by this WP for 2003 and 2007:

- Clinical trials on medical devices
- Other treatment trials (e.g. radiotherapy, surgery, transplantation, cell therapy, tissue engineering…)
- Diagnostic studies
- Other interventional clinical research (complementary and herbal medicines, biobanks, physiology, pathophysiology, psychology)
- Observational clinical research

However, due to the difficulties in collecting information on these types of research, especially for the year 2003, it was expected that the results would be mainly descriptive and only few metrics would be available.

Further objectives of this WP were to provide information on:

- regulatory requirements indirectly induced by the Directive (and in particular, submission to Ethics Committees, to Competent Authorities if any, the need for a sponsor, insurance requirements, adverse event reporting)
- metrics (number of studies, number of centres, number of patients, costs)

before and after the implementation of Directive 2001/20/EC (2003 and 2007).

The results of the recently finished ECRIN survey on legal requirements for the different categories of research have been taken into account in this final report.

Work Package 5: Impact on competent authorities, pharmacovigilance, monitoring, and on the infrastructure and funding of clinical trials

The leader of this Work Package 5 was the Hospital Clinic I Provincial de Barcelona, located in Barcelona, Spain, providing the required resources to complete the tasks within this Work Package in time and on budget.

Objectives

To assess the impact of the Directive 2001/20/EC on

- the structure, capacities and processes of competent authorities
- the reliability and efficiency of the EU pharmacovigilance system
- study monitoring costs, quality and credibility
- the development of infrastructures for clinical trials performance
- the development of public and public-private funding opportunities and
- appropriateness to support clinical research.

Description of work and role of participants

The coordinator of this Work Package was Professor Xavier Carné supported by Project Manager Raquel Hernandez and the statistician Bruno Scherrer who was responsible for the same tasks as described in WP 2.

This Work Package received non-confidential anonymous information from the EudraCT database and performed a survey on the impact of Directive 2001/20/EC and related legislation, taking into account both industry-sponsored and academic research, on various aspects of clinical trials. This survey was performed with the contribution of the relevant stakeholders, namely the national Competent Authorities, the Clinical Trials Facilitation Group and the EMEA, national funding agencies and national and EU-wide clinical research infrastructures, including the ECRIN network. The Work Package investigated the following areas:

- Approval of clinical trials by Competent Authorities (CA) is a new feature that had a major impact on their structure, capacities and processes. This survey assessed the need for structural and procedural changes, the cost of CTA provision for the competent authority itself (staff, workload), and on the fee charged to the sponsor by the Competent Authority for initial review and substantial amendments.
- Impact of national requirements for SUSAR reporting to the national Competent Authority, staff resources for management and evaluation of SUSARs and of Annual Safety Reports by the CA, and systems for electronic transmission to the EudraVigilance database.
- In close collaboration with WPs 3 and 4, this WP assessed the impact of the new legislative framework on assurance of quality and credibility of studies, including monitoring, for non-commercial trials and their cost for the commercial and non-commercial sponsors.
- As a result of the increased level of requirements for clinical research, most EU countries have invested in clinical research infrastructures (e.g., the UKCRC in the UK, the CeNGEPS in France), supporting clinical trials (clinical trials units), supporting hospital based clinical research (clinical research centres), and supporting the role of the public sponsors (e.g., GCP units in Denmark). In collaboration with WPs 3 and 4 this WP reviewed information on the cost of these infrastructures, and their impact on the professionalism and quality of clinical research in the EU Member States.
- Finally, the increased cost of academic clinical research led EU countries to allocate specific funding to clinical research through calls for application. The origin of these funds is variable: e.g., research ministry (in Germany), health ministry and public health insurance system (in France), medicines agencies (in Italy and in Spain). This results in different strategies (research oriented, public health oriented, cost-oriented). In addition, some countries provide funding to the infrastructure for clinical research. This WP's review covered the differences in existing systems and the suitability of funding levels for clinical trials under the new requirements, and it investigated the situation in countries lacking public funding for clinical research.

Statistical methodology of the survey

From the questionnaire the following indicators were considered:

Main indicators of CT performance were:

- Number of clinical trials notified from 2000 to 2007 by CS and NCS separately regarding:
  - Medicinal products
  - Advanced therapy
  - Biotechnological products
  - Product with orphan designation
- Number of non-approvals
- Number of submitted multi-national trial protocols on medicinal products
- Number of submitted multi-centre trial protocols on medicinal products
- Number of submitted mono-centre trial protocols on medicinal products

- Number of amendments submitted
- Number of amendments refused
- Number of reported SAEs (SUSARs)

Main indicators of time lines were:

- Mean time to issue acknowledgement letter (all applications)
- Mean time to issue approval letter (all applications)
- Mean time to issue acknowledgement letter (Phase 1)
- Mean time to issue approval letter (Phase 1)
- Mean time to issue acknowledgement letter (Phase 2 to 4)
- Mean time to issue approval letter (Phase2 to 4)
- Mean time to issue acknowledgement letter (biological products)
- Mean time to issue approval letter (biological products)
- Mean time to issue acknowledgement letter (xenognic/somatic cell therapy)
- Mean time to issue approval letter (xenogenic/somatic cell therapy)

Main indicators of workload were:

- Workload for scientific assessment
- Workload for administrative work
- Workload for pharmacovigilance tasks

Main indicators of costs

- for CTA:
  - Standard rate for commercial sponsors
  - Standard rate for SMEs
  - Standard rate for orphan drugs
  - Standard rate for non-commercial sponsors

- for substantial amendments:
  - Standard rate for commercial sponsors
  - Standard rate for SMEs
  - Standard rate for orphan drugs
  - Standard rate for non-commercial sponsors

Funding

For each item a number of analyses were conducted. For the interpretability of the results the most relevant were:

1. Main descriptive statistics

2. Index estimation

In this survey more countries provided data for 2007 than for 2003 as most competent authorities found it difficult and time consuming to retrieve old data (2000-2002) from their archives. For that reason, statistically, the index was chosen as an optimal trade-off between a perfect comparability of data over time and the use of the maximal number of available data. The index was set to 100 in 2007 and in relation to that all other year indexes were calculated. Index estimation provides a

picture of the overall trend over time for a given item of interest. The time course of the index was chosen in the graphs to present the comparison of EU- and non-EU institutions.

3. Relative change

To assess the change after the CTD's implementation the relative change calculation was chosen. It was calculated on matched data (countries which provided data in 2003 and 2007) and was equal to the mean change between 2007 and 2003 divided by the mean in 2003. The relative change gives an indication of a positive or negative change over time for a given item of interest. A positive change is indicative of an increase of activity for a given item of interest and can be statistically significant or not.

Work Package 6: Impact on Ethics Committees, participant protection and transparency

The leader of this WP was the Ethics Committee of the Medical University Vienna, located in Vienna, Austria, providing the required resources to complete the tasks within this Work Package in time and on budget.

Objectives

To assess the impact of Directive 2001/20/EC and related legislation on Ethics Committees, on the protection of participants, and on transparency in clinical research.

Description of work and role of participants

The coordinator of this WP was Dr. Christiane Druml supported by Assistant Project Coordinator Dr. Johannes Pleiner and the statistician Bruno Scherrer who was responsible for the same tasks as described in WP 2.

This WP evaluated the following areas:

- A major impact of Directive 2001/20/EC is the 'single opinion' from research Ethics Committees. However, the CTD's interpretation and implementation is, especially for the aspects of Ethics Committees and ethical review, very different from one country to another. National differences in generation and review timeframes of this single opinion, responsibilities of central/lead and local ethics committees exist. In addition, the workload, hence the staff/member needs and costs for ethics committees, has substantially increased. Different approaches to cover these costs may have an impact of the independence of Ethics Committees. Taking advantage of existing data (EFGCP Report on Ethics Committees in Europe, VISEAR, etc), this WP organised a survey to measure the impact of the CTD on the workload, financial conditions, independence of Ethics Committees in the EU, and procedures to come to a single vote. Finally, the coordination between Competent Authorities and Ethics Committees is a critical issue during approval of the clinical trial and substantial amendments as well as in the critical safety situations. The survey also addressed the issue of communication (between ECs, and between ECs and CAs), both at the national and at the international level. A particular burden to Ethics Committees is the management of SUSARs. The survey identified the procedures and required resources for management and evaluation of SUSARs.
- The survey also identified the level of sponsors' adherence to the CTD's requirement for providing a final study report summary within 1 year after end of the clinical part of the trial and of publishing all results. Another aspect of this survey was the evaluation of Ethics Committees usage of the final study report for the protection of patients.

- Through literature review and casuistics the involvement of patients associations in different disease areas, the improvement in the active patients' involvement in clinical research – through for instance their participation in Ethics Committees, in EMEA activities, and in the capacity of patients (including vulnerable populations) to participate in clinical studies was investigated in the WP.

Main indicators of EC and CT performance:

- Number of positive opinions in 2003 and 2007 regarding:
  - All types of clinical trials
  - Medicinal products
  - Medical devices
  - Surgical procedures
  - Radiotherapy
  - Non therapeutic clinical investigations (Diagnostic products…)
  - Non interventional observational studies
- Number of negative opinions
  - protocols
  - amendments
- Number of applications submitted by commercial sponsors
  - All types of clinical trials
  - Medicinal products
  - Medical devices
  - Surgical procedures
  - Radiotherapy
  - Non therapeutic clinical investigations (Diagnostic products…)
  - Observational studies
- Number of applications submitted by non-commercial sponsors
  - All types of clinical trials
  - Medicinal products
  - Medical devices
  - Surgical procedures
  - Radiotherapy
  - Non therapeutic clinical investigations (Diagnostic products…)
  - Observational studies
- Number of applications for multi-national trial protocols on medicinal products
- Number of applications for multi-centre trial protocols on medicinal products
- Number of applications for mono-centre trial protocols on medicinal products

Other indicators of activity:

- Number of SAE/SUSAR reports
- Number of meetings for protocol discussion
- Average duration of meetings
- Number of final study reports

Main indicators of time lines:

- Average time between the receipt of a complete application for a protocol and the issue of the opinion letter

- Average time between the receipt of an original application for a protocol and the issue of the opinion letter
- Average time between the receipt of a substantial amendment and the issue of an opinion
- Average time for the discussion of protocol

Main indicators of workload:

- Workload for scientific assessment
- Workload for administration of protocol and substantial amendment review
- Workload for administration of SAEs, SUSAR reports and administration tasks
- Workload for quality assurance

Main indicators of costs:

- Average fees per initial application, as single opinion provider, for commercial sponsors
- Average fees per initial application, as single opinion provider, for SME sponsors
- Average fees per initial application, as single opinion provider, for orphan drugs
- Average fees per initial application, as single opinion provider, for non-commercial sponsors
- Average fees per substantial amendment, as single opinion provider, for commercial sponsors
- Average fees per substantial amendment, as single opinion provider, for SME sponsors
- Average fees per substantial amendment, as single opinion provider, for orphan drugs
- Average fees per substantial amendment, as single opinion provider, for non-commercial sponsors
- Average fees per initial application, when not providing the single opinion, for commercial sponsors.
- Average fees per initial application, when not providing the single opinion, for SME sponsors
- Average fees per initial application, when not providing the single opinion, for orphan drugs
- Average fees per initial application, when not providing the single opinion, for non-commercial sponsors
- Average fees per substantial amendment, when not providing the single opinion, for commercial sponsors
- Average fees per substantial amendment, when not providing the single opinion, for SME sponsors
- Average fees per substantial amendment, when not providing the single opinion, for orphan drugs
- Average fees per substantial amendment, when not providing the single opinion, for non-commercial sponsors
- Budget

Work Package 7: Final Meeting

The leader of this Work Package 7 was EFGCP with the same team as in Work Packages 1 and 2.

Objectives

To organise and run a Conference for all stakeholders for presentation, discussion, collection of views in Break-out groups and agreement on consolidated conclusions in the final Plenary Session on the outcomes of the WP2 to WP6 surveys an information collection for the preparation of the Final Report.

Description of work and role of participants

The coordinator of this Work Package was Fanny Senez, COO of EFGCP, supported by the part-time Assistant Coordinator Corinne Gaillard and the Project Team.

The Conference was a one-day event organised on 2 December 2008 in Brussels, Belgium. Great emphasis was placed on equal representation from all stakeholder groups on the invitation list and registration. Nearly 300 participants representing all stakeholders (industry and academic sponsors, investigators, Ethics Committees, European Commission, Competent Authorities and patient representatives) from all over Europe learned about the survey results and discussed in Break-out Groups the detailed results, their possible interpretations, their potential impact on future legislation and possible recommendations. The results from these discussions were reported to the Plenary for general discussions.

The Work Package reports and the outcome of this meeting are the basis for this Final Report including consolidated conclusions, proposals for "best practices", as well as recommendations for possible changes of the regulatory environment for Clinical Research with medicinal products and other types of clinical research that will be published and disseminated to the relevant stakeholders as described in WP 1.

Survey Results

After the survey pilot run with 3 surveys from all 4 stakeholder groups had been completed, the surveys were performed between 30 May 2008 and 30 September 2008. According to the planned sampling scheme, in total 930 requests for survey completion were sent to competent authorities, ethics committees, commercial and non-commercial sponsors end of May. Despite numerous follow-up activities the response rate was very low and thus it was decided to send the survey to all known stakeholder contacts. In total, 1608 surveys were thus addressed. As presented in Table 2, a total of 248 stakeholder representatives responded.

Table 2: Overall survey response

	Commercial Sponsors	**Non-Commercial Sponsors**	**Ethics Committees**	**Competent Authorities**
Respondents	**53**	**106**	**64**	**28 from 27 countries**
Response rate	Top 15: 66%	Large: 44%	Czech Rep.: 14.4%	In total: 89.9%
Response rate	Top 100: 13.6%	Medium: 39%	France: 22.5%	EU countries: 89.2%
Response rate	Rank >100, large companies: 7.7%	Small + unclassified: 12%	Belgium: 1.3%	Non-EU countries approached: 100%
Response rate	Rank >100, small to medium-size companies: 5.7%			
Function	Function of size	Function of size	Function of country	

Source: ICREL compiled data

The high percentage of non-respondents in the surveys on the ethics committee, commercial and non-commercial sponsor stakeholder groups was thus a major issue in this project as it reached 90% and the uncertainty regarding the non-respondents' situation, experience and opinions was huge. Efforts were made to find out about the reason for non-responses. The arguments provided were:

- Lack of interest or feeling that their response would not change anything;
- Impossibility to retrieve the requested information;
- Too much work and too few available resources to provide the answers;
- No answers could be provided for 2007 because the sponsors did not perform clinical trials in Europe anymore;
- Feeling that the comparison of 2003 and 2007 was impacted so heavily by internal changes (change of procedures, structure, etc) that no impact of the CTD could be distinguished;
- Feeling that their personal responses might bias the results.

The received information showed that the response rate was dependent upon the size of the organisations. Large organisations tended to have slightly better response rates. This was plausible because smaller organisations have less resources to answer, feel more frequently that their response might not be important and do not have historical databases to retrieve the information efficiently. However, if this low response, e.g. the number of CTAs, was dependent upon the size of the organisation, unadjusted results were biased in favour of large organisations (leading to an overestimation regarding the overall number of CTAs). Adjusted results were then more appropriate, if the stratifier was size dependent and in absence of outliers in strata with a large weight.

The statistical evaluation and presentation of the results was adapted to the topics of the individual questionnaires and will be described below.

Competent Authorities

Statistical Methodology

Design of the survey

This was a longitudinal, retrospective, observational and comparative study (survey) that was carried out to assess the possible impact of Directive 2001/20/EC on the clinical trial investigations performance and on the workload, time lines and funding of the competent authorities.
The mean difference between year 2007 (after enforcement of the CTD) and 2003 (before enforcement) was estimated to verify whether a marked change occurred in indicators of clinical investigation performance further to the CTD's enforcement. The trend over time from 2000 to 2007 was estimated as well.

Target population

The questionnaire for competent authorities was sent to 28 European Union (EU) and 2 non-EU national authorities that provide clinical trial authorisation for trials with investigational medicinal products. The non-EU countries are members of the European Free Trade Association. From one EU country two identifiable national authorities were targeted. A total number of 30 competent authorities from 29 countries were surveyed.

Content of the questionnaire

The competent authorities' questionnaire consisted of 17 questions designed to collect the following information:

1. Categories of clinical research for which the regulatory agency is competent;
2. Potential changes in the organisational structure after the implementation of the Directive;
3. Potential changes in the clinical trial authorisation process after the implementation of the CTD;
4. Number of clinical trial authorisation applications (CTAs) submitted to the different competent authorities by commercial sponsors from 2000 to 2007, with separate identification for orphan drugs, biotechnological products and advanced therapies;
5. Number of CTAs submitted to the different competent authorities by non-commercial sponsors from 2000 to 2007, with separate identification for orphan drugs, biotechnological products and advanced therapies;
6. Number of CTAs non-approved were issued by the different competent authorities from 2000 to 2007;
7. Number of clinical trials (CT) submitted for approval or notification from 2000 to 2007 broken down by multinational, national multi-centre or mono-centre trials;
8. Number of substantial amendments received by the different competent authorities from 2000 to 2007;
9. Time (in days) lasted between the receipt of a valid application (or notification) until the statement of authorisation (or acknowledgment) has been issued from 2000 to 20007 broken down by phase I, phase II to phase IV, biological products and xenogenic cell therapy trials;
10. Number of full time equivalents required by the different competent authorities for performing scientific, administrative and pharmacovigilance tasks from 2000 to 2007;
11. Number of Serious Adverse Events or Suspected Unexpected Serious Adverse Reactions received by the different competent authorities from 2000 to 2007;

12. Year in which the different competent authorities started entering data in the EudraCT and EudraVigilance databases;
13. Average fee for CTAs (or notifications) charged to commercial, non-commercial, Small and Medium-Size Enterprise and orphan drug trial sponsors from 2000 to 2007;
14. Average fee for substantial amendments charged to commercial, non-commercial, Small and Medium-Size Enterprise and orphan drug trial sponsors from 2000 to 2007;
15. Overall annual budget of the different competent authorities from 2000 to 2007;
16. Suitability of fees for CTAs and substantial amendments to cover the costs incurred by the Clinical Trial department in each regulatory agency;
17. Open questions soliciting five strengths, five weaknesses and five suggested changes to the CTD.

Description of the respondents

25 out of a total of 28 questionnaires sent to EU competent authorities were completed. Only 3 competent authorities did not respond. In addition two others competent authorities from the EFTA were targeted to serve as comparators. For the statistical analysis 27 (25 EU plus 2 non-EU) questionnaires were eligible although two competent authorities provided very few data. Table 3 shows the summary statistics.

Table 3: Summary Statistics

Size of the studied population = sampling frame	28 competent authorities
Number of respondents from EU countries	25 competent authorities
Number of non respondents from EU countries	3 competent authorities

Source: ICREL compiled data

With 89.2%, the number of EU respondents is very high and close to a complete representation of the clinical research carried out in Europe. Table 4 shows a list of the respondents.

Table 4: Responding competent authorities

Country	Institution
Austria	Bundesamt für Sicherheit im Gesundheitswesen (BASG)/ AGES PharmMed
Belgium	Federal Agency for Medicines and Health Product (FAGG-AFMPS)
Bulgaria	Bulgarian Drug Agency
Cyprus	Ministry of Public Health, pharmaceutical services
Czech Republic	State Institute for Drug Control
Denmark	Danish Medicines Agency
Estonia	State Agency of Medicines
Finland	National Agency for Medicines
France	French Agency for the Safety of Medical Products (AFSSAPS)
Germany	Bundesinstitut für Arzneimittel und Medizinprodukte / Federal Institute for Drugs & Medical Devices
Germany	Paul-Ehrlich Institute
Greece	National Organization for Medicines
Hungary	National Institute of Pharmacy
Ireland	Irish Medicines Board
Italy	Agenzia Italiana del Farmaco
Latvia	State Agency of Medicines of the Republic of Latvia
Malta	Ministry of Health, Elderly and Community Care

Country	Institution
Poland	Main Pharmaceutical Inspectorate
Portugal	Autoridade Nacional do Medicamento e Produtos de Saúde (INFARMED)
Slovakia	State Institute for Drug Control
Slovenia	Ministry of Health Agency for Medicinal Products
Spain	Agencia Española de Medicamentos y Productos Sanitarios (AGEMED)
Sweden	Medical Products Agency
The Netherlands	Centrale Commissie Mensgebonden Onderzoek
United Kingdom	Medicines and Healthcare Products Regulatory Agency (MHRA)

Non EU respondents	
Iceland	Icelandic Medicines Control Agency (Lyfjastofnun)
Norway	Norwegian Medicines Agency

Source: ICREL compiled data

For confidentiality reasons and according to the promises to the respondents, all data are presented anonymously.

Results

For interpretability reasons only those results were presented in this Final Report from which a meaningful evaluation could be provided. However, all results can be accessed in the Statistical Report CA and Appendix CA available on the EFGCP website[17].

General information

Categories of clinical research for which your Competent Authority has competence? (Question 1 in the Questionnaire to CAs)

This question was designed to capture general information of the regulatory agencies that responded. The categories displayed were based on the categories agreed for the survey on "Clinical Research in Europe: national differences in legislative and regulatory frameworks" developed further in the ECRIN-TWG Deliverable 4[18].

The questionnaire categories were as follows:

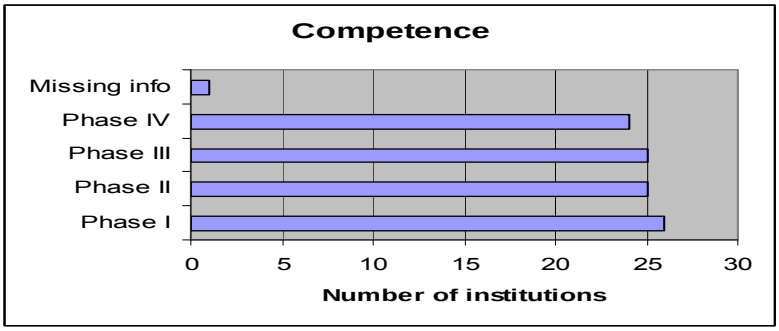
1. Clinical trials with medicinal products
   - 1.1. Phase I-IV
   - 1.2. Biotechnological products
   - 1.3. Advanced therapies (somatic cell, gene therapy and tissue bio-engineering)
2. Clinical studies with medical devices
3. Surgery trials
4. Radiotherapy trials
5. Clinical studies on diagnostic procedures incl. biomarkers
6. Studies with minimal invasive procedures
7. Non-interventional/observational studies

[17] www.efgcp.be/ICREL

[18] ECRIN - TWG Deliverable 4. Clinical research in Europe: national differences in legislative and regulatory frameworks; www.ecrin.org

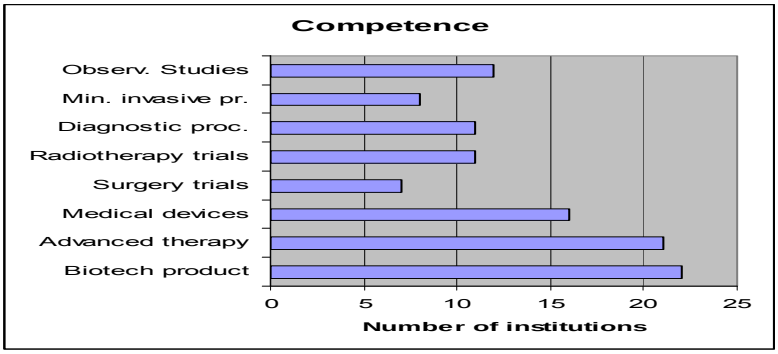
Figure 1 shows the number of competent authorities with competence in clinical trials with medicinal products broken down by phases and Figure 2: shows the number of competent authorities with competences in other categories of research distinct to the medicinal products.

Figure 1: Number of competent authorities by phases



Source: Figure CA3 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

Figure 2: Number of competent authorities per other categories of research



Source: Figure CA4 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

The majority of competent authorities had competence in all phases of clinical research, and concerning product categories in biotechnology products, followed by advanced therapy products and medical devices.

Did your organisational structure change since the implementation of the Clinical Trials Directive? Has your clinical trials authorisation process changed since the implementation of the Clinical Trials Directive? (Questions 2 and 3)

In order to know how the CTD impacted on the competent authorities, they were asked if their organisational structure had changed as results of the CTD, or/and if their authorisation process altered.

Had the authorisation process changed, they were also asked for the nature of this change. The options given where as follows:

a) From notification to authorisation

Option "a", was applicable to countries where previous to the CTD, clinical trials no information of the regulatory agency before study start was required while since after its implementation , clinical trials need an authorisation from the regulatory agency before they can be initiated.

b) From no information on phase I to authorisation

Option "b" was applicable to countries where before the implementation of the CTD only Phase I clinical trials did not require submission to the regulatory agency.

c) From no information to authorisation

Option "c" was indicated for countries with a notification process before and an authorisation process by the regulatory agency since implementation of the CTD.

Table 5: Changes after implementation of the Directive

	Yes	No
Organisational structure change	15	11
Authorisation process change:	16	10
- From no information to authorisation	4	
- From no information on phase I to authorisation	2	
- From notification to authorisation	8	

Source: Table CA3 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

Over a total of 26 respondents, 15 competent authorities reported to have changed their organisational structure and 16 to have changed their process of authorisation. Therefore more than half of the respondents, 57.7% and 61.5% respectively, underwent some kind of change either affecting their organisational structure or their authorisation process after the implementation of the CTD.

Fourteen competent authorities responded to the nature of the change: 8 reported to have passed from requiring notification to authorisation, 2 from no information about Phase I trials to authorisation and 4 from notification of all phases to authorisation.

However, three authorities, counted as "non respondents," mentioned that the reason for not responding was that none of the three options were applicable to them. They missed the fourth option "from authorising to notifying." This comment was also supported by various participants in the ICREL Conference's competent authorities break out session that took place on 2 December 2008 in Brussels. When this competent authority questionnaire was developed, the ICREL team was not aware of this option and thus the compilation of answers to this question does not reflect the situation in all surveyed countries.

Research performance

How many trials were submitted for approval/notification by commercial sponsors per year from 2000 to 2007? How many trials were submitted for approval/notification by non-commercial sponsors from 2000 to 2007? (Questions 4 and 5)

In Question 4, the number of CTAs submitted by the industry (commercial sponsors) and in Question 5 the ones sponsored by academia (non-commercial sponsors) were collected from the national competent authorities.

The combined number of CTAs from both stakeholder groups could provide an interesting estimation of the EU global trend in clinical research activity. See Table 6.

Table 6: Total number of CTAs per year

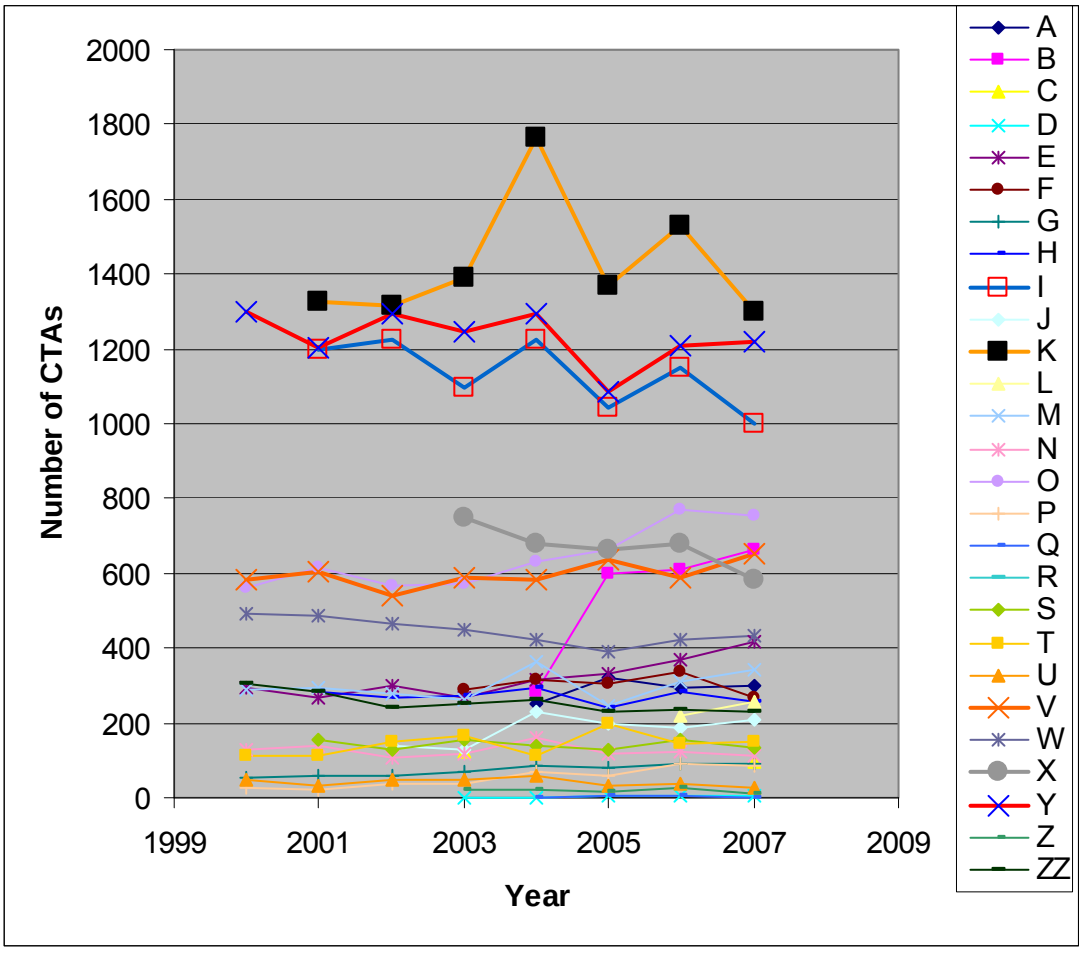
Year	2000	2001	2002	2003	2004	2005	2006	2007
Total number of CTA	3897	6802	6918	8022	9277	8708	9608	9363
Sample size EU	11	15	16	20	22	22	23	24

Source: Table CA28 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

From 2000 to 2007, an increase over the years was apparent; however this number had to be interpreted with caution: the figure in 2007 was constituted from the answers of 24 competent authorities while for 2000 only 11 authorities provided data. Therefore, the rate of increase did not reflect the true development of clinical trial activity in the EU.

However, the review of the individual curve from countries which provided data for all years, presented in Figure 3, revealed two main trends: on one hand, the regulatory agencies at the bottom, with a small number of CTAs, tended to slightly increase their activity over time.

Figure 3: Total number of CTAs by competent authority



Source: Statistical Report figure CA34, available on www.efgcp.be/ICREL > Report

All competent authorities provided data except from country R. Therefore the slope of R is 0.

On the other hand, those countries with the largest amounts of CTAs ended up with smaller numbers of CTAs in 2007 than in 2000. See curves of countries I, K and Y.

These three regulatory agencies corresponded to three of the five most active clinical research countries in Europe according to market indicators[19] and all showed a decrease in the total number of CTAs over time. This decreasing trend was most pronounced between 2004 and 2005, thus directly after implementation of the CTD.

In support of this rationale, see Table 7 where the total number of CTAs of I, K, and Y is shown. K and I did not provide data for 2000.

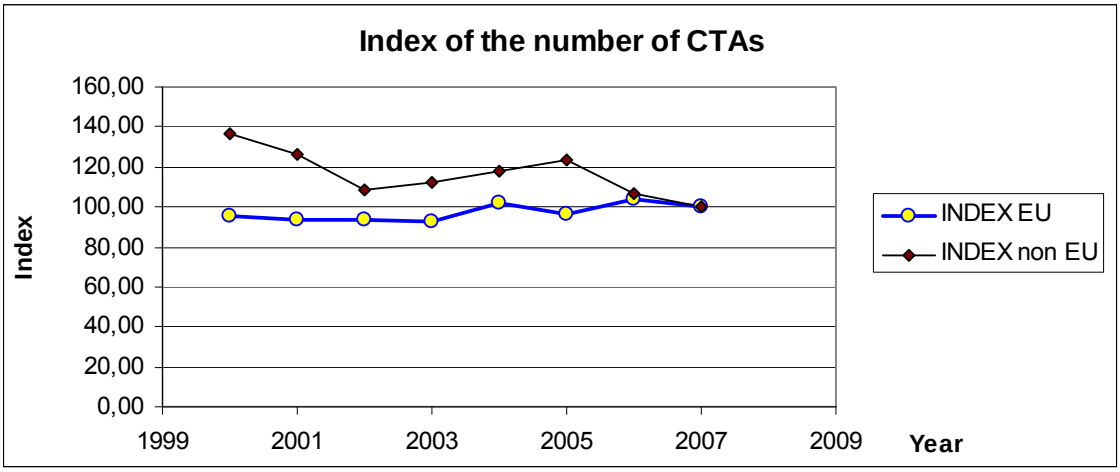
Table 7: Total number of CTAs

Institutions	2000	2001	2002	2003	2004	2005	2006	2007
K	-	1326	1316	1393	1765	1371	1530	1298
I	-	1200	1227	1098	1223	1045	1148	1000
Y	1300	1203	1296	1244	1296	1085	1206	1218

Source: ICREL compiled data

However, applying the index computation the overall clinical research activity trend showed a very small increment in the number of CTAs. See Figure 4.

Figure 4: Index of total number of CTAs



Source: Figure CA35 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

The relative change was also positive, showing a non significant increase of 1.50% observed in 2007 with respect to 2003.

In conclusion, the EU CTD had no apparent negative impact on the overall clinical research activity in Europe. Nevertheless, important clinical research countries in Europe experienced a certain decrease in their research activity likely due to a fall in the number of CTAs sponsored by non-commercial entities. See next results of Q5.

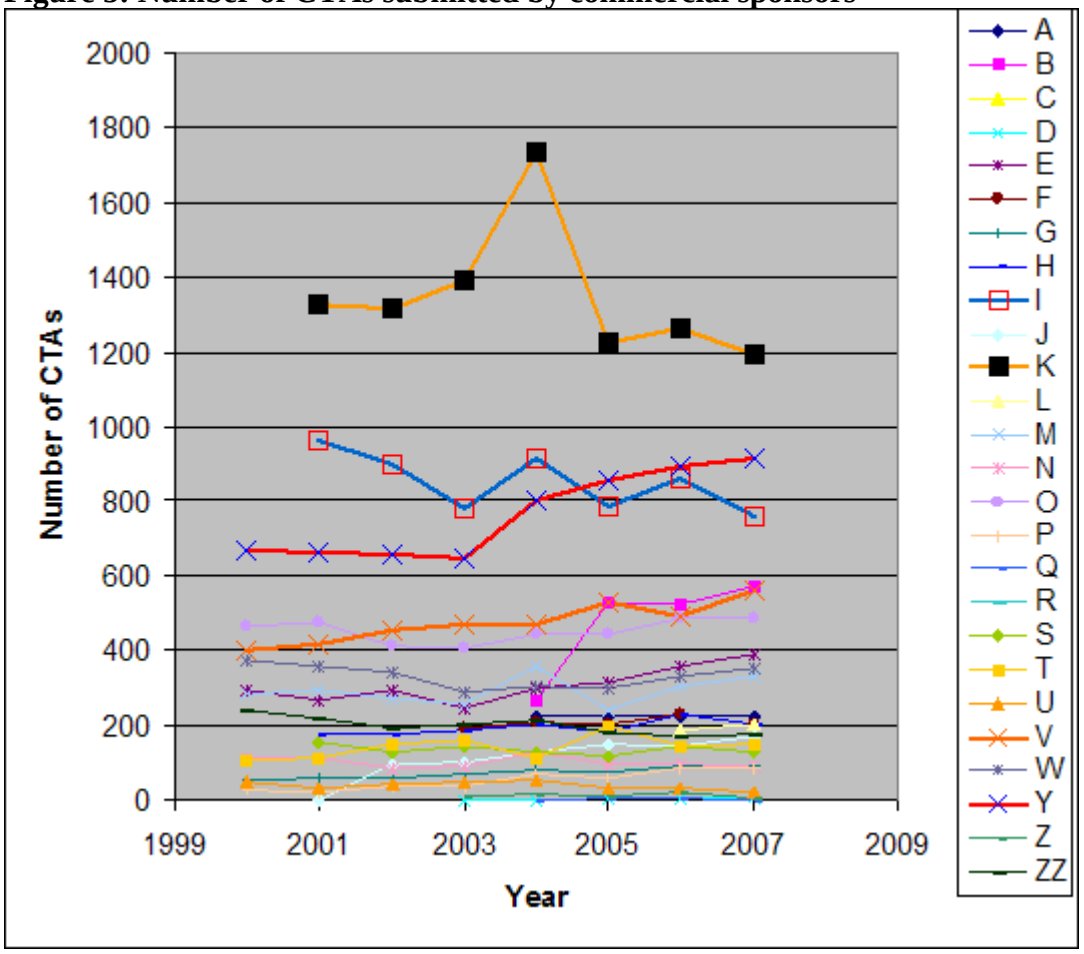
Number of CTAs submitted by commercial sponsors

This question was designed to have an approximate picture of the clinical research activity financially supported by commercial sponsors.

[19] Thiers FA, Sinskey AJ, Berndt ER, Trends in the globalization of clinical trials. Nature Reviews Drug Discovery, 7:13-14, 2008.

Figure 5 shows the number of CTAs submitted by commercial sponsors from 2000 to 2007 for each surveyed country.

Figure 5: Number of CTAs submitted by commercial sponsors



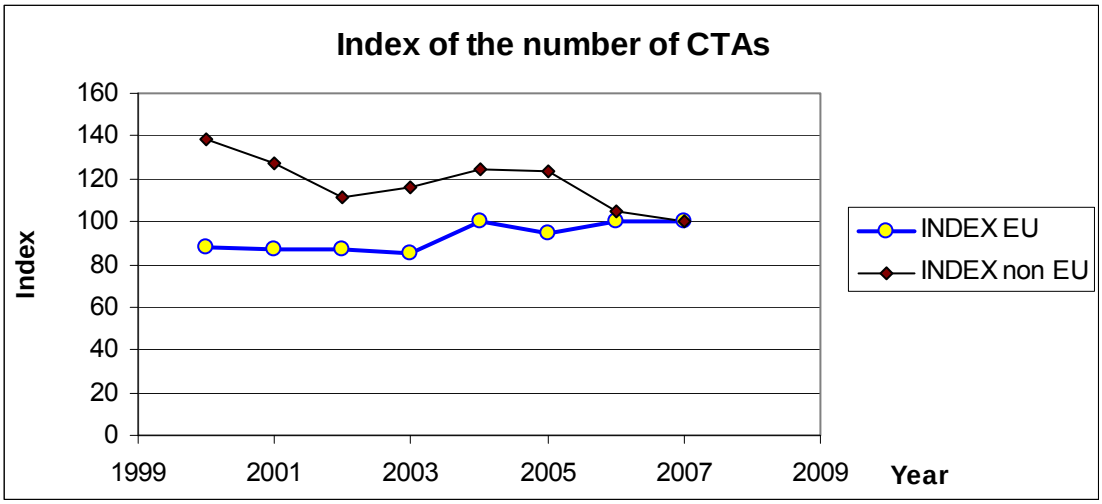
Source: Figure CA6 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

Competent authority X only provided the combined number of CTAs submitted by commercial and non-commercial sponsors. Therefore this country was excluded from the evaluation of CTAs provided by commercial sponsors. For country R the slope was 0.

The time course shape for each competent authority was country dependent; however, for the majority of authorities with lower number of CTAs, a steady increase could be observed while two of the largest authorities in numbers of CTAs, competent authorities (K and I) showed a marked drop in the number of CTAs from 2004 onward.. This noticeable decrease was confirmed by the competent authorities concerned.

However, from an overall perspective, using the index estimation to compare EU data versus non-EU data, the number of CTAs sponsored by commercial entities increased from 2003 to 2004, and from 2004 onward it remained almost stable. See Figure 6.

Figure 6: Index of the number of CTAs submitted by commercial sponsors



Source: Figure CA7 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

The mean increase of 10.53% from 2003 to 2007, based on matched data from 19 countries is statistically significant.
In conclusion these results indicate that there was no evidence of any negative impact of the CTD on the number of CTAs financially supported by commercial sponsors. On the other hand, this increase could not be attributed to the CTD as other concurrent factors may have impacted the overall commercial clinical research situation in Europe.

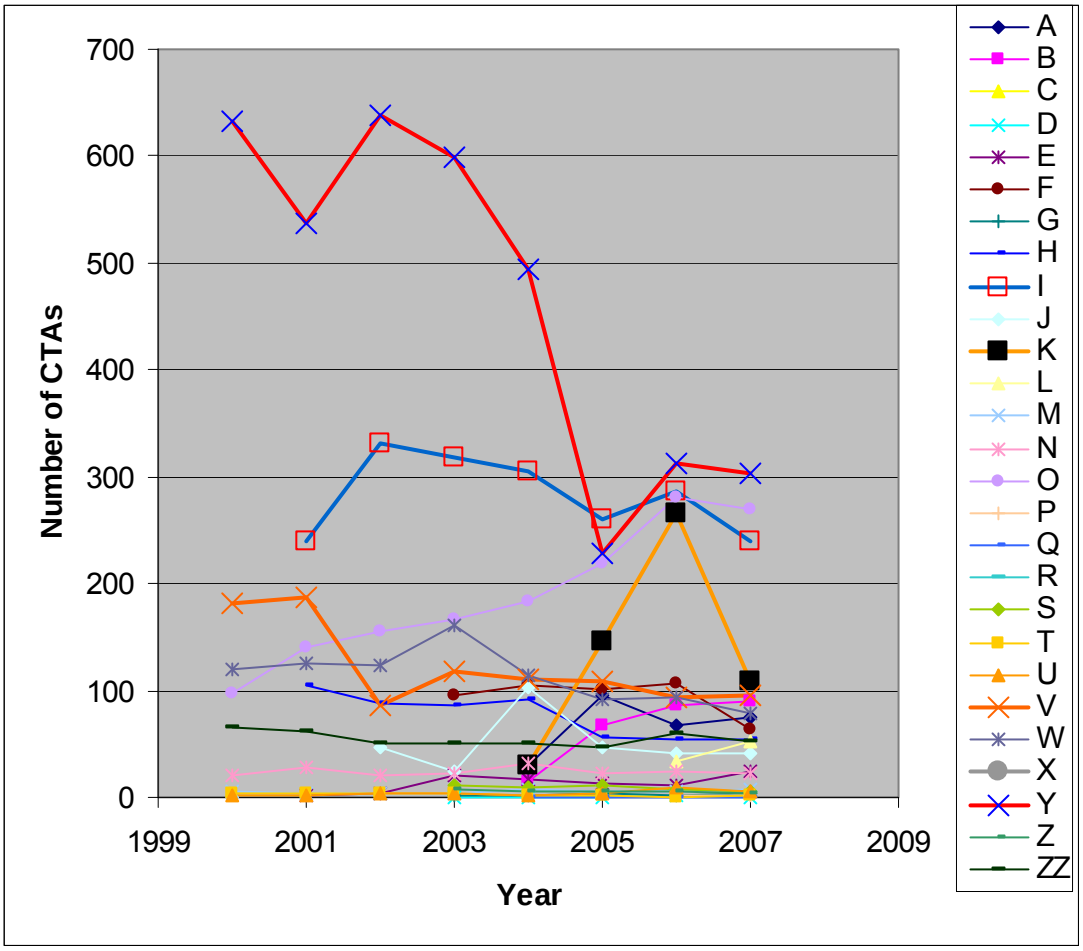
Number of CTAs submitted by non-commercial sponsors

In the conference organised by the EMEA and the DG Enterprise and Industry on "The impact of the EU Directive on clinical research" held in London on 3 October 2007, numerous voices supported the impression of a negative impact of the CTD on academic clinical research[20].

This question was designed to provide arguable data which would back-up or refute this perception. Figure 7 shows the number of CTAs submitted by non-commercial sponsors over the years 2000 to 2007.

[20] Hartmann M, Hartmann-Vareilles F, The clinical trials directive: how is it affecting Europe's non-commercial research? PLOS Clinical Trials, June 2006, e13

Figure 7: Number of CTAs submitted by non-commercial sponsors



Source: Figure CA20 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

As presented above, country X was excluded from this evaluation as it only provided combined data for CTAs from commercial and non-commercial sponsors. For country R the slope was 0.

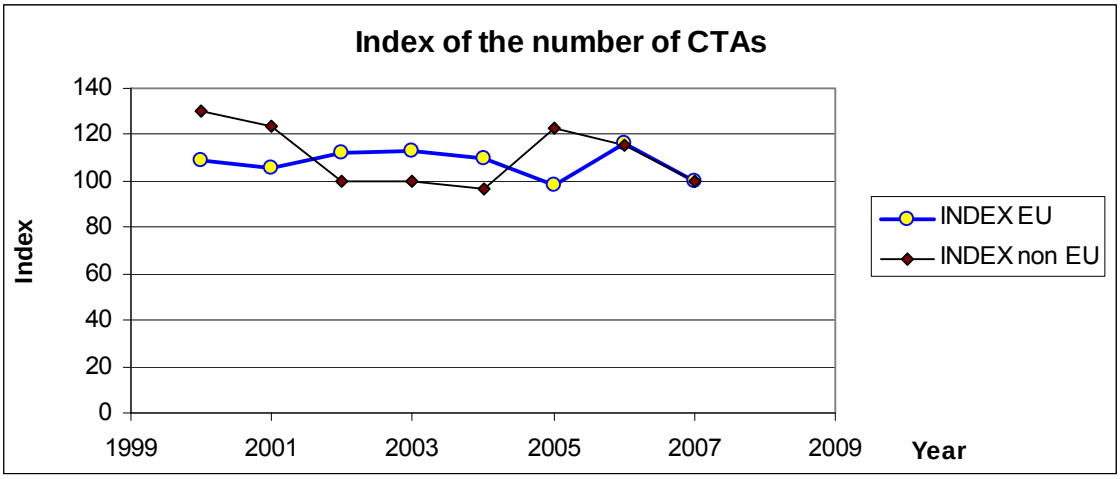
Similarly to the number of CTAs submitted by commercial sponsors, the time course shape of the curves for the number of CTAs submitted by non-commercial sponsors was country dependent. However, most of the institutions – independent of the CTA volume they handle – showed a decline in the number of non-commercial CTAs over time. In addition, in the institutions with the highest numbers in CTAs, i.e. countries I, V and Y, this drop was more pronounced. In country Y the decrease started already in 2003 but become drastic in 2004 and 2005.

Grouping the institutions by trends a dichotomy could be detected: the number of CTAs increased substantially in institutions A, B, E, G, K, O and U and decreased gradually in institutions F, H, J, V, W, X, and Y.

There is no apparent common denominator between institutions to provide a plausible explanation for this discrepancy; however this matter deserves further consideration and exploration.

The index computation of available data indicated there was a slight increase in the overall number of CTAs from non-commercial sponsors in EU from 2001 to 2003 followed by a decrease to a similar extent from 2003 to 2005, an increase in 2006 and again a decrease in 2007. See Figure 8.

Figure 8: Index of the number of CTAs submitted by non-commercial sponsors



Source: Figure CA21 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

However, when calculating the relative change from 2003 to 2007 based on matched data from 17 institutions, a statistically not significant decrease of non-commercial CTAs of 25.57% could be detected.
Therefore it is arguable that the assumption of a decrease in the academic clinical research activity due to the enforcement of the CTD might be true although the respective results of this survey were not statistically significant.

Number of CTAs for biotechnology products, orphan diseases and advanced therapies by commercial and non-commercial sponsors

Many competent authorities had difficulties to break-down the CTAs in product categories. The results from the data provided had therefore to be considered with caution. However, certain trends could be identified.

A clear increase of CTAs for biotechnology products could be detected. The relative change of commercially-sponsored clinical trials with biotechnology products increased by 224%. This change was statistically highly significant. The relative change of non-commercially sponsored clinical trials with biotechnology products of 111% did not reach the significance level due to too few data.

Less information was provided on CTAs for orphan diseases. The number of reported CTAs for this category increased from 9 CTAs in 2003 to 169 in 2007 for submissions from commercial sponsors and from 1 to 26 biotechnology CTAs from non-commercial sponsors, but these results were influenced by the increase of responding competent authorities as well.

Also the data collected on CTAs for advanced therapies had to be considered with caution. The sample sizes were small and no results reached statistical significance but there seemed to be a clear increasing tendency on the non-commercial sponsor side, while the statistical evaluation of the commercial sponsor CTAs provided contradictory results.

In conclusion, the level of information on CTAs of these three categories was limited, but in all three cases an increasing trend could be detected. However, these results did not allow the conclusion that this trend was impacted by the CTD as science and legislation on these drug categories developed as well between 2000 and 2007.

How many non-approvals of CTAs were provided by the Competent Authority, and uses of an appeal system were there per year between 2000 and 2007? Question 6)

An effect over time of the number of non-approved CTAs was considered as an indicator of performance. The hypothesis was that a positive change of this value may be an indirect consequence of the requirement for clinical trial approval introduced by the CTD. Below, Table 8 presents the mean and total number of CTAs not approved by the competent.

Table 8: Mean and total number of non-approved CTAs

Year	2000	2001	2002	2003	2004	2005	2006	2007
MEAN / inst. EU	10.57	15.29	11.00	6.40	8.71	8.76	12.94	11.52
Total number of CTA	74	107	77	96	148	149	220	242
Sample size EU	7	7	7	15	17	17	17	21

Source: Table CA31 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

The mean was defined as the fraction of the total number of non-approved CTAs divided by the number of responding authorities per year.

The figures indicated an increase of the number of non-approved CTAs, especially over the last two years of the observation period which might have been related to the CTD implementation; however, non-matched data were inconclusive. In addition, it had to be taken into consideration when the CTD was implemented in the respective countries. In several countries the implementation took only place in 2006 or even in 2007. Table 9 provides an overview.

Table 9: Year of implementation of the CTD in Europe

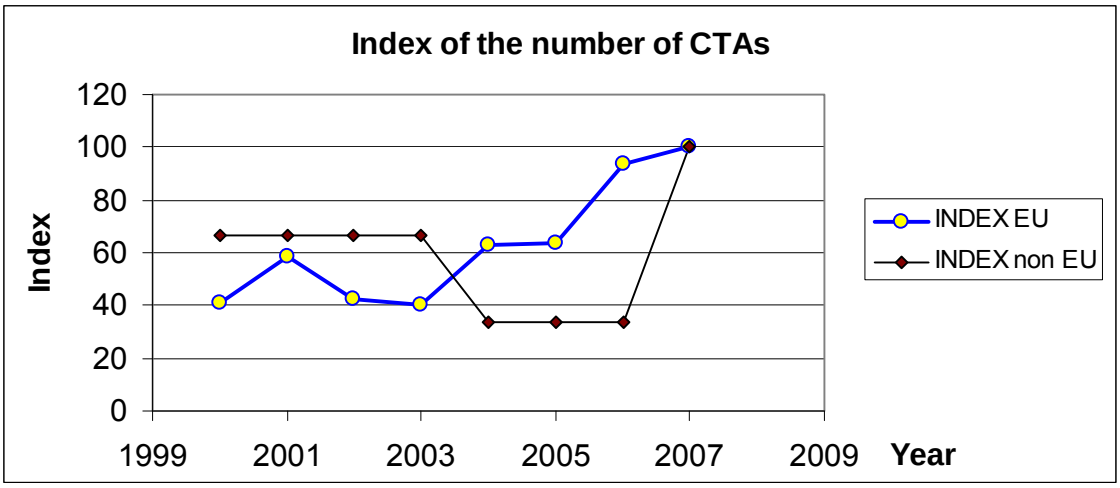
Austria	May 2004
Belgium	May 2004
Bulgaria	Publication and enforcement of law: 13 April 2007
Cyprus	April 2004
Czech Republic	December 2007
Denmark	May 2004
Estonia	March 2005
Finland	May/June 2004. Most aspects of the Directive were already introduced in the Medical Research Act in 1999
France	Law on Public Health Policy published and enforced on 9 Aug. 2004. Final decrees 2006
Germany	6 August 2004
Greece	Ministerial Decree published on 31.12.2003
Hungary	15 September 2005
Ireland	May 2004
Italy	1 January 2004
Latvia	Law fully implemented 28 February 2006. Not fully in lines with CTD and guidelines
Lithuania	15 May 2004
Luxembourg	Legislation published on 22 June 2005
Malta	Legal notices enforced in December 2004 and the implementing guidelines finalised in January 2005
Netherlands	1 March 2006
Poland	May 2004
Portugal	19 August 2004

Romania	1 May 2006
Slovakia	1 May 2004. Some amendments of the law finalised on 1 June 2006
Slovenia	8 April 2006
Spain	May 2004
Sweden	1 May 2004
United Kingdom	1 April 2004

Source: BARQA GCP Committee Summary Table of the Implementation of the EU CT Directive – updated 27 September 2005

However, the increase in means per institution was supported by the indexed data. See Figure 9 of the Index of the number of non-approved CTAs in the EU versus non-EU competent authorities.

Figure 9: Index of the number of non-approved CTAs



Source: Figure CA40 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

And also the calculation of the mean change of non-approved CTAs in 2007 with respect to 2003 from matched data of 17 competent authorities showed a statistically significant increase of 81.11%.

In 2003 eleven competent authorities reported the existence of an appeal system in 8 countries (72.7%). In 2007 nineteen authorities responded to this question and confirmed the existence of an appeal system in 16 countries (84.2%). Over the years relatively constantly between 10% and 25% of the competent authorities reported that the appeal system was used.

In conclusion, the data appeared to support the hypothesis of a possible direct relation between the implementation of the CTD and an increase in the non-approved CTAs by the competent authorities as well as the implementation of an appeal system. However, the use of the appeal system remained a rare event.

How many trials on medicinal products submitted for approval/notification yearly from 2000 to 2007, were multi-national trials, national multi-centre trials, mono-centre trials? (Question 7)

Only a limited number of competent authorities could provide a break-down of the CTAs submitted into the categories multi-national, national multi-centre and mono-centre trials, especially in the period before implementation of the CTD. Nevertheless, the data received show clear trends.

Number of multi-national clinical trials

The mean number of multi-national clinical trials per competent authority submitted for approval in each of the study years remained relatively steady while the total number increased 3-fold from 2000 to 2007. However, this increase in our data was also impacted by the increasing number of responding competent authorities. An overview is presented in Table 10.

Table 10: Mean and total number of multinational CTs in the EU

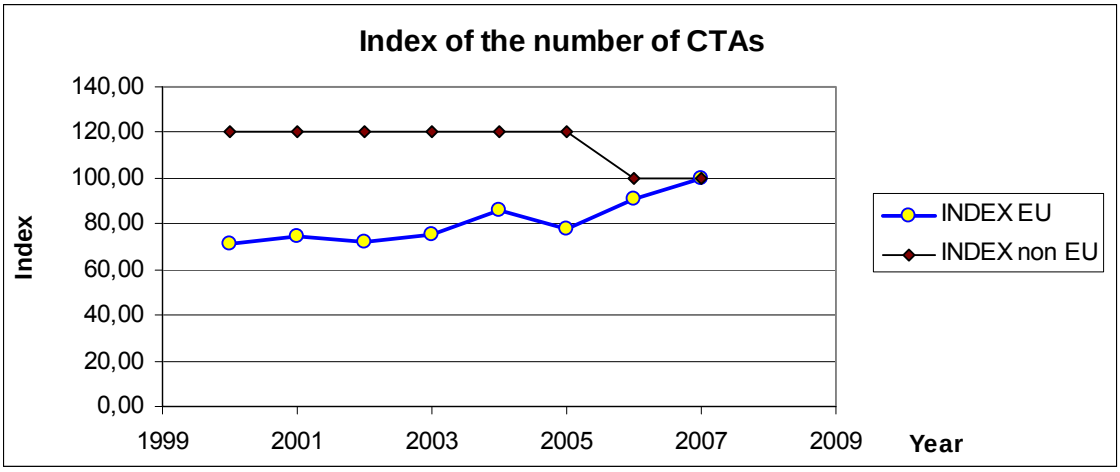
Year	2000	2001	2002	2003	2004	2005	2006	2007
MEAN / inst. EU	227.40	237.00	228.40	161.27	248.60	210.50	233.08	233.33
Total number of CTA	1137	1185	1142	1774	2486	2526	3030	3500
Sample size EU	5	5	5	11	10	12	13	15

Source: Table CA36 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

The mean was defined as the fraction of the total number of CTs divided by the sample size in each year.

The relative change based on matched data from 10 authorities showed a 27.39% increase observed in 2007 with respect to 2003 which was just at the limit of significance. This was supported by the analysis per index data. See Figure 10 of the index of the number of multi-national CTs in the EU.

Figure 10: Index of multi-national CTs per year in the EU



Source: Figure CA46 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

Number of multi-centre clinical trials

The mean number of national multi-centre CTs per competent authority decreased from 2000 to 2007, markedly as of 2004. The overall increase in national multi-centre clinical trials in that period was impacted by the strongly increasing number of respondents in the same period, as presented in Table 11.

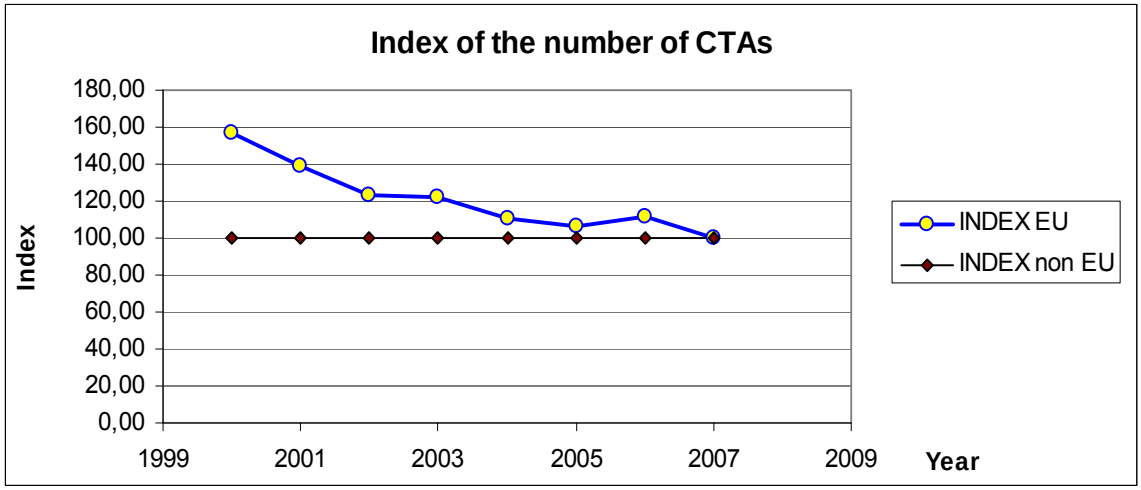
Table 11: Mean and total number of national multi-centre CTs per year in the EU

Year	2000	2001	2002	2003	2004	2005	2006	2007
MEAN / inst. EU	108.67	96.67	85.67	109.38	69.45	73.00	85.67	71.36
Total number of CTA	326	290	257	875	764	730	771	999
Sample size EU	3	3	3	8	11	10	9	14

Source: Table CA39 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

As the sample size for the years 2000 to 2002 was rather small in relation to 2007, the index data gave a better estimation and are presented in Figure 11.

Figure 11: Index of the number of national multi-centre CTs in the EU



Source: Figure CA51 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

Index data showed a nearly steady decline in the number of national multi-centre trials with its lowest values in 2005 and 2007. However, the largest decrease occurred before 2004 and thus before the implementation of the CTD. Since 2004 the decrease was modest. Calculation of the mean change of national multi-centre CTs in 2007 relative to 2003 on matched data revealed a not statistically significant decrease of 14.2%.

Number of mono-centre clinical trials

Similarly to the previous categories, the data collected showed an increase over time of the total number of national mono-centre CTs. See Table 12. However, this was again impacted by the strong increase of respondents over the years. The mean per competent authority increased strongly in 2004, slightly decreased since then but remained on a higher level than before 2004. This decrease was primarily due to one country which experienced a very strong decrease in mono-centre trials since 2004.

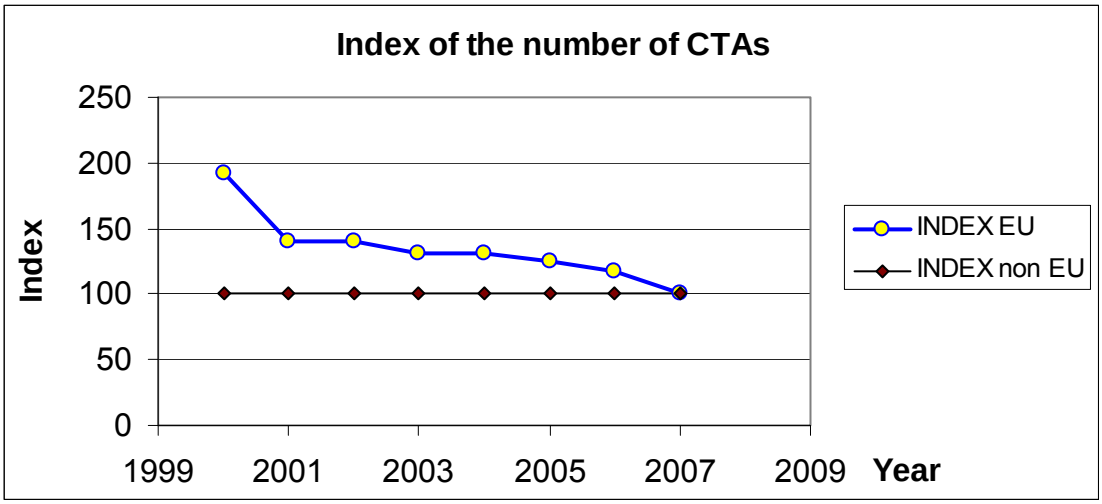
Table 12: Mean and total number of national mono-centre CTs in the EU

Year	2000	2001	2002	2003	2004	2005	2006	2007
MEAN / inst. EU	57.5	66	66	63.636	118.6	104.25	90.714	75.333
Total number of CTA	230	264	264	700	1186	1251	1270	1130
Sample size EU	4	4	4	11	10	12	14	15

Source: Table CA42 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

Index data imputation and the relative change calculation revealed a slight decrease between 2003 and 2007. See Figure 12 below.

Figure 12: Index of the number of national mono-centre CTs in the EU



Source: Figure CA56 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

In conclusion, the number of multi-centre clinical trials clearly increased since the implementation of the CTD while national-multi-centre trials decreased strongly before and slightly after implementation of the CTD. Mono-centre trials decreased only slightly during the observation period. Thus, an impact of the CTD on this development is hard to detect.

How many substantial amendments have been submitted, and how many of those not approved, yearly from 2000 to 2007? (Question 8)

Substantial amendments are a measure for the need for changes to the protocol after its original approval and occur in nearly every trial due to facts identified or occurred after start of the CT. A sudden increase could be the result of an additional external factor like a new approval process, while a continuous increase could be the result of an increase in the overall clinical trial activity.

Table 13 shows the number of amendments to the protocol submitted for approval.

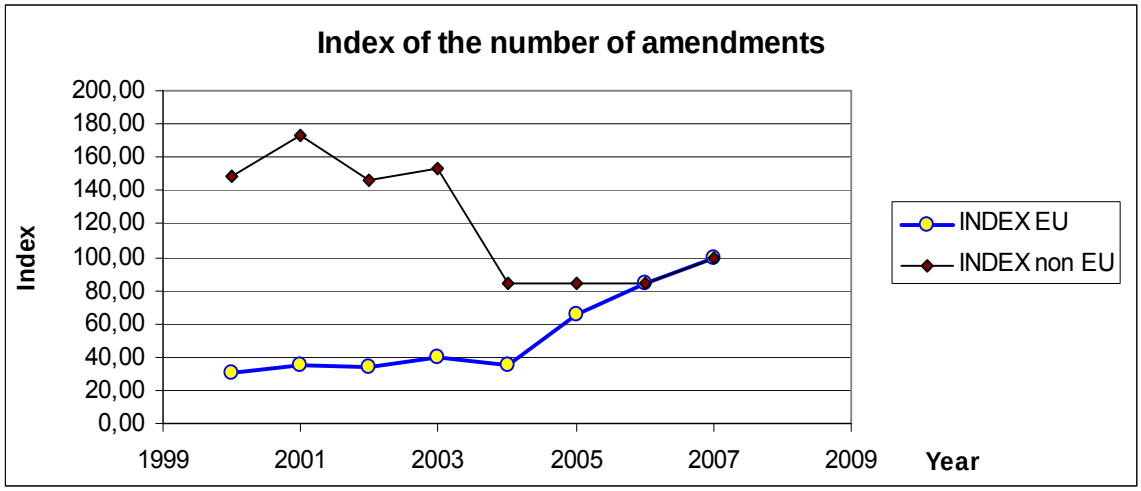
Table 13: Mean and number of protocol amendments per year

Year	2000	2001	2002	2003	2004	2005	2006	2007
MEAN / inst. EU	575.50	740.00	620.25	573.27	401.36	700.56	829.84	998.48
Total number of amendments	2302	5180	4962	6306	5619	11209	15767	20968
Sample size EU	4	7	8	11	14	16	19	21

Source: Table CA45 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

The mean number of protocol amendments per competent authority increased substantially after 2004. This increase was supported by the total number of substantial amendments, by the index data (see Figure 13) and by the relative change calculation (74.6%).

Figure 13: Number of protocol amendments submitted for approval in the EU



Source: Figure CA61 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

In line with this development, also the number of non-approved substantial amendments increased strongly after 2004, however, this was in line with the overall increase of the substantial amendments and remained a rare event.

This strong increase of substantial amendments falls exactly into the period of the CTD implementation and can not be explained with other concurrent developments.

Time lines

What was the average time (days) between the receipt of a notification/complete application and the issue of the acknowledgement / authorisation letter for all types of applications submitted, for Phase 1 trials, Phases 2 to 4 trials, trials on biological products, and trials on xenogenic/somatic cell therapy, yearly from 2000 to 2007? (Question 9)

This question was designed to collect the time elapsed until obtaining the competent authority authorisation or the acknowledgment of notification for all applications, for phase I applications, phase II to IV applications, for biological products CTA and for xenogenic/somatic/cell therapy CTA.

The time for submission for dossier validation was not included.

However, this question must have been too complex because only few competent authorities were in a position to answer this question with all sub-categories and in many cases the pattern of the responses obtained was not consistent with the intended s rationale. Obviously, the text and format for that question were not clearly understandable despite the positive testing in the pilot phase and/or the competent authority did not collect information on timelines according to this question's format.
Subsequently, only one topic, the time from valid submission to approval for all types of applications, held sufficient credible data to be analysed. Detailed evaluation of the other parameters can be found in "Statistical Report CA", available on www.efgcp.be/ICREL > Report.

The design of the question 9 can be seen in Figure 14.

Figure 14: Question 9 lay out

	All notifications / applications [1]		Clinical trial applications for **Phase 1**		Clinical trial applications for **Phases 2 to 4**		Clinical trial applications for **biological products**		Clinical trial applications for **xenogenic/ somatic cell therapy**	
	Notifi-cation time for acknowledgement (days)	**Authori-sation:** time to issue approval letter (days)	**Notifi-cation** time for acknowledgement (days)	**Authori-sation:** time to issue approval letter (days)	**Notifi-cation** time for acknowledgement (days)	**Authori-sation:** time to issue approval letter (days)	**Notifi-cation** time for acknowledgement (days)	**Authori-sation:** time to issue approval letter (days)	**Notifi-cation** time for acknowledgement (days)	**Authori-sation:** time to issue approval letter (days)
2000										
2001										
2002										
2003										
2004										
2005										
2006										
2007										

[1] Before the implementation of the EU Clinical Trials Directive, most country laws required only notification, not approval.

Source: ICREL CA questionnaire

As presented in Table 14, the information on the time elapsed from having received a valid application until the issue of an authorisation was answered by only a small number of competent authorities. Even for 2007, only 15 regulatory agencies provided information on an element of the new legislation which was one of the main achievements of the CTD. The results obtained showed that the mean time per competent authority was of 60.3 days in 2003 and of 48.6 days in 2007.

Table 14: Mean time to obtain authorisation per competent authority

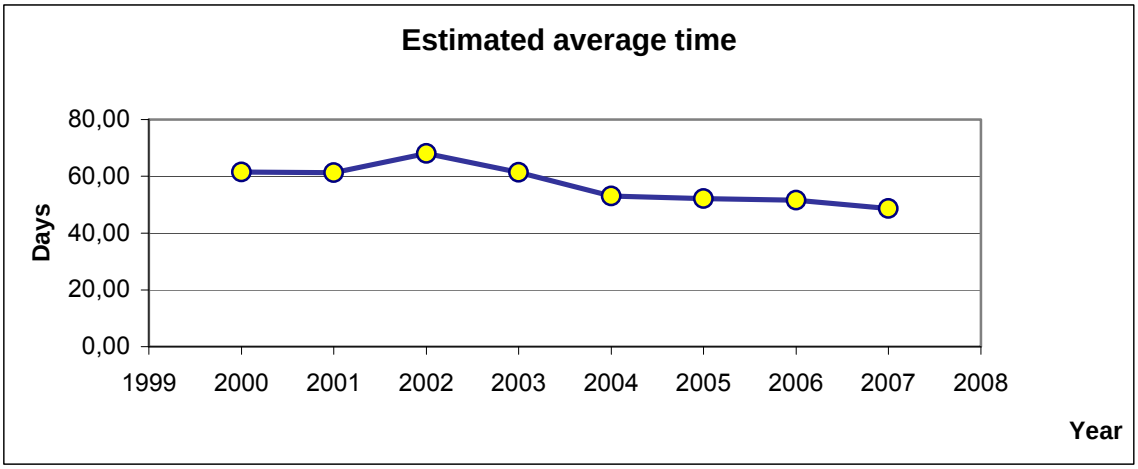
Year	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**
MEAN / inst. EU	64	63.83	70.14	60.375	50.43	49.63	47.34	48.66
Sample size EU	6	6	7	8	8	9	11	15

Source: Table CA54 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

The mean was defined as the fraction of total number of days for authorisation divided by the number of respondents for each year.

An estimation of the average time to obtain authorisation is shown in Figure 15. The average time in each of the years was the product of the estimation of the average time in 2007 and the estimation of the relative change from that year to 2007.

Figure 15: Estimated average time to obtain authorisation in the EU



Source: Figure CA73 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

The average time in 2007 for all EU institutions to issue an authorisation was around 50 days, far below the 60 days requested by the EU CTD. Indeed the estimated average after 2004 remained always below 60 days and tended to decline over time.

This decrease in days for the authorisation process presented by the competent authorities was also observed using the relative change calculation based on matched data. The relative change observed in 2007 with respect to 2003 was of -15.86%.

Workload

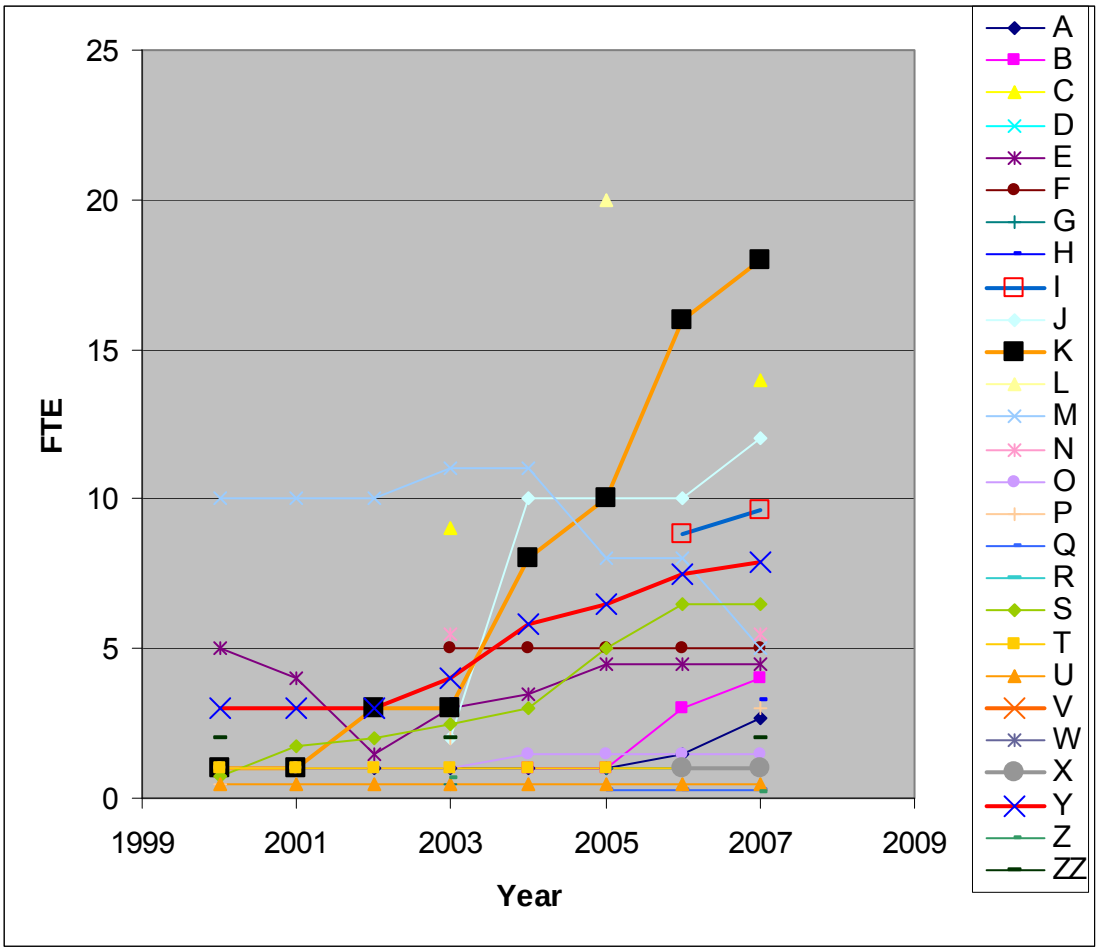
One key criticism passed on the CTD was the additional bureaucracy and the resulting increase of workforces required to full all new requirements. The next two questions were designed to measure the workforces (in full-time equivalents, FTEs) required for different tasks related to the CTD in competent authorities.
One FTE is one full-time position or two half-time positions. . If a task requires 2.5 days per week to be done, it will require one half-time employee or half the time of one full-time employee; this is 0.5 FTE.

Between 2000 and 2007, how many full-time equivalents (as internal and external resources) worked each year on your following tasks? (Question 10)

Scientific involvement/assessment of Clinical Trial Notification or Clinical Trial Authorisation and (substantial) amendments

The number of FTEs required for the scientific assessment of CTAs was country specific as presented in Figure 16.

Figure 16: Time course of the number of FTEs per institution for the scientific assessment of CTAs and amendments



Source: Figure CA90 in Statistical Report CA, available on www.efgcp.be/ICREL > Report.

The mean number of FTEs involved in the scientific evaluation of the clinical trial applications and substantial amendments as reported by competent authorities are presented in Table 15.

Table 15: Mean number of FTEs per institution required for scientific evaluation in the EU

Year	2000	2001	2002	2003	2004	2005	2006	2007
MEAN / inst. EU	2.37	2.58	2.55	3.39	4.27	3.94	4.75	5.31
Sample size EU	10	9	9	16	12	14	16	20

Source: Table CA72 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

The mean was defined as the fraction of total number FTEs divided by the number of responding competent authorities for each year.

The above table shows that the average number of FTEs increased over time. The comparison of the information from an equal number of respondents in 2003 and 2006 showed that the scientific evaluation of CTAs after implementation of the CTD needed in the average 1.3 FTEs more than before.

In the main comparison of this survey – the years 2003 and 2007 – the increase was nearly 2 FTEs.

The relative change calculation from 16 respondents clearly supported this observation with a statistically significant increase of FTEs of +68.39% observed in 2007 with respect to 2003.

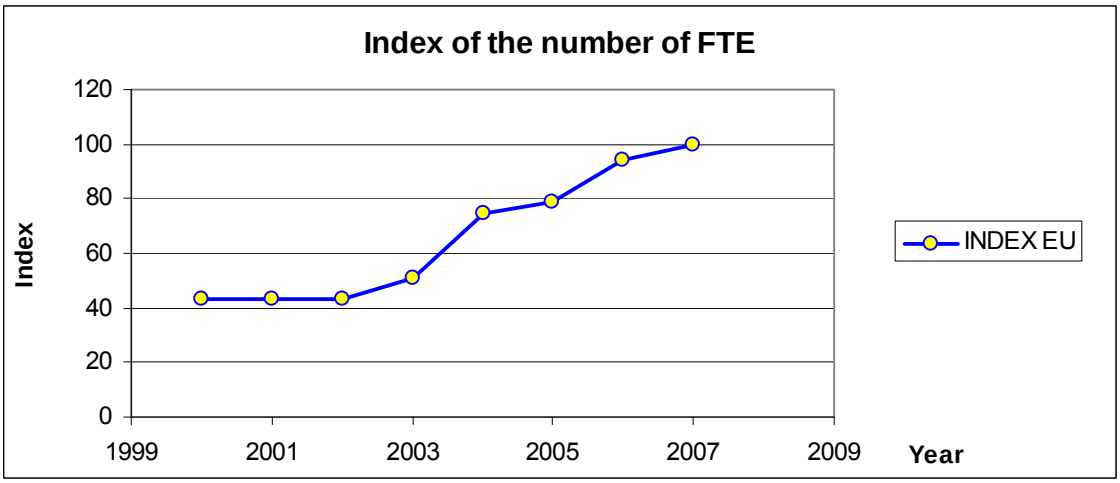
In addition, the index data indicated that in 2003 the average number of FTEs required for the scientific evaluation of clinical trial dossiers was half of that required in 2007. See Table 16 and Figure 17 with the index data.

Table 16: Index of the average number of FTEs for scientific evaluation in the EU

	Year	2000	2001	2002	2003	2004	2005	2006	2007
EU	Relative change		0.00%	-1.08%	17.39%	47.94%	5.26%	19.91%	5.79%
EU	INDEX EU	43.59	43.59	43.12	50.62	74.89	78.83	94.53	100
EU	Average FTE (matched)	2.31	2.31	2.29	2.69	3.98	4.19	5.02	5.31
EU	Sample size (matched)		9	9	9	11	12	14	16

Source: Table CA74 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

Figure 17: Index of the number of FTEs for scientific evaluation in the EU



Source: Figure CA91 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

Administrative tasks for Clinical Trial Notification or Clinical Trial Authorisation and (substantial) amendments

The mean number of FTEs involved in CTA administrative tasks reported by competent authorities can be seen in Table 17.

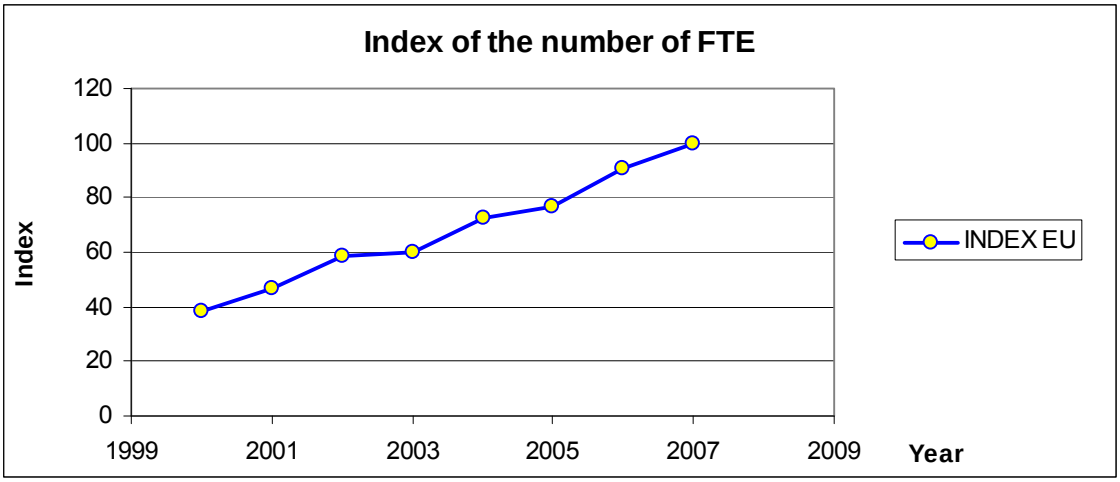
Table 17: Mean number of FTEs per institution required for administrative tasks in the EU

Year	2000	2001	2002	2003	2004	2005	2006	2007
MEAN / inst. EU	1.25	1.61	2.02	2.12	2.43	2.28	2.81	3.30
Sample size EU	10	9	9	17	12	14	16	21

Source: Table CA75 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

The above table shows that the average number of FTEs required for CTA administrative tasks increased over time. The comparison of 2007 vs. 2003 denoted an increase of 1.2 FTEs.
The relative change based on matched data from 17 competent authorities supported this observation with a statistically significant increase of +55.19% observed in 2007 with respect to 2003 and also the index data showed a clearly linear increase. See Figure 18.

Figure 18: Index of the number of FTEs for administrative tasks in the EU



Source: Figure CA95 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

SAE (Serious adverse event) / SUSAR (Suspected unexpected serious adverse reaction) reports / Pharmacovigilance tasks

The mean number of FTEs per competent authority involved in pharmacovigilance tasks, including administrative tasks such as safety data entry, data retrieving, etc. reported by competent authorities are presented in Table 18.

Table 18: Mean number of FTEs per institution required for pharmacovigilance tasks in the EU

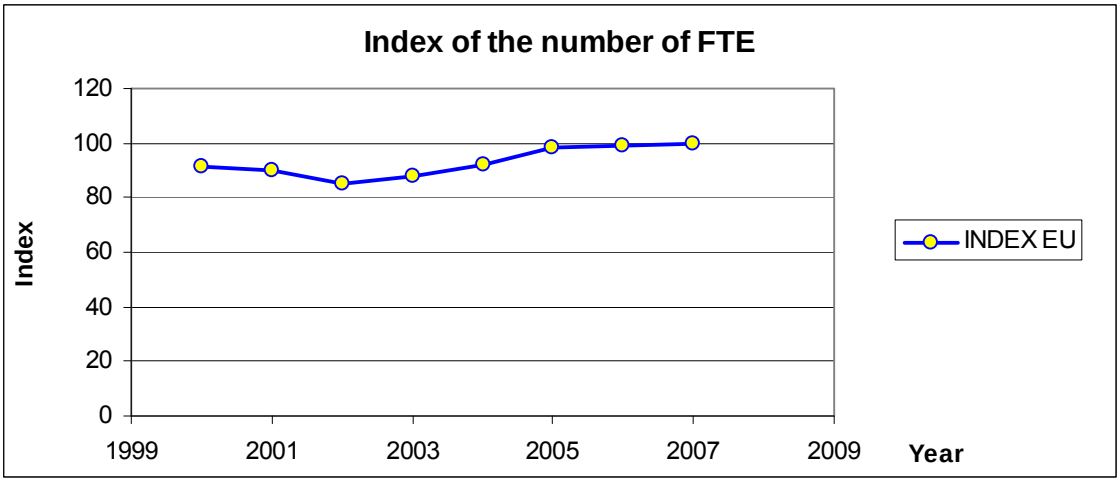
Year	2000	2001	2002	2003	2004	2005	2006	2007
MEAN / inst. EU	6.31	7.05	6.69	4.10	5.23	4.75	4.51	3.93
Sample size EU	8	7	7	14	10	12	13	18

Source: Table CA78 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

Although the mean number of FTEs per institution involved in pharmacovigilance in 2007 was inferior to 2003, 3.9 FTEs and 4.1 FTEs respectively, impacted by the strong increase of respondents from 2003 to 2007, the relative change based on matched data revealed a statistically significant increase in staff of 17.84% in 2007 with respect to 2003.

Index data also suggested a yet modest – increase over time in the number of FTEs for pharmacovigilance tasks – see Figure 19.

Figure 19: Index of the number of FTEs for pharmacovigilance tasks



Source: Figure CA99 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

In summary, the strong and statistically significant increase of staff for scientific review tasks coincided exactly with the implementation of the CTD and had therefore to be seen in relation with the CTD. The same held true for the smaller but statistically significant increase of staff involved in pharmacovigilance tasks but no conclusion could be drawn on the impact of the CTD on staffing for administrative tasks as an increasing trend was observable since 2000.

How many SAE (Serious adverse event) / SUSAR (Suspected unexpected serious adverse reaction) reports did you receive from 2000 to 2007? (Question 11)

This question aimed at exploring the development of expedited safety reporting to competent authorities between 2000 and 2007. The introduction of the SUSAR definition in the CTD occurred with the intention to reduce the number of expedited reports and thus to reduce the workload for all parties involved in this process.

The amount of SAE and SUSAR reports received per year varied widely between countries. During the whole observation period country I received 5 to 10 times more reports than the average of all countries with a maximum before implementation of the CTD. Since then the number decreased but was in 2007 still 7 times higher than the average. The competent authority from that country confirmed that the figures provided were correct. As this country happened to introduce the CTD only in 2006 into its national legislation and to provide more representative information on all other competent authorities a second analysis - excluding the data from that country - was performed.

Table 19 presents the mean number of SAE or SUSAR reports received per competent authority per year excluding competent authority I.

Table 19: Mean number of SAEs or SUSARs per institution in the EU excluding institution I

Year	2000	2001	2002	2003	2004	2005	2006	2007
MEAN / inst. EU	296.8	496.4	528	356.6	651.3	849.4	1928.9	5724.1
Sample size EU	5	7	8	10	8	11	12	16

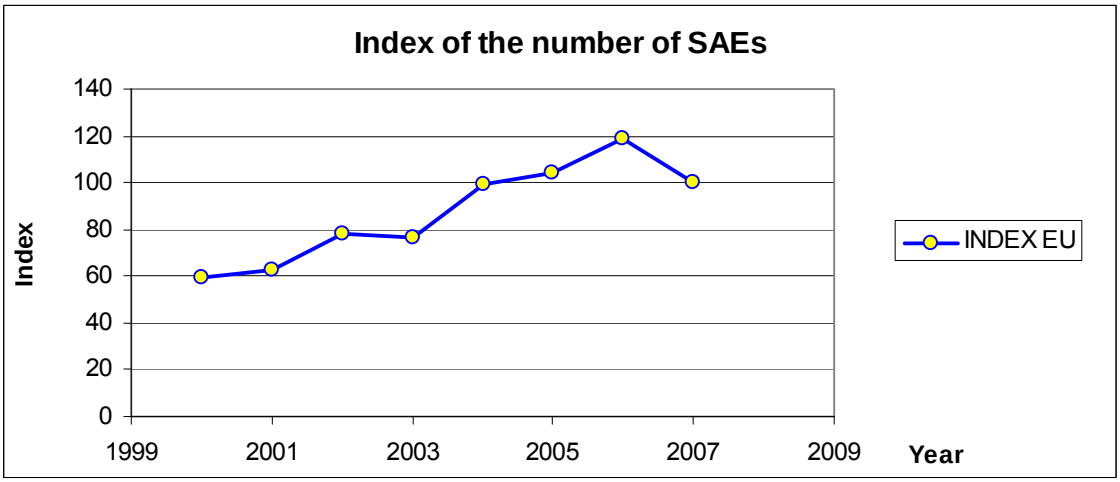
Source: Table CA81 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

The mean was defined as the fraction of the total number SAEs or SUSARs divided by the number of responding competent authorities for each year.

As presented in Table 18, the mean number of reports per competent authority, excluding competent authority I, increased very strongly from 2003 to 2007. This was confirmed by the calculation of the relative change in those two years with an increase of 672%. The magnitude of this increase was strongly influenced by very strong increase from 2003 to 2007 in country K. Excluding that country as well from the analysis still led to an increase of 119%.

Index data over all competent authorities also presented an increase in the number of SAEs or SUSARs between 2003 and 2007. See Figure 20. The decrease in 2007 was impacted by the large decrease in country I.

Figure 20: Index of the number of SAEs or SUSARs in the EU



Source: Figure CA103 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

Thus, in contrast to the expectation, the implementation of the CTD did not result in a decrease in the number of the expedited safety reports to competent authorities but in a strong increase. This confirmed the impression reported in literature and meetings by all stakeholders in the process.

Since when do you enter data in the EudraCT and EudraVigilance database? (Question 12)

The CTD implemented the requirement for two databases to be established at the EMEA: the EudraCT database for information on clinical trials with medicinal products and the EudraVigilance Clinical Trial Module (EVCTM), one of the two parts of the EudraVigilance Database Management System. While sponsors are only supposed to use the EudraCT database to receive a unique number for each clinical trial, competent authorities are requested to enter CTA and inspection information into EudraCT as well as SUSAR reports and other safety information from clinical trials into EVCTM. This required extra workforce and financial resources as well as IT connectivity adaptation from the competent authorities.

Although the effective date for implementation of the Directive was 1 May 2004, the year in which the competent authorities started entering data in EudraCT and EudraVigilance served as example of the real time it took to fulfil these requirements.

Table 20 lists the competent authorities' first year of data entry into the two databases.

Table 20: First year entering data in EudraCT and EudraVigilance, per institution

Institution	EUDRACT	EudraVigilance
A	2004	
B	2005	2008
C	2007	2007
D	2005	2006
E	2004	2004
F	2004	2008
G	2004	2005
H	2004	2007
I	2006	
J	2004	2004
K	2004	2008
L		
M		2005
N	2004	2007
O	2004	
P	2004	
Q	2005	2005
R	2005	2005
S	2005	2005
T	2005	2005
U	2004	
V	2004	
W	2004	2006
X	2006	2006
Y	2004	2006
Z*	2004	2005
ZZ*	2004	2004

Source: table CA47A in CA Appendix, available on www.efgcp.be/ICREL > Report
Empty cells: no response.
* Non-EU country

From the above table it can be noted that of the 23 EU respondent institutions, 14 were able to enter data in EudraCT in 2004, 6 in 2005, 2 in 2006 and 1 in 2007. One of the respondent competent authorities had not implemented any data entry in any database in 2007 yet, and 9 further competent authorities had not started to enter data into the EudraVigilance database in 2007, including some major clinical trial countries.

Obviously, entering data into EudraVigilance was more difficult for the competent authorities because amongst those 19 EU competent authorities which reported to enter data into both databases, only 2 were able to do so in 2004, while 6 started to enter data into EudraVigilance in 2005, 4 in 2006, 3 in 2007 and 3 reported to plan entering in 2008.

In conclusion, most competent authorities allocated their resources sequentially to data entry into the two EU databases, first implementing EudraCT and afterwards EudraVigilance.

Cost

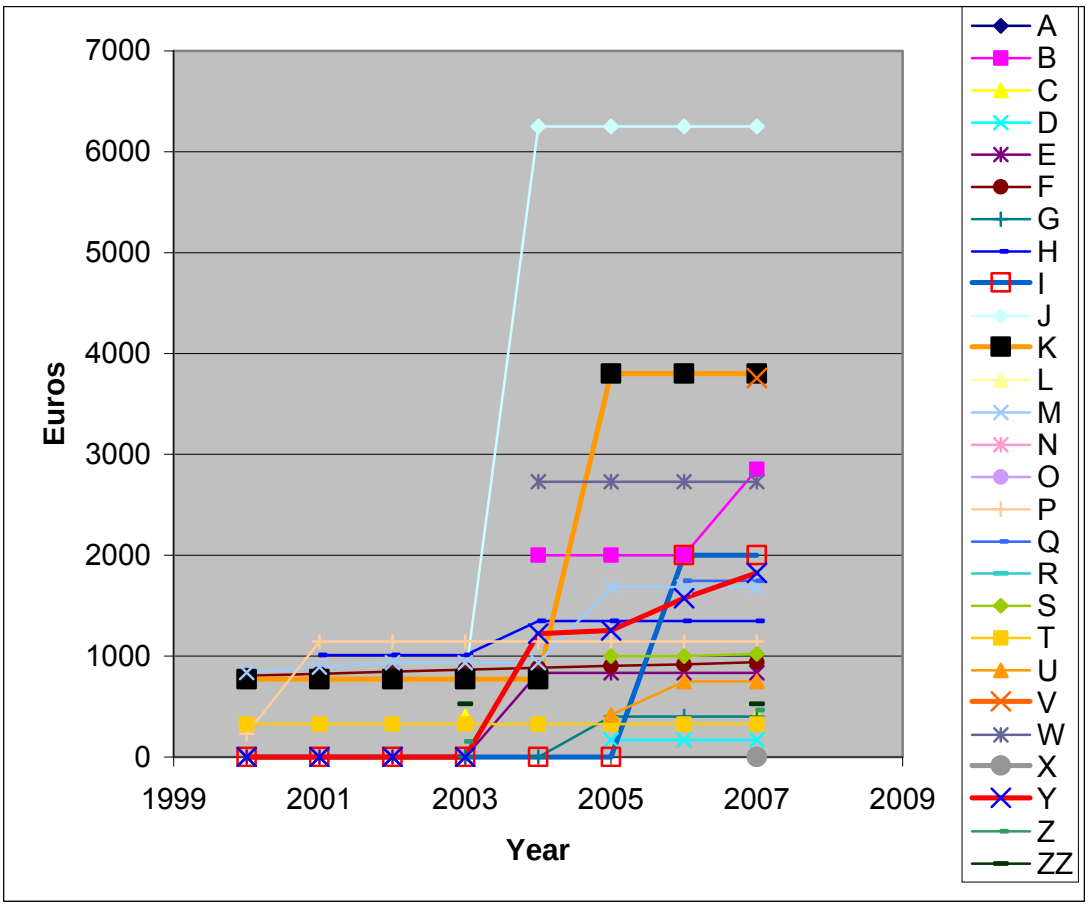
Competent authorities in the EU choose different approaches to cover the additional costs resulting from their obligation to fulfil CTD requirements. Charging sponsors for service provided like fees for CTAs and substantial amendments was one option. The following two questions aimed at measuring clinical trial cost factors for commercial and non-commercial sponsors stemming from their interaction with the competent authorities, with special emphasis on costs for SMEs and sponsors of orphan drug trials.

Yearly from 2000 to 2007, what was the average amount of fees to be paid to the Competent Authority by commercial and non-commercial sponsors regarding notifications/clinical trial authorisations (Question 13)

Standard rate for a notification/CTA for commercial sponsors

The development of the notification/CTA fee level for commercial sponsors was very country specific. Figure 21 shows the development of these fees for the responding competent authorities:

Figure 21: Time course of the notification/CTA fees per institution charged to commercial sponsors



Source: Figure CA108 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

In Table 21 the average fees for a notification, respectively CTA per institution – charged to commercial sponsors – are presented:

Table 21: Average notification/CTA fees charged to commercial sponsors in the EU

Year	2000	2001	2002	2003	2004	2005	2006	2007
MEAN / inst. EU	371.17	551.79	559.33	519.40	1418.79	1516.3	1686.9	1698.98
Sample size EU	8	9	9	12	13	16	17	20

Source: Table CA85 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

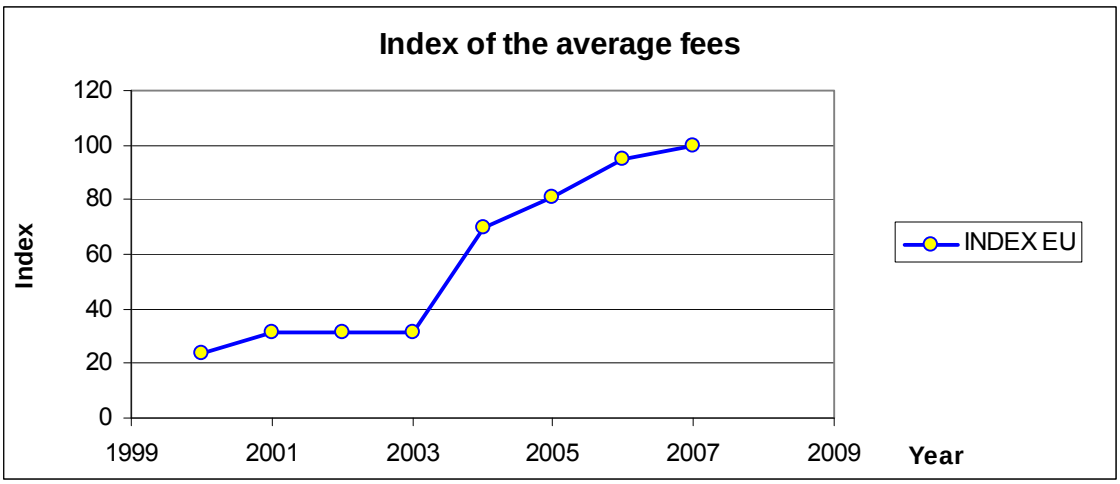
The mean was defined as the fraction of the total of the amounts for a notification/CTA in all responding competent authorities divided by the number of responding competent authorities per year. The figures were expressed in Euros.

While the increase of the mean fees was modest between 2000 and 2003, there was a jump to a nearly 3-fold higher average fee in 2004, followed by a comparably modest increase as between 2000 and 2003. This magnitude of the increase in 2004 was strongly impacted by the steep fee increase of two competent authorities, but in fact, a number of authorities raised there fees at that time. Other competent authorities increased their fees between 2005 and 2007, partly in line with the implementation of the CTD in these countries. However, the relative change from 2003 to 2007

calculated from matched data, showed a statistically significant increase of the notification/CTA fees of 236.2%.

Also the time course of the index illustrated this marked increase from 2003 to 2004. See Figure 22.

Figure 22: Index of the average fees for notifications/CTAs charged to commercial sponsors



Source: Figure CA109 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

As the fee increases occurred during the period of the CTD implementation in national legislations an impact of the CTD on the fee structure of the competent authorities could be assumed.

Rate for SME sponsors, sponsors of orphan drug trials and non-commercial sponsors

An increase of clinical trial costs as a result of the CTD was of particular concern to SMEs, non-commercial sponsors and sponsors of orphan drug trials. The intention of this question was to find out whether competent authorities had considered the different types of sponsors in their fee structure.

The average fees for notifications/CTAs charged to SMEs in the EU are shown in Table 22.

Table 22: Average notification/CTA fees charged to SMEs in the EU

Year	2000	2001	2002	2003	2004	2005	2006	2007
MEAN / inst. EU	603.5	582.47	593.783	596.915	1282.18	1336	1578.66	1703.23
Sample size EU	4	6	6	6	8	9	10	12

Source: Table CA88 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

The average fees for notifications/CTAs charged to sponsors of orphan drug trials in the EU are shown in Table 23.

Table 23: Average notification/CTA fees charged to sponsors of orphan drug trials in the EU

Year	2000	2001	2002	2003	2004	2005	2006	2007
MEAN / inst. EU	482.8	582.47	593.783	596.915	904.43	1336	1578.66	1703.23
Sample size EU	5	6	6	6	8	9	10	12

Source: Table CA91 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

The average fees for notifications/CTAs charged to non-commercial sponsors in the EU are shown in Table 24.

Table 24: Average notification/CTA fees charged to non-commercial sponsors in the EU

Year	2000	2001	2002	2003	2004	2005	2006	2007
MEAN / inst. EU	315.11	265.95	269.64	272.77	695.65	877.30	868.92	1017.86
Sample size EU	5	6	6	6	8	11	12	14

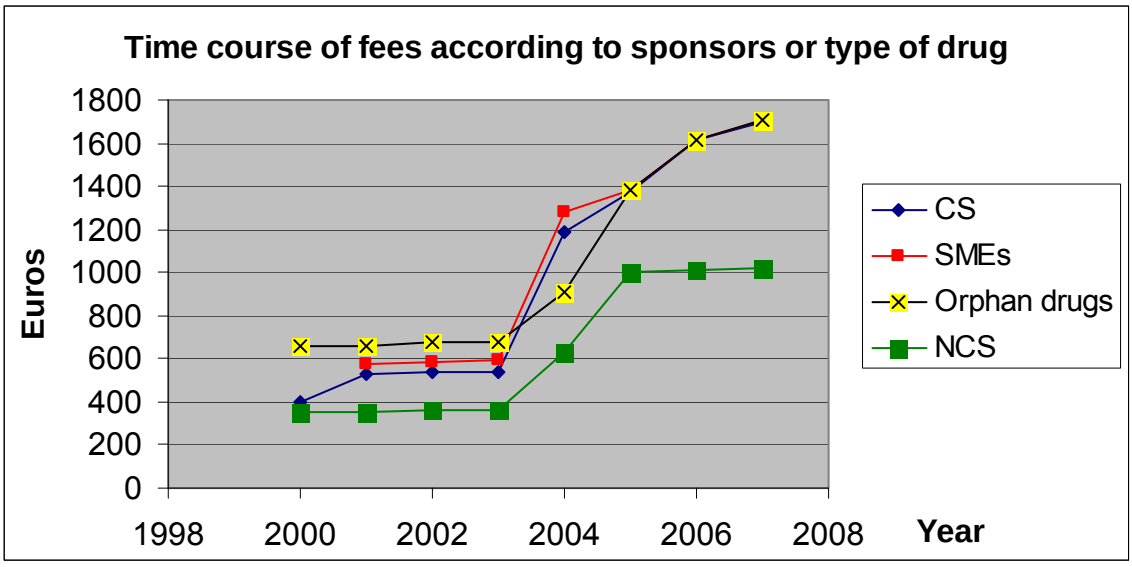
Source: Table CA94 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

Not all respondents to the previous question were able to provide a break-down of their fee structure to answer this question. But also the provided information was able to demonstrate the actual situation: the average notification/CTA fee level in 2000 to 2003 and in 2005 to 2007 was very similar for commercial, SME and orphan drug trial sponsors and clearly higher than the fee charged to non-commercial sponsors. But the jump of fees from 2003 to 2004 was 2- to 3-fold in all sponsor categories. The relative change from 2003 to 2007 based on matched data was substantial with 196.16% for SME and orphan drug trial sponsors and 282.85% for non-commercial sponsors but did not reach statistical significance due to the small sample size.

The shape of the index curves of fees for SMEs, orphan drug trial and non-commercial sponsors were practically identical with the index curve of fees for commercial sponsors.

Figure 23 presents a comparison between the estimations of the average notification/CTA fees for all 4 sponsor categories. The average fees in a particular year were the product of the estimation of the average fee in 2007 by the estimation of the relative change from that particular year to 2007. Practically no difference between the two curves could be detected.

Figure 23: Estimation of the mean fees charged for notifications/CTAs to commercial sponsors, non-commercial sponsors, small and medium-size enterprises and sponsors of orphan drug trials



Source: Figure CA121 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

Obviously, most competent authorities did not apply different fees for commercial sponsors of different sizes and orphan drug trials. For non-commercial sponsors, however, the rate level was and remained clearly lower and the magnitude of the jump in 2004 was less pronounced.

Yearly from 2000 to 2007, what was the average amount of fees to be paid to the Competent Authority by commercial and non-commercial sponsors regarding substantial amendments? (Question 14)

The need for approval of substantial amendments by competent authorities was for many countries a new requirement enforced by the CTD, requiring additional staff resources in competent authorities. As a consequence many competent authorities started to charge fees for the approval of substantial amendments. This question aimed at identifying the magnitude of these additional costs to sponsors and potential differences for the sponsor sub-categories.

Table 25 shows the average fees for institution and year charged to commercial sponsors for approval of substantial amendments to the protocol.

Table 25: Average fees for substantial amendments in the EU charged to commercial sponsors

Year	2000	2001	2002	2003	2004	2005	2006	2007
MEAN / inst. EU	15.15	64.01	64.78	88.43	199.80	228.23	256.56	239.46
Sample size EU	6	7	7	8	9	12	13	15

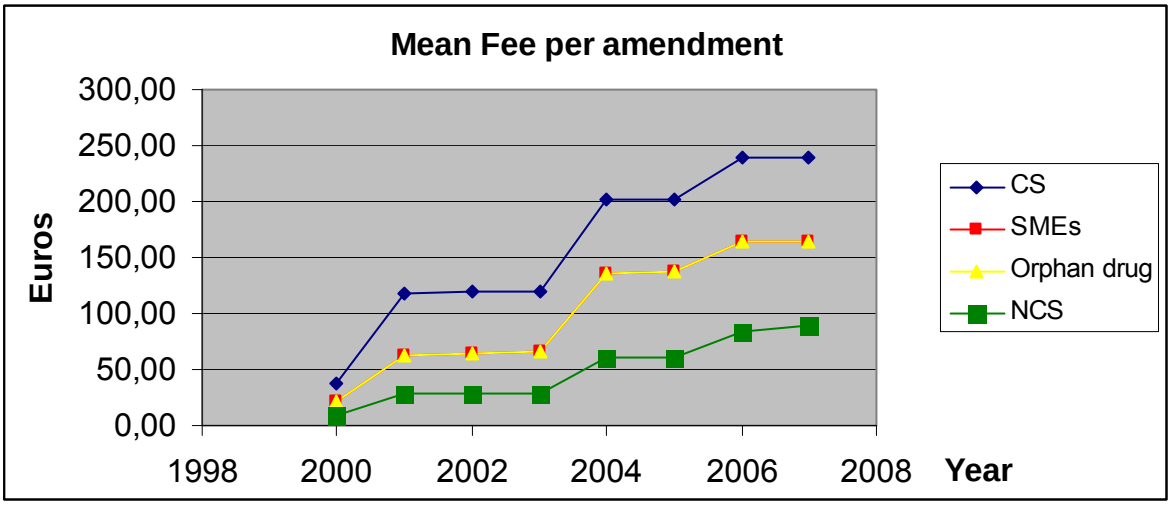
Source: Table CA97 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

Mean was defined as the fraction of the total of the amounts for a substantial amendment in all responding competent authorities divided by the number of responding competent authorities for each year. The figures were expressed in Euros.

The above table shows that in 2003 the average amount charged to commercial sponsors for substantial amendment in any EU institution was 88€ and in 2007 that amount increased to 239 €. The largest increase occurred between 2003 and 2004 when the average fee practically doubled.

A comparison of the average fees per substantial amendment charged to the 4 categories of sponsors under evaluation in this question is presented in Figure 24. The average fees in a particular year were the product of the estimation of the average fee in 2007 by the estimation of the relative change from that particular year to 2007.

Figure 24: Mean fees per substantial amendments charged to commercial sponsors, SMEs, non-commercial sponsors and sponsors for orphan drug trials



Source: Figure CA134 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

The curves for SMEs and sponsors for orphan drug trials were identical, but in contrast to the notification/CTA fees the fee level for these sponsors was lower than the commercial sponsor fee. The non-commercial sponsor fee curve was again on a clearly lower level and did again not show the same steep increase from 2003 to 2004 as the three other sponsor curves. However, between 2005 and 2007 the average non-commercial sponsor fee raised again so that the relative change from 2003 to 2007 was around 200% for non-commercial, SME and orphan drug trial sponsors, while the relative change for commercial sponsors lay by 116%.

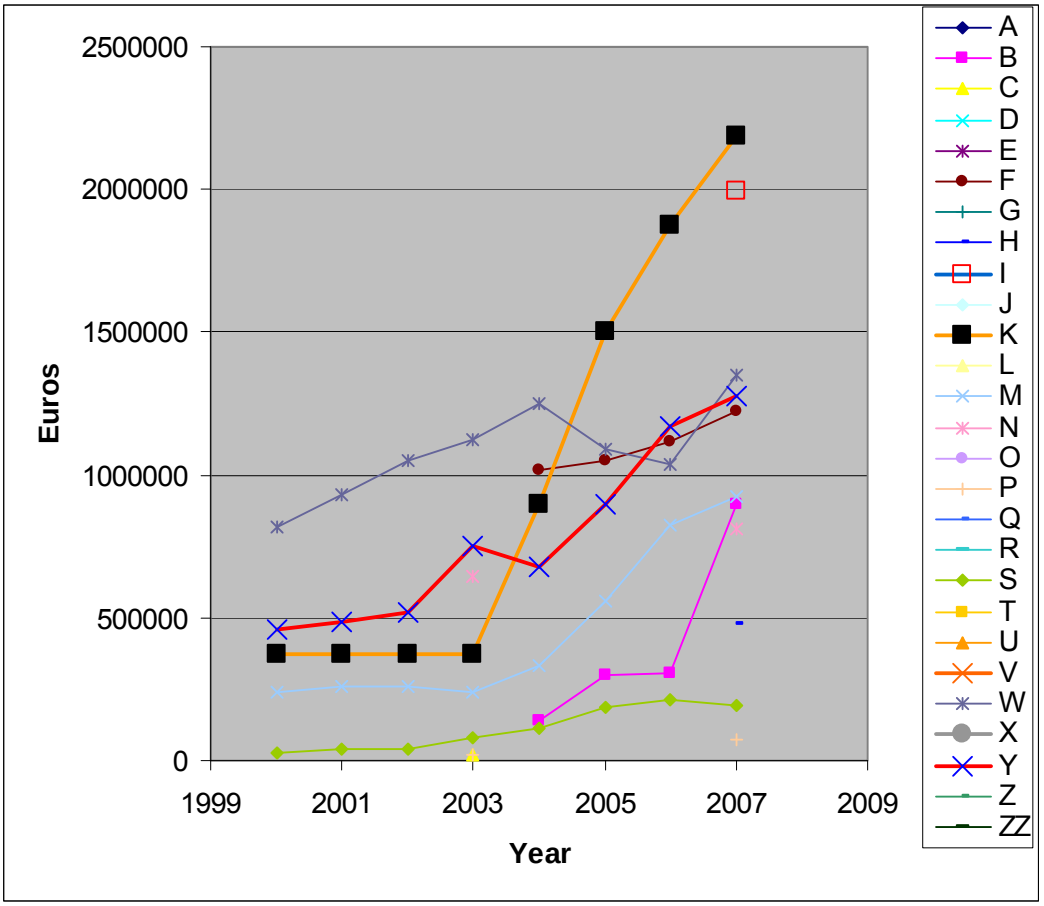
In summary, the average fee level for substantial amendments charged to all sponsor categories was clearly linked to the implementation of the CTD.

What was your overall budget (including staff salaries) for your notification/clinical trial authorisation organisation from 2000 to 2007? (Question 15)

With the implementation of the CTD competent authorities in the EU needed to implement a number of additional tasks in the context of clinical trial approval and safety supervision. The aim of this question was to measure a potential financial impact of these CTD requirements on the competent authorities and their annual budgets for these tasks.

Practically all responding competent authorities reported an increase of their budget as of 2004. The extent of this increase, however, was very country specific as presented in Figure 25.

Figure 25: Time course of the annual budget per institution



Source: Figure CA135 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

Table 26 shows the mean annual budget per institution in each of the study years.

Table 26: Mean annual budget in Euros in the EU

Year	2000	2001	2002	2003	2004	2005	2006	2007
MEAN / inst. EU	383408.9	418423.7	447994.85	403594.15	634594.75	796766.4	933848.06	954409.12
Sample size EU	5	5	5	9	7	7	7	12

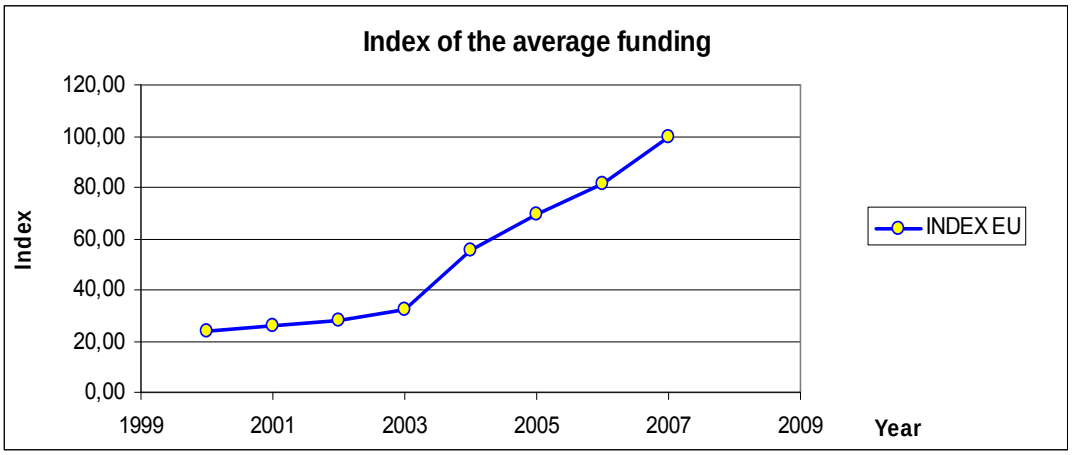
Source: Table CA109 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

The mean was defined as the fraction of the total of annual budgets divided by the number of responding competent authorities in each year. The figures were expressed in Euros.

The mean annual budget per institution in 2004 was 1.5 times higher than in 2003, and in 2007 it was 2.3 times higher than in 2003.

This increase over time was also demonstrated in the index of the average annual budget in the EU. See Figure 26.

Figure 26: Index of the average annual budget in the EU



Source: Figure CA136 in Statistical Report CA, available on www.efgcp.be/ICREL > Report

The curve was stable for the years 2000 to 2003 and showed a steep increase from 2003 onwards.

The relative change observed in 2007 with respect to 2003 was 160.41% and was statistically significant.

These results led to the conclusion that the competent authorities experienced an important increase in their annual budgets as a result of the CTD implementation and the related additional tasks for competent authorities.

Have fees for Clinical Trial Authorisations and substantial amendments covered the costs of your notification/clinical trials authorisation organisation from 2000 to 2007? (Question 16)

The last question of this questionnaire aimed at receiving an opinion on whether the fees for notifications/CTAs and substantial amendments were sufficient to cover the additional budget requirements of the competent authorities in the EU.

Table 27 provides an overview over the competent authorities' opinion on the suitability of the charged fees to cover their additional costs.

Table 27: Suitability of charged fees for notification/CTAs and substantial amendments to cover the additional costs

Institution	Suitability
A	
B	no
C	no
D	no
E	
F	no
G	no
H	no
I	yes
J	yes
K	no
L	
M	yes
N	no
O	
P	yes
Q	
R	
S	no
T	
U	no
V	no
W	no
X	
Y	no
Z	no
ZZ	no

Source: ICREL compiled data

Of the 17 EU institutions that responded to that question, 13 responded negatively and only 4 said their fees cover the costs of their clinical trial department. Of those who responded "yes" competent authorities M and P were institutions from countries with relatively low clinical research activity which might explain why they had not much need for additional staff resources and their financial coverage. In contrast, competent authorities J and I were larger institutions that raised their fees drastically.

In summary, the majority of competent authorities charged fees insufficient for coverage of the costs of their clinical trial departments.

What is your opinion on the impact of the European Union Clinical Trials Directive: strengths, weaknesses and suggested changes? (Question 17)

The last question of the questionnaire allowed respondents to comment on the strengths, weaknesses and suggestions.

The top five most frequent answers regarding the strengths, weaknesses and suggestions of change of the European Clinical Trials Directive given by the regulators are detailed below.

The strength most frequently reported, harmonisation, was also considered as the weakest point of the new legislative environment, which showed that the general perception of the regulators with regards to the CTD was that although some level of harmonisation had been reached there was still significant room for improvement.

Strengths (count)

- Common harmonised standards (12)
- Improved quality of clinical trials in Europe (8)
- Better exchange of information between Competent Authorities (5)
- Improved safety of participants (4)
- GCP/GMP compliance (3)

Weaknesses (count)

- Lack of harmonisation of procedures (10)
- Increased bureaucracy and workload (8)
- Unclear definition of substantial amendments (4)
- Unclear SUSAR reporting requirements (4)
- Increase difficulties for academic research (3)

Proposed changes (count)

- Define clearer SUSAR reporting requirements (4)
- Mutual recognition of CTAs for certain trials (2)
- Simplified procedure for non-commercial sponsors (1)
- Standardise content and format of CTA applications (1)
- Extensiveness and value evaluation of EudraCT application form (1)

Statistical Methodology

The aim of the survey was to assess the possible impact of the Clinical Trials Directive on review areas, workload, timelines, financial conditions of ethics committees and few more aspects related to EC responsibilities.

The statistical methodology for evaluation of the EC survey was similar to the methodologies applied to the surveys on commercial and non-commercial sponsors and is described here in detail:

Due to later described difficulties in collecting information, the number of EC strata was considerably reduced and only the country was retained as a stratification factor. Moreover, empty (countries without any respondent) strata were excluded from the statistical population. The remaining statistical population consisted of 18 countries.

For each question concerning a quantity of interest, the results were presented in two main tables.

The first table concerned unadjusted results:

Unadjusted results	2003	2007	Delta
Mean	49.58	57.79	8.21
Standard deviation	56.15	73.44	28.50
n	38	38	38
SEM	9.11	11.91	4.62
Total number	43183	50335	7151
Change in percent over 4 years			16.561
Change in percent per year			3.905
t-value (Ho: Mean change = 0)			1.776
p-value (Ho: Mean change = 0)			0.084
p-value (Ho: P(delta >0) = P(delta <0))			0.505

- **Mean**: Arithmetic mean of the quantity of interest based on matched data. The mean of available data was presented in the Appendix EC at the end of the table concerning data used for statistical purposes.
- **Standard deviation**: Standard deviation of the quantity of interest, calculated on matched data. The standard deviation of available data was presented in the Appendix EC at the end of the table concerning data used for statistical purposes.
- **Sample size**: Number of respondents with matched data. The sample size concerning available data was presented in the Appendix EC at the end of the table regarding data used for statistical purposes.
- **SEM**: Standard error of the mean concerning matched data.
- **Mean change over four years**: Mean difference (delta) between 2007 and 2003 as a percentage of the mean in 2003 (based on matched data).
- **Paired t-test**: t-test for matched data comparing the means in 2007 and in 2003. A positive delta-mean corresponded to an increase of the mean. The test assumed the normality of the individual differences between 2007 and 2003 (called delta). The normality of the distribution could be

assessed through the frequency distribution presented systematically. The test result might not have been inferred to the statistical population, but it allowed verifying whether the change could be explained by a purely random process within the set of respondents.

- **Sign test**: the sign test allowed verifying whether the number of positive deltas differed significantly from the number of negative deltas (i.e. whether the number of ECs with an increase was significantly different from the number of ECs with a decrease). The test result might not have been inferred to the statistical population, but it allowed verifying whether the excess of the number of ECs with an increase (decrease) with respect to the number with a decrease (increase) could be explained by a purely random process within the set of respondents.
- **Total number of the quantity of interest**: the total number was equal to the mean multiplied by the population size (871). For some quantities, this total number did not have any interest.

The second table concerned adjusted results:

Adjusted results	
Adjusted mean 2003	54.42
Adjusted change (2007 / 2003)	6.51
Adjusted total 2003	47403
Adjusted total change	5669
Increase over 4 years in %	11.96
Increase per year in %	2.86
Variance of delta mean	56.47100531
t statistics (Ho: no change)	0.866121067
Approx. p-value	0.394660231

- **Adjusted mean:** Adjusted mean was a weighted mean were the weight was that of the stratum:

$$\bar{d}_{adjusted} = W_h \bar{d}_h$$

where W_h was the weight of stratum h and $\bar{y}_h$ was the mean of the stratum h. Due to missing data, the weight of each country was recalculated for each quantity of interest.

The weight of stratum h was therefore equal to

$W_h = N_h / \Sigma N_h$

where the sum concerned only countries with at least one observation for the quantity of interest.

- **Adjusted change of delta (2007 / 2003)** is the adjusted mean of the difference (delta) between 2007 and 2003. The adjusted mean change is based on matched data only (ECs with data in 2003 and 2007).
- **Adjusted variance of the mean**: The adjusted variance of delta mean was given by

$$var(\bar{D})_{adjusted} = \sum W_h^2 (1 - f_h) var(D)_h / n_h$$

where f_h was the sampling fraction ($f_h = n_h/N_h$), n_h the number of respondents in the stratum h, N_h the size of stratum h and $var(D)_h$ the variance within stratum h. If the stratum was composed of one respondent, then the within stratum variance could not be estimated and was replaced by the mean square error (ANOVA comparing country means).

- **SEM**: Standard error of the mean which was equal to the square root of the adjusted variance of the mean.
- **t-value**: Wald statistics equal to the adjusted mean divided by the SEM.
- **Approx. p-value**: was the p-value of the Wald test, assuming normal distributions within strata.*Nota bene*: p-value and estimations of adjusted results may be quite different from the p-value and estimations of unadjusted results when the quantity of interest differs largely according to strata. Adjusted results should be more reliable.
- **Adjusted total** was the adjusted mean multiplied by the population size (871).
- **Adjusted total change** was an estimation of the change in the total quantity of interest such as the total number of CTAs. It was the mean change multiplied by the total number of ECs (871).

The **relationship between the change in 2007** with respect to 2003 and **the level in 2003** *d* calculated for several variables. It allowed checking whether the change was dependent upon the level observed in 2003. Regarding relationships, the Spearman coefficient of correlation was preferable if one or two observations had a major leverage effect (large value of X) or if the relationship was monotonic but not linear. The Spearman correlation is a rank coefficient of correlation without any assumption regarding the distribution of Y.

A significant relationship between the change and the level in 2003 showed that the level in 2003 explains the observed change in 2007 with respect to 2003.

Besides data regarding quantitative indicators (or metrics), open questions regarding strengths, weaknesses and suggested changes to the CTD were collected during the survey.

The methodology of the survey allowed to estimate change over time (2007 with respect to 2003) in the indicators but not to address directly the question of the impact of the CTD.

Results

Sampling process

TARGET POPULATION

The target population was composed of all *ethics committees reviewing any clinical investigations (CI) in the EU*.

PLANNED SAMPLE SIZE

A total of at least 150 questionnaires should have been completed with at least the total number of studies submitted or approved in 2003 and 2007. Such a sample size would have allowed to detect (significant effect: $\alpha = 0.05$ one-sided), with 80% power, a factor that explains 1% of the total variance. This sample size would have allowed as well to detect ($\alpha = 0.05$ two-sided), with 85% power, a standardized difference of 0.25 (a difference between means equal to 0.25 standard deviation). This good power of differentiation (sensibility) was based on the normal approximation.

SAMPLING FRAME

The **sampling frame** consisted of the list per country of all known Ethics Committees in Europe. It represented a total of 1,905 ECs throughout Europe, with the inclusion of very small ECs in Italy.

PLANNED SAMPLING EFFORT

The **sampling fraction** was dependent upon the level of clinical trial activity in each country. One of the best indicators of activity level is the number of CTAs, because this number is probably highly correlated with several other indicators such as the number of clinical trials actually carried out in the country. CTAs were considered an indicator, as the CTD initially was directed only at CTs with medicinal products. However, the survey looked at the workload of ECs regarding all applications. Another indicator was the number of active sites of investigations, because if a site is open in a given country, then the EC should have provided an authorisation. In the absence of information regarding the number of CTAs per country, the number of active sites was used to adjust the sampling effort in each country (Table 28).

Table 28: Optimal number, planned number and sampling fraction per country and type of EC

Country Type of ECs	Total number of ECs	Weight of stratum	Mean number of sites / EC	Optimal number of ECs	Planned number of sampled EC	Sampling fraction
Austria	**27**	1.417%	20.00			
Reference ECs	7	0.367%	45	6.97	7	100%
Local ECs	20	1.050%	11.25	2.86	3	15.0%
Belgium	**153**	8.032%	6.44			
Reference ECs	34	1.785%	15.46	7.59	8	23.53%
Local ECs	119	6.247%	3.86	3.81	4	3.36%
Bulgaria	**36**	1.889%	0.94			
Central EC	1	0.052%	3.49	0.03	1	100%
Local ECs	35	1.837%	0.87	0.14	2	5.71%
Cyprus	**1**	0.052%	34			
Central EC	1	0.052%	34	0.67	1	100%
Czech Rep.	**104**	5.459%	7.683			
Multi-centric	9	0.472%	24.40	3.81	4	44.44%
Mono-centric	95	4.987%	6.100	5.77	6	6.31%
Denmark	**12**	0.629%	41			
Reference ECs	11*	0.577%	32.80	7.04	7	63.63%
Central EC	1	0.052%	131.20	4.45	1	100%
Estonia	**2**	0.105%	24.50			
Reference ECs	2	0.105%	24.50	0.85	2	100%
Finland	**21**	1.102%	18.47			
Reference ECs	21	1.102%	18.47	6.01	6	28.57%
France	**40**	2.010%	80.650			
Reference ECs	40	2.010%	80.650	90.12	40	100%
Germany	**56**	2.940%	75.250			
Reference ECs	56	2.940%	75.250	114.51	56	100%
Greece	**1**	0.052%	293			
Central EC	1	0.052%	43.5	13.70	1	100%
Hungary	**2**	0.105%	43.5			
Clinical EC	1	0.052%	43.5	0.95	1	100%
Scientific EC	1	0.052%				
Ireland	40	0.682%	17.00			
IMP EC	**13**	0.682%	17.00	3.32	3	23.07%

Country Type of ECs	Total number of ECs	Weight of stratum	Mean number of sites / EC	Optimal number of ECs	Planned number of sampled EC	Sampling fraction
Non IMP EC	excluded	0%	1.915			
Italy	**1065**	55.906%				
Large ECs	15	0.787%	30.44	8.64	9	60%
Medium ECs	27	1.417%	14.15	5.32	5	18.52%
Small ECs	95	4.987%	6.004	5.65	6	6.31%
Very small ECs	928	**48.714%**	0.679	2.61	3	0.32%
Latvia	**4**	0.373%	8			
Reference ECs	4	0.373%	8.5	0.39	2	50.00%
Lithuania	**2**	0.186%	63			
Reference ECs	2	0.186%	63	3.19	3	100%
Luxembourg	**1**	0.052%	49			
Central EC	1	0.052%	49	1.12	1	100%
Malta	**1**	0.052%	34			
Central EC	1	0.052%	34	0.67	1	100%
Netherlands	**32**	1.680%	43.562			
Reference ECs	32	1.680%	42.562	29.48	29	90.62%
Poland	**52**	2.730%	22.615			
Reference ECs	52	2.730%	22.615	19.77	20	38.46%
Portugal	**1**	0.052%	183			
Central EC	1	0.052%	183	7.09	1	100%
Romania	**1**	0.052%	87			
Central EC	1	0.052%	87	2.51	1	100%
Slovakia	**8**	0.419%	6.12			
Central EC	1	0.052%	17.81	0.27	1	100%
Reference EC	7	0.367%	4.45	0.27	2	8.57%
Slovenia	**1**	0.052%	87			
Central EC	1	0.052%	87	2.50	1	100%
Spain	**136**	7.139%	15.265			
Reference ECs	136	7.139%		29.83	30	22.05%
Sweden	**7**	0.367%	105.571			
Reference ECs	7	0.367%		22.98	7	100%
United Kingd.	198	6.614%	13.913			
Reference EC	**126**	6.614%	13.913	24.28	24	19.04%
Non IMP ECs	72	Excluded				
Total	1,905	100%	11.12		298	15.64%

Source: Table EC 2 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

SAMPLING STRATEGY IMPLEMENTATION

The questionnaire was sent to the planned samples composed of 300 ECs.

Despite 4 to 5 contacts per EC between June and September 2008, the response rate was extremely low, so it was decided to extend the mailing of the questionnaire to more ECs (except for the numerous very small ECs in Italy) and some other with unknown contact persons.

- 708 questionnaires were finally sent;
- 64 questionnaires were completed;

- 5 refused to participate;
- 586 gave no response despite 4 to 5 contacts and several deadline extensions.

Description of respondents

The number of respondents was 64, originating from 18 countries. The corresponding population size was 871 ECs. The very small ECs from Italy were discarded as well as the non IMP ECs from Ireland and the UK (Table 29).

Table 29: Number of respondents per country

Country	(Retained) Population size	Number of respondents
Austria	27	4
Luxembourg	1	1
Belgium	153	2
Cyprus	1	1
Czech Republic	104	15
Denmark	12	4
Estonia	2	2
Finland	21	2
France	40	9
Germany	56	1
Hungary	2	2
Ireland	13	1
Italy	137	2
Portugal	1	1
Spain	136	4
Sweden	7	5
The Netherlands	32	5
United Kingdom	126	3
TOTAL	871	64

Source: Table EC 4 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

Results

For interpretability reasons only those results are presented from which a meaningful evaluation can be provided. However, all results are presented in the Statistical Report available on the EFGCP website[21].

The results are as follows.

General information

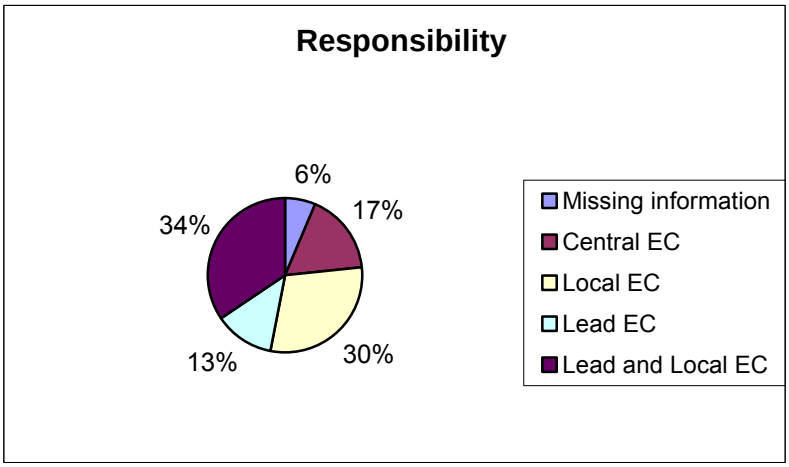
Type of responsibility:

General information on the responding ethics committees (ECs) was collected to better understand the background and potential issues of the respondents. Especially the EC's responsibility of either serving as a lead or local EC was expected to impact the answers. It turned out that about a third of

[21] www.efgcp.be/ICREL > Report

the responding ECs s could serve as lead and local EC, one third as central/lead EC and one third as local EC (see Figure 27). Thus a good representation of all viewpoints could be expected.

Figure 27: Type of responsibility



Source: Figure EC 4 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

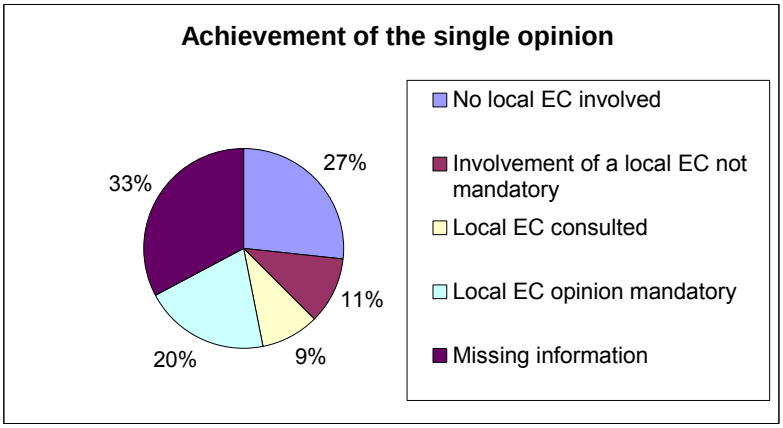
Is your Ethics Committee entitled to issue a "single opinion?" If yes: How does your Ethics Committee achieve this "single opinion?" And: Do you consider the procedure required for a "single opinion" difficult? (Question 1 in the Questionnaire to ECs)

A main achievement of the CTD was the implementation of a single opinion from ECs in one country in the case of multi-centre trials. However, the EC systems to achieve this single opinion are different in the different EU member states. This question aimed at getting an overview of the approaches chosen by the EU member states. Thirty eight responding ECs were entitled to issue a "single opinion", whereas 13 were not; there was missing information from other 13 ECs.

Achievement of the single opinion

The system to achieve a single opinion was quite heterogeneous between responding ECs and ranged from mandatory local EC involvement to no local EC involvement at all (see Figure 28).

Figure 28: Achievement of the single opinion



Source: Table EC 5 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

Difficulty of the procedure for a single opinion

12 ECs found the procedure for a single opinion difficult, whereas 32 ECs did not; 18 ECs provided no information. All respondents (39) that were not entitled to issue a single opinion (4) considered the procedure difficult (100%, p = 0.0004).

Categories of clinical research for which your Ethics Committee has competence? (Question 2)

Another important part of general information was the understanding of the type of studies the responding ECs were responsible for. In fact, the majority of respondents had competences for all phases of clinical trials with medicinal products as presented in Table 30.

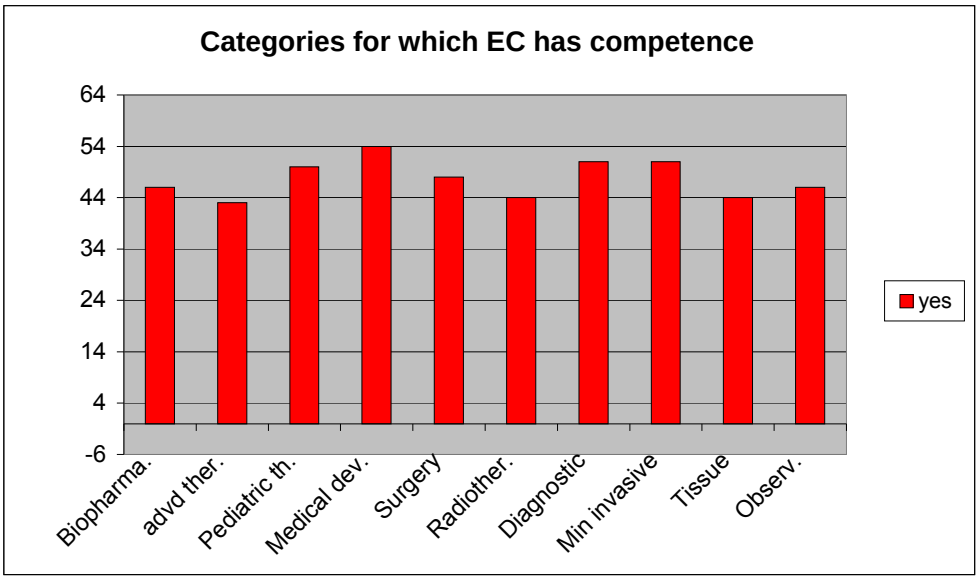
Table 30: Competences of ECs for different phases of clinical research

	Phase I	Phase II	Phase III	Phase IV
Yes	44	55	55	52
No or missing	20	9	9	12
TOTAL	64	64	64	64

Source: Figure EC8 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

In addition, most ECs had competences for all categories of clinical research as shown in Figure 29.

Figure 29: Categories of clinical research for which EC has competence



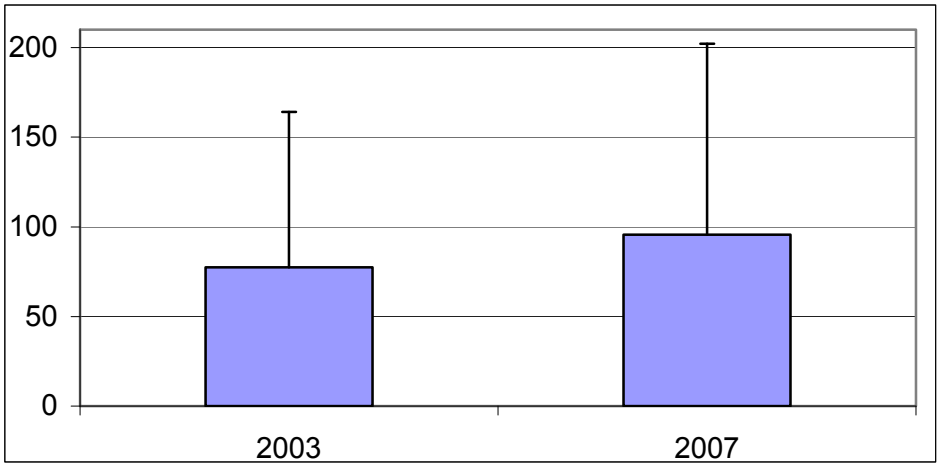
Source: Figure EC 9 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

For how many clinical studies has your EC issued a positive opinion in 2003 and 2007? (Question 3)

The aim of this question was to find out whether the CTD had an impact on the number of positive opinions issued for different types of studies by ECs. In addition, this question provided the opportunity to learn about the development of the number of studies not covered by the CTD but requiring EC review according to GCP.

Positive opinions for all clinical studies:
A significant (p = 0.003) increase of positive opinions of +23.46% (see Figure 30) was observed in 2007 (average of 95.6 CIs per EC) with respect to 2003 (77.46 CI on average) in the unadjusted results.

Figure 30: Number of positive opinions on all types of clinical studies



Source: Table EC 19 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

Also the number of institutions with an increase in 2007 with respect to 2003 was significantly larger than the number of institutions with a decrease. Adjusted results showed the same level of increase (+24.3%), but this increase did not reach the significance level. In addition, a significant positive linear relationship between the change in 2007 with respect to 2003 and the number of CTs in 2003 as well as a significant positive rank correlation was observed, meaning that the larger the number of studies was in 2003 the larger was the increase in 2007 with respect to 2003. It could also be demonstrated, that the ethics committees in more countries (10) had a significant increase of the number of studies than a decrease (3 countries).

Positive opinions for CTs with medicinal products:
Evaluation of the number of clinical trials with medicinal products showed in the unadjusted results (see Table 31), a, statistically not significant, +16.6% increase from 2003 to 2007. Adjusted results confirmed the magnitude of this result with an increase of +12.0%.

Table 31: Positive opinions for CTs with medicinal products

	2003	2007
Mean number of CTs per EC	49.58	57.79
Standard deviation	56.15	73.44
Number of respondents with information for both years	38	38
Change in % over 4 years		+16.56%

Source: Table EC7 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

Positive opinions for CTs with medical devices:
The number of clinical trials with medical devices approved by ethics committees was considerably lower than that of CTs with medicinal products. However, unadjusted results (see Table 32) showed a statistically significant increase of +52.9% in the number of approved clinical trials.

Table 32: Positive opinions for CTs with medical devices

	2003	2007
Mean number of CTs per EC	4.48	6.85
Standard deviation	7.29	10.28
Number of respondents with information for both years	27	27.
Change in % over 4 years		+52.89%

Source: Table EC 9 Statistical Report EC, available on www.efgcp.be/ICREL > Report

Adjusted results (+16.2%) could not confirm this magnitude. This difference could be explained - like in several other sections of this survey – by the fact that the adjusted results were more impacted than the unadjusted results by the answers from Belgium, Italy, Spain and UK, countries with a larger weight due to the larger number of ECs in the population.

Positive opinions for CTs with surgical procedures:
A non significant increase of +27.78% was observed in the unadjusted results in 2007 (2.87 CTs) with respect to 2003 (2.25 CTs on average). The observed increase in adjusted results was larger with +54.4%, but again not statistically significant.

Positive opinions for CTs with radiotherapy:
Considering the very low average number per EC of trials in this field (1 CT on average), the magnitude of the observed non significant increase of +78.947% in 2007 (1.789 CTs) with respect to 2003 in the unadjusted results and in the adjusted results (+124.3%) should not be over interpreted.

Positive opinions for other (non therapeutic) interventional clinical studies, diagnostic procedures, prevention, incl. biomarkers, genetic markers, imaging submitted by commercial sponsors
In this category all other types of non-therapeutic clinical studies were summarized as in the pilot phase of this survey it became clear that it is impossible for most ECs to further break-down the non therapeutic interventional study categories.

Practically no changes in the number of approved non therapeutic interventional studies between 2003 and 2007 could be observed with a decrease of -1.84% in unadjusted results and of -5.6% in adjusted results. However, a significant rank correlation was observed: the larger the number of non therapeutic interventional trials was in 2003 the larger was the decrease in 2007.

Positive opinions for non-interventional/observational studies:
A non significant increase of +69.08% in unadjusted results was observed in 2007 with respect to 2003, but the number of ECs that observed an increase was significantly larger than the number of ECs not observing this effect. Adjusted results showed an increase of +41.7%.

How many negative opinions to a protocol did your EC issue yearly 2003 and 2007? How often did a sponsor use the appeal system? (Question 4)

The intention of this question was to find out whether the CTD implementation led to a difference in negative opinions. The answers from the responding ECs confirmed the sponsor experience that the overall number of negative opinions to protocols issued by ECs was generally small (approximately 2-3 negative opinions per year and EC).

With the limitation of the area of responsibility of local ECs it was not surprising to find that there was a non significant decrease of -19.1% of the mean number of negative opinions issued by a "local" EC from 2003 to 2007 in the unadjusted results, supported by a decrease in the adjusted results of -37.8%.

In contrast there was an increase of +29.58% of the number of negative opinions issued by a "lead/central/multicenter" EC, but this change did not reach the level of significance and the absolute numbers remained quite small (2.96 in 2003 versus 3.83 in 2007).
26 ethics committees reported that they did not have any appeal system in 2003 and only 18 ethics committees reported that they did not have any appeal system in 2007.

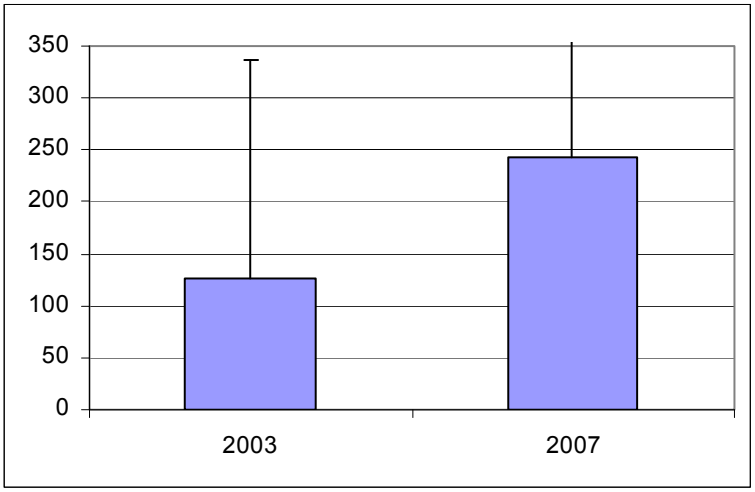
In those ECs with an appeal system in place, there was a non significant increase of +187.5% of the mean use of an appeal system observed in 2007 with respect to 2003 in the unadjusted results. This strong increase was confirmed by a highly significant increase of +170.5% in the adjusted results. The number of institutions with an increase of uses of an appeal system in 2007 with respect to 2003 was significantly ($p = 0.025$) larger than the number of institutions with a decrease in uses of an appeal system.

How many Substantial Amendments did you receive yearly 2003 and 2007? How many negative opinions to substantial amendments did your EC issue? How often did a sponsor use the appeal system? (Question 5)

The CTD intended to ensure the ongoing involvement of ethics committees in the performance of the clinical trials they reviewed by implementing the need for approval of substantial amendments be competent authorities and/or ethics committees depending on the type of change. This question aimed at finding out about the number of substantial amendments requiring EC involvement before and after the implementation of the CTD as well as the experience with negative opinions on substantial amendments.

The number of substantial amendments received by ECs increased considerably and statistically significantly over time and was almost doubled in 2007 compared to 2003 (+92.91% in the unadjusted results – see Figure 31 – and +64.2% in the adjusted results). And the number of ECs that experienced an increase was significantly larger than the number of ECs that saw a decrease of substantial amendments. Interestingly, there was a highly significant positive linear relationship between the number of amendments received by ECs in 2003 and the increase in 2007 with respect to 2003.

Figure 31: Number of substantial amendments per EC



Source: Table EC 27 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

The number of negative opinions issued for substantial amendments by local ECs did not change over time and was very small (mean below 1 for 2003 and 2007). Lead ECs experienced a non significant increase of +150% in unadjusted results and +164% in adjusted results but it has to be kept in mind that the absolute numbers were still very small.

The use of an appeal system for a substantial amendment was reported in only very rare cases for 2003 and in no case for 2007.

How many applications for commercially sponsored studies were submitted yearly 2003 and 2007? (Question 6)

This question and question No 7 on the number of applications from non-commercial sponsors were supposed to provide a detailed understanding of the changes in clinical research activities from 2003 to 2007 in different trial categories sponsored by industry and academia.

All types of commercially sponsored clinical studies

As not all ECs were in a position to provide a breakdown of the categories of clinical trials it was important to receive also an overall number for the commercially sponsored applications received by ECs. Table 33 shows the overall number of commercial applications in 2003 and 2007:

Table 33: All commercially sponsored clinical studies

	2003	2007
Mean number of applications per EC	45.43	52.51
Standard deviation	39.03	52.90
Number of respondents with information for both years	35	35
Change in % over 4 years		15.60%

Source: Table EC 47 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

This non-significant increase of +15.60 in the unadjusted results was supported by the statistically significant increase of +24.98% in the adjusted results.

Commercially sponsored CTs with investigational medicinal products

The largest category of commercially sponsored clinical trials reviewed by ECs was performed with investigational medicinal products. Table 34 provides an overview of unadjusted results.

Table 34: Commercially sponsored CTs with investigational medicinal products

	2003	2007
Mean number of applications per EC	37.10	45.33
Standard deviation	47.26	71.72
Number of respondents with information for both years	30	30
Change in % over 4 years		22.19%

Source: Table EC 35 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

This magnitude of this non-significant increase of +22.19% from 2003 to 2007 was confirmed by the also not significant increase of +7.23% in the adjusted results.

Commercially sponsored CTs with medical devices

Table 35 shows the unadjusted results for the development of commercially sponsored clinical trials with medical devices from 2003 to 2007.

Table 35: Commercially sponsored CTS with medical devices

	2003	2007
Mean number of applications per EC	3.68	3.59
Standard deviation	5.71	3.84
Number of respondents with information for both years	22	22
Change in % over 4 years		-2.47%

Source: Table EC 37 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

Practically no change in the mean number of the commercially sponsored CTs with medical devices was observed in 2007 with respect to 2003 in the unadjusted and adjusted (+0.06%) results.

Commercially sponsored CTs with surgical procedures

Commercially sponsored clinical trials with surgical procedures were very rare in 2003 and 2007 and thus there was practically no change observed in that period (see Table 36) in the unadjusted (-18.18%) and adjusted results (+4.76%).

Table 36: Commercially sponsored CTs with surgical procedures

	2003	2007
Mean number of applications per EC	0.55	0.45
Standard deviation	0.95	1.05
Number of respondents with information for both years	20	20
Change in % over 4 years		-18.18%

Source: Table EC 39 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

Commercially sponsored CTs with radiotherapy

Like for commercially sponsored CTs with surgery procedures only few trials with radiotherapy were reported. Table 37 presents the unadjusted results:

Table 37: Commercially sponsored CTs with radiotherapy

	2003	2007
Mean number of applications per EC	0.67	1.33
Standard deviation	2.38	4.69
Number of respondents with information for both years	18	18
Change in % over 4 years		+100.0%

Source: Table EC 41 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

In contrast to surgery trials, there was an increase of commercially sponsored radiotherapy trials from 2003 to 2007 of +100% in unadjusted results and of +138.3% in adjusted results.

Other (non therapeutic) interventional clinical studies, diagnostic procedures, prevention, incl. biomarkers, genetic markers, imaging submitted by commercial sponsors

Table 38 presents the unadjusted results of other non therapeutic interventional study categories from commercial sponsors:

Table 38: Other commercially sponsored non-therapeutic interventional studies

	2003	2007
Mean number of applications per EC	4.68	3.68
Standard deviation	5.66	5.26
Number of respondents with information for both years	19	19
Change in % over 4 years		-21.35%

Source: Table EC 43 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

While unadjusted results showed a non significant decrease of -21.35%, the adjusted results showed a non significant increase of +30.9%. The decreasing trend was supported by the finding of a significant negative linear relationship as well as of a significant negative rank correlation: the larger the number of CTs was in 2003 the larger was the decrease in 2007 with respect to 2003.

Commercially sponsored non interventional/observational studies

In most of the EU member states non interventional/observational studies do not fall under the CTD. Therefore it was interesting to see how this category developed from 2003 to 2007. Table 39 shows the results of this survey for unadjusted results:

Table 39: Commercially sponsored non interventional/observational studies

	2003	2007
Mean number of applications per EC	2.41	5.00
Standard deviation	4.03	6.85
Number of respondents with information for both years	22	22
Change in % over 4 years		+107.5%

Source: Table EC 45 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

The observed increase of +107.5% of commercially sponsored non interventional/observational studies from 2003 to 2007 in the unadjusted results was statistically significant and also the number of institutions showing an increase in 2007 was significantly larger than those showing a decrease. Also the adjusted results showed an increase of +99.2% but this increase did not reach the significance level.

How many applications for non-commercial sponsor driven studies were submitted yearly 2003 and 2007? (Question 7)

All types of non-commercially sponsored studies

The overall unadjusted results of the change in non-commercially sponsored studies submitted to ECs from 2003 to 2007 are presented in Table 40.

Table 40: Any type of non commercially sponsored studies

	2003	2007
Mean number of applications per EC	43.46	63.49
Standard deviation	65.97	101.82
Number of respondents with information for both years	37	37
Change in % over 4 years		+46.08%

Source: Table EC 61 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

The increase all types of non-commercially sponsored studies between 2003 and 2007 of +46.08% in unadjusted results was highly significant. And also the increase of +52.98% in adjusted results was statistically significant. This increase in non-commercial studies is in contrast to what was expected but it has to be taken into consideration that this overall result includes all categories of clinical studies and that the development of the different sub-categories has to be evaluated.

Non-commercially sponsored CTs with medicinal products

The unadjusted results of the change in non-commercially sponsored CTs with medicinal products from 2003 to 2007 are presented in Table 41.

Table 41: Non-commercially sponsored CTs with medicinal products

	2003	2007
Mean number of applications per EC	5.39	6.04
Standard deviation	8.56	7.33
Number of respondents with information for both years	26	26
Change in % over 4 years		+12.14%

Source: Table EC 49 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

The observed increase in non-commercially sponsored CTs with medicinal products of +12.14% in the unadjusted results was supported by the likewise non significant increase of +25.21% in the adjusted results.

Non-commercially sponsored CTs with medical devices

The absolute mean number of CTs with medical devices sponsored by academia was lower than that of commercially sponsored medical device trials. However, the increase observed from 2003 to 2007 in unadjusted results (see Table 42) and +63.07% in adjusted results showed a clear upward trend.

Table 42: Non-commercially sponsored CTs with medical devices

	2003	2007
Mean number of applications per EC	1.32	2.74
Standard deviation	2.16	6.18
Number of respondents with information for both years	19	19
Change in % over 4 years		+108.0%

Source: Table EC 51 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

The results were strongly impacted by the data from one EC. But even after exclusion of these data the positive trend remained on a magnitude of nearly +40%.

Non-commercially sponsored CTs with surgical procedures

The absolute mean number of non-commercially sponsored CTs with surgical procedures was higher than that on the commercial sponsor side, yet still small. However, Table 43 shows that an increase of +65.2% could be observed in the unadjusted results.

Table 43: Non-commercially sponsored CTs with surgical procedures

Unadjusted	2003	2007
Mean number of applications per EC	1.33	2.17
Standard deviation	3.11	2.75
Number of respondents with information for both years	18	18
Change in % over 4 years		+65.2%

Source: Table EC 53 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

The increase in adjusted results of +182.2% was even stronger. The magnitude of the increase, however, has to be considered with caution due to the small numbers. This increasing trend was in line with the findings in positive opinions on CTs with surgical procedures independent of the sponsor type.

Non-commercially sponsored CTs with radiotherapy

As observed with commercially sponsored CTs in radiotherapy, the mean number of reported applications for non-commercial applications in this category was very small (see Table 44).

Table 44: Non-commercially sponsored CTs with radiotherapy

	2003	2007
Mean number of applications per EC	0.60	0.80
Standard deviation	0.99	1.94
Number of respondents with information for both years	15	15
Change in % over 4 years		+33.33%

Source: Table EC 55 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

But also on the non-commercial side an increase of radiotherapy trials from 2003 to 2007, albeit smaller and again not significant, with +33.33% for unadjusted results and +19.54% for adjusted results could be observed.

Other (non therapeutic) interventional clinical studies, diagnostic procedures, prevention, incl. biomarkers, genetic markers, imaging submitted by non-commercial sponsors

Table 45 presents the unadjusted results of other (non therapeutic) interventional study categories from non-commercial sponsors:

Table 45: Other non-commercial (non therapeutic) interventional studies

	2003	2007
Mean number of applications per EC	24.61	26.13
Standard deviation	25.47	23.35
Number of respondents with information for both years	23	23
Change in % over 4 years		+6.18%

Source: Table EC 57 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

Practically no changes from 2003 to 2007 could be observed for unadjusted (+6.18%) and adjusted (-12.59%) results in other non therapeutic interventional studies submitted by non-commercial sponsors.

Non-commercially sponsored non interventional/observational studies

As observed on the commercial sponsor side, a significant increase of non interventional/ observational studies could be observed on the non-commercial sponsor side (see Table 46).

Table 46: Non-commercially sponsored non interventional/observational studies

	2003	2007
Mean number of applications per EC	6.250	13.500
Standard deviation	12.303	24.095
Number of respondents with information for both years	20	20
Change in % over 4 years		+116.0%

Source: Table EC 59 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

The increase in the adjusted results of +49.27% was less pronounced and not significant.

How many applications for trials with medicinal products, yearly 2003 and 2007, were multinational trials, national multi-centre trials, mono-centre trials? (Question 8)

This question aimed at finding out whether the percentage of mono-centre, multi-centre and multi-national CTs with medicinal products changed from 2003 to 2007 in the experience of the ECs.

Applications for multi-national CTs with medicinal products

In Table 47 the development of multi-national CTs with medicinal products from 2003 to 2007 are presented.

Table 47: Applications for multi-national CTs with medicinal products

	2003	2007
Mean number of applications per EC	22.59	30.78
Standard deviation	33.08	47.47
Number of respondents with information for both years	32	32
Change in % over 4 years		36.24%

Source: Table EC 63 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

The observed non significant increase of multi-national CTs of +36.23% from 2003 to 2007 in unadjusted results was supported by the more moderate, likewise non significant increase of +15.25% observed in the adjusted results.

Applications for national multi-centre CTs with medicinal products

Table 48 shows the non-adjusted results for applications for national multi-centre trials:

Table 48: Applications for national multi-centre trials with medicinal products

	2003	2007
Mean number of applications per EC	305.96	326.08
Standard deviation	1425.90	1528.18
Number of respondents with information for both years	24	24
Change in % over 4 years		+6.58%

Source: Table EC 65 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

There was practically no change in applications for national multi-centre CTs with medicinal products from 2003 to 2007.

Applications for mono-centre CTs with medicinal products

In Table 49 the unadjusted results on applications for mono-centre trials with medicinal products in 2003 and 2007 are presented.

Table 49: Applications for mono-centre trials with medicinal products

	2003	2007
Mean number of applications per EC	24.33	32.00
Standard deviation	69.06	105.85
Number of respondents with information for both years	27	27
Change in % over 4 years		+31.50%

Source: Table EC 67 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

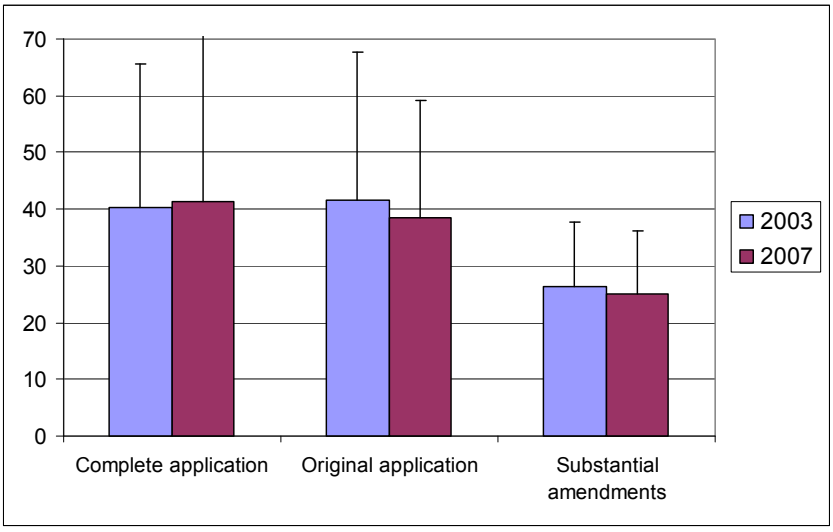
The increase of +31.50% observed in the unadjusted results was contradicted by the decrease of -17.3% presented in the adjusted results. This discrepancy could be explained by the impact of one outlier value. After exclusion of this value it became obvious that there was practically no change in mono-centre trials (unadjusted results: +4.74%, adjusted results: -6.79%).

What was the average time (days) between the receipt of a complete application for a protocol and the issue of the opinion letter? What was the average time between the receipt of the original application and the issue of the opinion letter for a protocol and what was the average time between the receipt of an application for a substantial amendment and the issue of an opinion, yearly 2003 and 2007? (Question 9)

This question was supposed to reveal changes in the timelines for the ethical review process for protocols and substantial amendments before and after implementation of the CTD. A differentiation was made between the time frames for complete and incomplete applications, such investigating the additional time required for the formal review of the applications.

Figure 32 presents the timelines (in days) for all three review conditions in 2003 and 2007.

Figure 32: Time-lines for ethical review of protocols and substantial amendments



Source: Tables EC 69, EC 71 and EC 73 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

Despite the restricted time lines implemented by the CTD for ethical review, no difference in ethics committee review timelines in 2003 and 2007 for originally complete and originally incomplete protocol applications as well as for the review of substantial amendments could be observed.

In 2003 and 2007, how many Ethics Committee employees/members resp. full-time equivalents worked (as internal and external resources, paid or volunteer staff) worked on the following tasks? (Question 10)

Anecdotal reports from different countries criticized the need for more staff in ethics committees required to fulfill the additional administrative burden implied by the CTD. This question aimed at achieving a better understanding of the staffing situation in ethics committees in 2007 compared to 2003.
Full-time equivalent (FTE) was defined as one full-time position or two half-time positions.

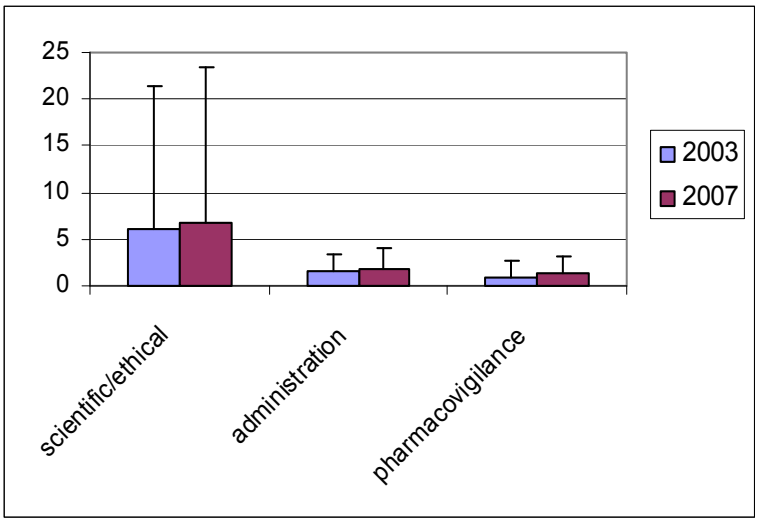
Number of FTEs for scientific and ethical assessment

A small (+13.29%) but significant increase in FTEs per EC was observed in the unadjusted results, and also the number of ECs that experienced an increase was significantly larger than those observing a decrease.
The increase observed in adjusted results (+7.65%) did not reach the significance level. However, there might be a potential source of error in this question, as some respondents seem to have counted EC members as employees.

Number of FTEs for administration of protocol / substantial amendment review

A small but highly significant increase of FTEs involved in administration of protocol and substantial amendment review was observed between 2003 and 2007: of +22.49% in unadjusted results (see Figure 33) and of +52.14% in adjusted results.

Figure 33: Number of FTEs required for EC tasks



Source: Tables EC 75, EC 77 and EC 79 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

Also the number of ECs with an increase of FTEs for administrative tasks for protocol and substantial amendment review in 2007 with respect to 2003 was significantly larger than the number of ECs with a decrease in the number of FTEs required for these tasks.

Number of FTEs for Administration of SAEs (Serious adverse event) / SUSARs (Suspected unexpected serious adverse reaction) reports / Pharmacovigilance tasks

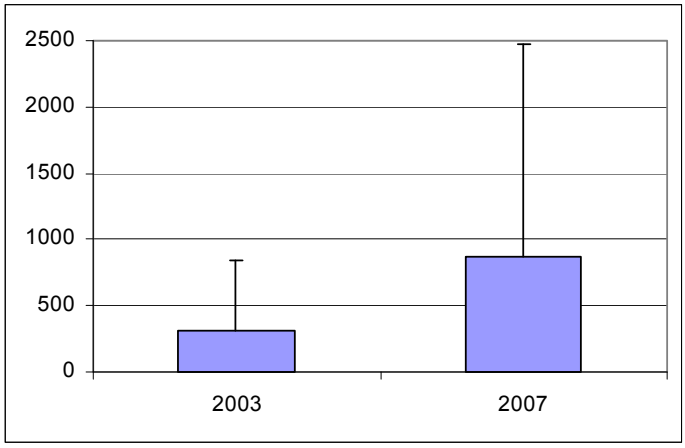
In the unadjusted as well as in the adjusted results there were significant increases of +24.48% and +39.15%, respectively, observed for FTEs required for pharmacovigilance tasks in 2007 with respect to 2003. And also the number of ECs that experienced an increase in staff for this category of tasks was statistically significantly higher than those that faced a decrease.

How many SAE/SUSAR reports did you receive yearly in 2003 and 2007? (Question 11)

This question aimed at investigating the true additional burden for ECs required by the review and handling of expedited safety reports.

Figure 34 presents the average number of SAEs, respectively SUSARs in 2003 and 2007:

Figure 34: SAE/SUSAR reports to ECs



Source: Table EC 81 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

A significant increase (unadjusted results: +183.01%, adjusted results: +138.88%) of the number of SAE, respectively SUSAR reports was observed in 2007 with respect to 2003. Also the number of ECs with an increase of SAEs/SUSARs in 2007 with respect to 2003 was highly significantly larger than the number of ECs with a decrease in SAEs/SUSARs. And also a statistically significant positive linear relationship and a positive rank correlation were observed: the larger the number of SAEs/SUSAR reports received was in 2003 the larger was the increase in the number in 2007 with respect to 2003.

Do you use external reviewers in assessing applications? (Question 12)

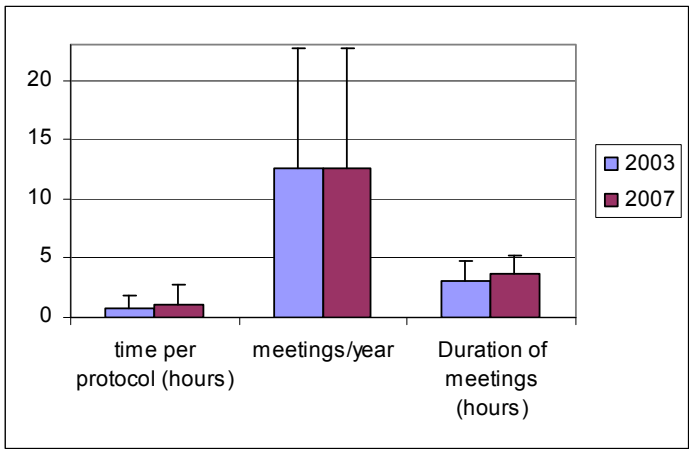
55% of the responding ECs reported to have used an external reviewer, whereas 45% did not.

How much time did you count on average for the discussion of a protocol? How many meetings did you have per year and how long was the average duration of an EC meeting (in hours) (Question 13)

This question was supposed to help better understand possible changes in the time required for the discussion of a protocol as well as the number and duration of meetings under the new EC systems.

Figure 35 shows the time per protocol review in hours, the number of meetings per year and the duration of meetings in hours.

Figure 35: Number and duration of EC meetings



Source: Tables EC 83, EC 85 and EC 87 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

A modest, non significant increase of review time per protocol was observed in unadjusted (+34.81%) and adjusted results (+25.03%). However, it has to be taken into consideration that the question did not ask for the preparation time required for protocol review but just for the review time during the meetings.

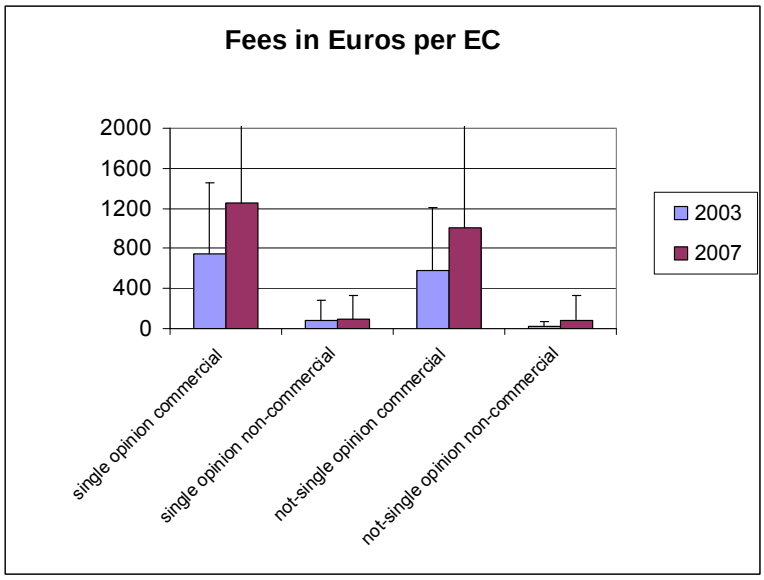
No change in the number of ethics committee meetings in 2003 and 2007 could be observed. Obviously the increase in applications seen above could be handled within the usual number of meetings. However, obviously the duration of the meetings needed to be prolonged as could be observed by the slight but significant increase in unadjusted (+6.9 %) results. The increase of +15.9% in the adjusted results did not reach the significance level.

As "single opinion" provider, what was the average amount of fees to be paid to your EC by commercial and non-commercial sponsors regarding initial applications, yearly in 2003 and 2007? (Question 14)

With establishment of different ethics committee systems the EU member states decided on different approaches to coverage of the EC costs – ranging from complete governmental subsidy to full cost coverage through "fee for service" and different fee levels for different categories of sponsors. This question aimed at finding out about the impact of lead/central EC fee changes between 2003 and 2007 on the costs for sponsors. Question 15 investigated the fees from local ECs for commercially and non-commercially sponsored protocols.

Figure 36 provides the compilation of average fees in 2003 and 2007 for ethical review of a protocol for commercial and non-commercial sponsors by a lead/central EC and by a local EC.

Figure 36: Protocol Review Fees for commercial and non-commercial sponsors charged by central/lead and local ECs



Source: Tables EC 89, EC 95, EC 105 and EC 111 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

Mean fees per protocol review by a lead/central EC for commercial sponsors increased from € 747 in 2003 to € 1304 in 2007. Unadjusted results showed a highly significant increase of +73.98% of the fees for commercial sponsors in 2007 with respect to 2003, confirmed by the also statistically significant increase of +54.46% in adjusted results. Also the number of ECs that reported an increase of fees for commercial sponsors in 2007 was significantly higher than the number of ECs reporting a decrease.

The mean protocol review fee level of lead/central ECs for SMEs was on a lower level (€ 544 in 2003 and € 977 in 2007), however, the increase was similar to that for the larger commercial sponsors with +79.58% in unadjusted results and +74.08% in adjusted results. Also here, the number of ECs reporting an increase in 2007 with respect to 2003 was significantly larger than the number of ECs with a decrease in the protocol review fees for SMEs.
The mean protocol review fee level of lead/central ECs for sponsors of orphan drug trials was again lower than that of the two other categories with € 418 in 2003 and € 608 in 2007. The increase in 2007 was more modest with unadjusted results of +45.4% and adjusted results of +16.8%, both results were statistically not significant.

The mean protocol review fee charged by lead/central ECs to non-commercial sponsors, observed from unadjusted data, was on a much lower level in 2003 (€ 84) and increased only slightly to an average of € 99. This increase (+17.71%) was statistically not significant. Adjusted results showed even a minimal decrease (-0.32%). Interestingly, a positive rank correlation was observed: ECs charging no fees in 2003 did not charge any fees in 2007 either, but those having requested fees in 2003 tended to increase them in 2007 with respect to 2003.

As "single opinion" provider, what was the average amount of fees to be paid to your EC by commercial and non-commercial sponsors regarding substantial amendments, yearly in 2003 and 2007? (Question 15)

The fees charged by central/lead ECs for the review of substantial amendments followed a similar pattern as the fees for the review of the protocol.

The mean fee level for substantial amendments charged by central/lead ECs to commercial sponsors rose from € 115 in 2003 to € 154 in 2007. This increase of 35%, detected in unadjusted and adjusted results, was not statistically significant. However, the number of ECs with an increase in 2007 with respect to 2003 was highly significantly larger than the number of ECs with a decrease in their fees.

Central/lead ECs' mean fee level for substantial amendment review charged to SMEs was clearly lower than that for larger commercial sponsors (€ 31 in 2003 and € 87 in 2007) but faced a stronger increase in that period (+175.89% in unadjusted results and +65.26% in adjusted results).

While the mean fee level of central/lead ECs for substantial amendments charged to sponsors of orphan drug trials was on a higher level in 2003 (€ 70), it faced a slight decrease in 2007 (€ 64). This decrease of -9.46% in unadjusted results and of -62.63% in adjusted results was not statistically significant.

The mean fee level of central/lead ECs for substantial amendments charged to non-commercial sponsors was very low with € 8.79 in 2003 and € 8.22 in 2007 and thus did practically not change.

When NOT providing the "single opinion," what was the average amount of fees to be paid to your EC by commercial and non-commercial sponsors regarding initial applications, yearly in 2003 and 2007? (Question 16)

Non-lead ECs, contributing as local ECs to the single opinion building, appeared to have charged quite similar fees for initial applications as the central/lead ECs themselves:

For commercial sponsors the mean fee was in 2003 by € 563 and in 2007 by € 939. This increase of +76.36% in unadjusted results was statistically significant while the increase of +42.95% in adjusted results did not reach the significance level. However, the number of ECs with an increase of fees in 2007 with respect to 2003 was significantly larger than the number of ECs with a decrease in their fees.

Also the mean fee level for protocol review by local ECs charged to SMEs was not much lower than that of central/lead ECs: it rose from € 440 in 2003 to € 833 in 2007. This increase of +89.27% in unadjusted results was supported by the increase of +164.48% in adjusted results.

The mean fees for protocol review charged by local ECs to sponsors of orphan drug trials was with € 277 in 2003 lower than that for SMEs, but the increase in 2007 to € 526 was equally high (+89.86%).

The mean fee for protocol review charged by local ECs to non-commercial sponsors was in 2003 very low with € 19 but faced a drastic increase of +349.59% to € 87 in 2007 (+68.14% in the adjusted results). However, the overall level was still much lower than for the other categories.

When NOT providing the "single opinion", what was the average amount of fees to be paid to your EC by commercial and non-commercial sponsors regarding substantial amendments, yearly in 2003 and 2007? (Question 17)

Fees for substantial amendment review were also charged by non-lead ECs, but their fee level was lower than that of central/lead ECs:

The mean fee level charged to commercial sponsors for substantial amendment review increased from € 55 in 2003 to € 136 in 2007. This increase of +149.35% in the unadjusted results was statistically significant while the increase of +53.61% in the adjusted result did not reach the significance level.

No information was received about the fees for substantial amendment review charged to the other categories in 2003 and thus no comparison with 2007 could be calculated. The mean fees charged in 2007 to SMEs were at € 72, for sponsors of orphan drug trials at € 35 and for non-commercial sponsors at € 3.33 and thus mirroring the approach of the lead/central ECs but on a lower level.

What was your overall yearly budget (including staff salaries) for your EC in 2003 and 2007? (Question 18)

Status, responsibilities and tasks of ethics committees changed with the implementation of the CTD. This question aimed at investigating the impact on the ECs' budget before and after the system changes. Table 50 provides information from unadjusted data on the changes in the ECs' mean budgets in 2003 and 2007.

Table 50: Yearly budget of individual ECs in Euros

	2003	2007
Mean budget per EC	41717.59	63789.94
Standard deviation	68237.70	96998.24
Number of respondents with information for both years	29	29
Change in % over 4 years		+52.91%

Source: Table EC 121 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

The increase from 2003 to 2007 of +52.91% as well as the increase of +43.47% in the adjusted results were statistically significant.

How many final study reports did you receive yearly in 2003 and 2007? (Question 19)

The CTD implemented the requirement that sponsors have to send a summary of the final report within one year after finalisation of patient involvement to the responsible ethics committees and competent authorities. This question aimed at finding out whether this process is reliably in place.

Table 51 provides information about the number of final study reports received and the changes from 2003 to 2007.

Table 51: Number of study reports received by ECs

	2003	2007
Mean number of study reports per EC	14.04	17.42
Standard deviation	24.04	26.64
Number of respondents with information for both years	26	26
Change in % over 4 years		+24.11%

Source: Table EC 123 in Statistical Report EC, available on www.efgcp.be/ICREL > Report

Obviously, ECs received study reports already before implementation of the CTD. The increase of +24.11% is not statistically significant, but the number of ECs that experienced an increase is significantly larger than those ECs that saw a decrease. Surprising is the low mean number per EC of 17 study reports per EC, taking into consideration that ECs issued in the average 77 positive opinions in 2003 and 96 in 2007 in total, respectively 49 and 57 for clinical trials with medicinal products which fully fall under the CTD in all EU countries.

Were patients represented in your EC in 2003 and 2007? (Question 20)

This question aimed at finding out in how far patient representatives were involved in ECs in EU member states in 2003 and 2007. Originally in the history of ECs, the guidelines required that scientists and lay members constitute an EC. The CTD emphasized even more the representation of patient representatives.

60% of the responding ECs had no patient representatives in their EC in 2003. This changed to 52% in 2007.

Open question: What is your opinion on the impact of the European Union Clinical Trials Directive: strengths, weaknesses and suggested changes? (Question 21)

Strengths (count)

- harmonisation of procedures (9)
- better protection of patients' interests/safety (6)
- More control over clinical trials (2)
- speed up review process (2)

Weaknesses (count)

- more workload/administrative burden (13)
- SUSAR reporting and dealing with them by the EC (4)
- No access to EUDRAVIGILANCE or other AE database (3)
- restrictive scope: interventional clinical trial with IMP (2)

Proposed changes (count)

- Open access to EudraVigilance or similar AE databank (3)
- Strengthen the role of the local EC (1)
- Simplify/harmonise submission requirements (1)
- SUSAR's unique declaration to EudraVigilance (1)

Commercial Sponsors

Statistical Methodology

The aim of this survey was to investigate different parameters in the clinical trial activities, study structure, timelines, workload, staffing and costs experienced by different categories of commercial sponsors before and after the implementation of the CTD.

For each question concerning a quantity of interest, the results were presented in two main tables.
The table on unadjusted results was already explained in the Statistical methodology section in "Research Ethics Committees" (p. 92).
The second table concerned adjusted results.

Table 52: Adjusted results example

Adjusted mean of delta	1.671
Adjusted variance of delta mean	1.004
Adjusted SEM of delta	1.002
t-value	1.667
Approx. p-value (Ho=no change)	0.095
Adjusted mean 2003	5.283
Adjusted mean change %	31.629
Adj. Mean change / year in %	7.112
Adjusted total 2003	3,540
Adjusted total change in 2007	1,120

Source: Example Table in Statistical Report CS, available on www.efgcp.be/ICREL > Report

- **Adjusted mean**: Adjusted mean was a weighted mean were the weight was that of the stratum:
  Top 15 = 15/670 = 0.02239
  Top 100 = 82/670 = 0.1224
  Beyond Top 100 = 573/670 = 0.8552
  $\bar{d}_{adjusted} = W_h \bar{d}_h$ where W_h was the weight of stratum h and $\bar{y}_h$ was the mean of the stratum h.

- **Mean of delta** was the mean of the difference (delta) between 2007 and 2003. The mean change was based on matched data only (companies with data in 2003 and 2007).

- **Adjusted variance of delta mean**: The adjusted variance of delta mean was given by
  $var(\bar{D})_{adjusted} = \sum W_h^2 (1 - f_h) var(D)_h / n_h$
  where f_h was the sampling fraction ($f_h = n_h/N_h$), n_h was the number of respondents in the stratum h, N_h was the size of stratum h and $var(D)_h$ was the variance of stratum h.

- **SEM**: Standard error of the mean which was equal to the square root of the adjusted variance of the mean.

- **t-value**: Wald statistics equal to adjusted mean divided by SEM

- **Approx. p-value**: was the p-value of the Wald test assuming normal distributions within strata.

***Nota bene*: p-value and estimations of adjusted results might have been quite different from the p-value and estimations of unadjusted results** when the quantity of interest differed largely according to strata. **Adjusted results were more reliable** if there was no major outlier in the "beyond top 100" stratum. The outlier had an impact on the within stratum mean and standard deviation. Moreover, the important weight of the "beyond top 100" stratum ($W_{>top100}$ = 0.8552) had a multiplicative effect. Unadjusted results were very sensitive to differences observed in large (top 100 or top 15) companies (over representation of top 100 including top 15). Adjusted results made a correction but became sensitive to outliers in the "beyond top 100" stratum.

- **Adjusted total was** the adjusted mean multiplied by the population size (670).

- **Adjusted total change was** an estimation of the change in the total quantity of interest such as the total number of CTAs. It was the mean change multiplied by the total number of companies (670).

The **relationship between the change in 2007** with respect to 2003 and **the level in 2003** was calculated for several variables. It allowed checking whether the change was dependent upon the level observed in 2003. Regarding relationships: the Spearman coefficient of correlation was preferable if one or two observations had a major leverage effect (large value of X) or if the relationship was monotonic but not linear. Spearman correlation is a rank coefficient of correlation without any assumption regarding the distribution of Y.

A significant relationship between the change and the level in 2003 showed that the level in 2003 explained the observed change in 2007 with respect to 2003. From an "economic" point of view the change in 2007 was relevant (more or less economic activity) and the relationship was therefore pertinent. It did not mean that the rate of change was dependent upon the level in 2003.

Difference between SMEs and other companies was estimated and tested through a parametric (t-test) and non-parametric (Wilcoxon test) approach. The Wilcoxon test is more reliable if data are not normally distributed.

Results

Sampling process

The survey was open to CSs from 1 June 2008 until 30 September 2008.

The questionnaire was sent to the planned samples composed of 300 companies: the 15 top 15 companies, the 82 remaining companies of the top 100 (excluding top 15) and 208 companies beyond the top 100. In addition, spontaneous participation was encouraged through flyers, e-mailings to different databases, mentioning at conferences and links to several international not-for-profit organisations' web pages.
Despite numerous reminders and call back, the response rate was very low and it was decided to extend the mailing of the questionnaire to more companies (see Table 53). The extended mailing was done to all companies for which sufficient information was available to send a questionnaire. The sampling within strata was therefore not perfectly at random. No spontaneous completion was received.

Table 53: Number of questionnaires sent and response rate

Strata	Companies in the sampling frame	Questionnaires sent	Respondents	Respondent rate
Top 15	15	15	10	66%
Top 100	82	81	11	13.58%
Beyond top 100, large companies	222	195	15	7.69%
Beyond top 100, small and medium-size companies	351*	299	17	5.69%
Total	670	590	53	8.98%

* Two companies were added to the sampling frame at the time of the implementation of the sampling strategy.
Source: Table CS2M in Statistical Report CS, available on www.efgcp.be/ICREL > Report

The total response rate was 8.98% and was better in large companies than in the small ones.
Table 53 shows that the rate of respondents decreased with the company size. Very large companies were over-represented and small companies were under-represented in the sample.

The two strata from "beyond Top 100" were pooled together because the stratum that should be composed of small or medium-size companies (approximate assessment) did not fit well with the precise definition of SMEs. Five out of 18 in the sample were not SMEs (response to the questionnaire corresponding to a precise definition). Moreover, 4 out of 12 that should not be SMEs were actually SMEs. Thus 17 (53.1%) companies were SMEs out of the 32 respondents belonging to the "beyond top 100" stratum.

Such discrepancies were not amazing because classification was not done with the same criteria. To avoid confusion between SMEs as defined in the glossary and the stratum with small and medium-size companies, SMEs in the results are companies that fit with the definition of the glossary. Such pooling may slightly bias results towards large companies of the "beyond top 100" stratum because sampling fraction and response rate of the "beyond top 100, small and medium-size companies" stratum were lower than that of the "beyond top 100, large companies" stratum.

Detailed description of all results from the commercial sponsor survey can be found in "Statistical Report CS" available on www.efgcp.be/ICREL > Report.

Description of respondents

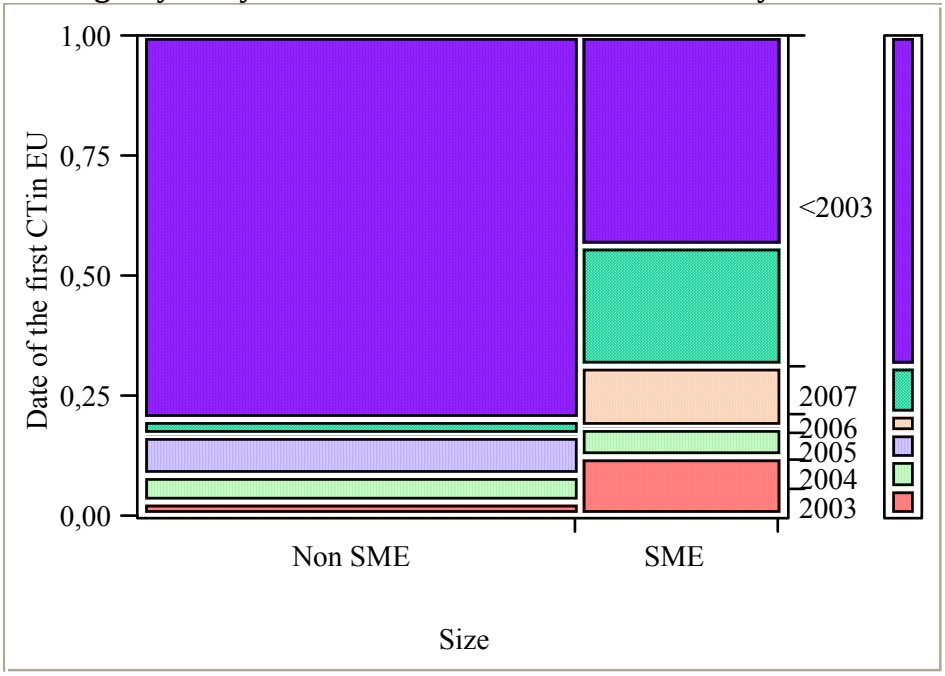
In the questionnaire for commercial sponsors we wanted first to receive some characteristics of the responding companies like seat of their headquarters, their experience with clinical trials before and after implementation of the CTD, their merger history and their clinical research areas of activity.

The 53 responding pharmaceutical companies had their headquarters in 12 different countries: USA (15), Denmark (8), Germany (7), Switzerland (6), France (4), Sweden (4), Japan (3), Belgium (2), UK (1), Spain (1), Israel (1), and Australia (1). All these companies had a legal representation in the EU and performed clinical trials in the EU between 2003 and 2007.

77.36% of all respondents carried out a CT in the EU before the enforcement of the CTD, namely 100% of the top 15 companies, 91% of the top 100 companies and 66% of the "beyond top 100" companies. Only 10 of the 17 SMEs (59%) had performed a CT before the implementation of the

CTD. Figure 37 is a Mosaic Plot presenting the year of the first CT as a function of the company size. Non-SME companies started significantly earlier with the performance of clinical trials than SMEs.

Figure 37: Date of first CT in the EU as a function of company size.
Contingency analysis of date of the first CT in the EU by size. Mosaic Plot



Source: Figure CS8 in Statistical Report CS, available on www.efgcp.be/ICREL > Report

While only one of the responding ten "Top 15 companies" and two of the responding eleven "Top 100 companies" received a first CTA only in 2005, the "Beyond 100 companies" and there again especially the SMEs, received their first CTAs between 2005 and 2007.

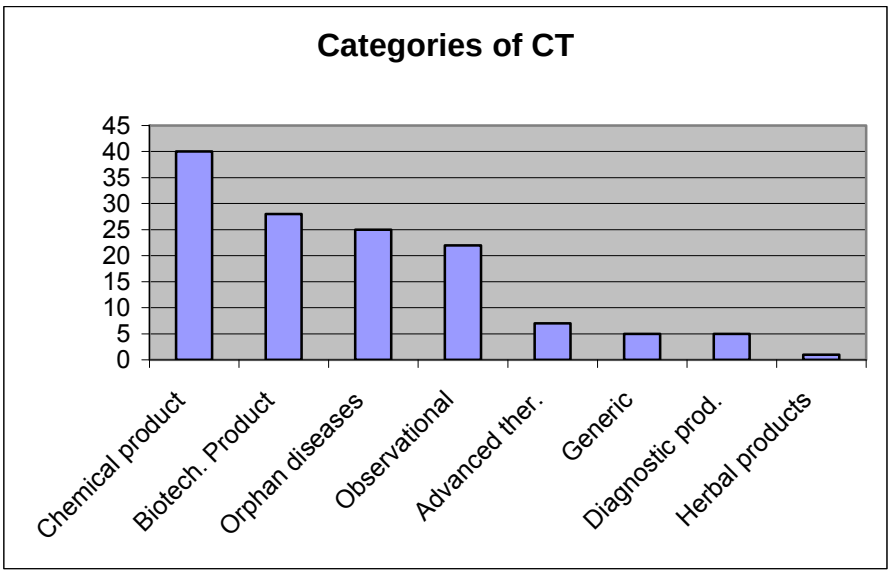
One of the responding "Top 15 companies", seven of the "Top 100 companies" and five of the "Beyond 100 companies" had undergone a merger between 2003 and 2007.

Categories of clinical research for which you have clinical trial activities? (Question 1 in the Questionnaire to CSs)

The companies were asked about their active research areas and could tick one or several defined areas or "multi-disciplinary". 95% of the large companies presented themselves as "multi-disciplinary" while only 39% of the "Beyond 100 companies" ticked that box. SMEs were significantly less frequently multi-disciplinary than non-SME companies.

The research activities in the different categories of research are presented in Figure 38.

Figure 38: Number of institutions out of 53 respondents that carried out CTs in the various clinical research categories



Source: Figure CS15 in Statistical Report CS, available on www.efgcp.be/ICREL > Report

How many clinical studies on medicinal products were approved by a Competent Authority and/or received a favourable opinion from Ethics Committee(s) in EU countries yearly in 2003 and 2007? (Question 3)

How many of the approved clinical trials on medicinal products were on advanced therapies, on biotechnological products, on orphan diseases or medicinal products with orphan designation, yearly in 2003 and 2007? (Question 4)

In Question 3 of the questionnaire, not only information on the total number of commercially sponsored clinical trials approved in 2003 and 2007 was requested, but also a break-down of the types of clinical trial categories: clinical trials on medicinal products, on diagnostic products including biomarkers and radio-diagnostics or non interventional/observational studies. In Question 4 the break-down of the number of trials with medicinal products in different product categories was requested: advanced therapies, biotechnological products and products with orphan designation.

Table 54 provides an overview over the findings.

Table 54: Mean number of CS-CTs for different categories

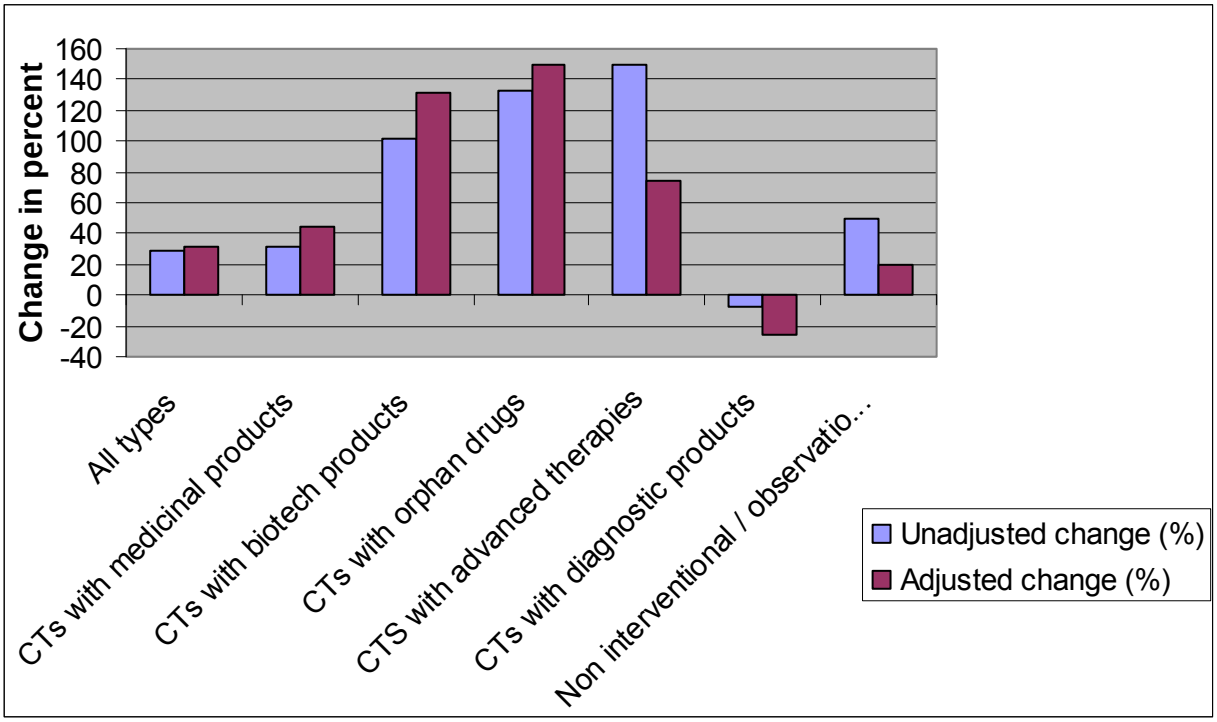
Type of Category	2003	2007	Unadjusted change (%)	Adjusted change (%)
All types	15.09	19.23	**29.11**	31.64
CTs with medicinal products	13.76	17.91	**31.83**	44.91
CTs with biotech products	4.61	9.32	**102.1**	131.08
CTs with orphan drugs	0.42	1.00	**133.3**	**149.43**
CTS with advanced therapies	0.08	0.2	150.0	73.85
CTs with diagnostic products	0.59	0.55	-7.69	-25.48
Non interventional / observational studies	2.13	3.17	48.98	19.73

Results presented in italics were statistically significant

Source: Tables CS 3 to16 in Statistical Report CS, available on www.efgcp.be/ICREL > Report

Figure 39 provides an overview over the adjusted and unadjusted changes of the different CS-CT categories.

Figure 39: Adjusted and unadjusted changes of the different CS-CT categories

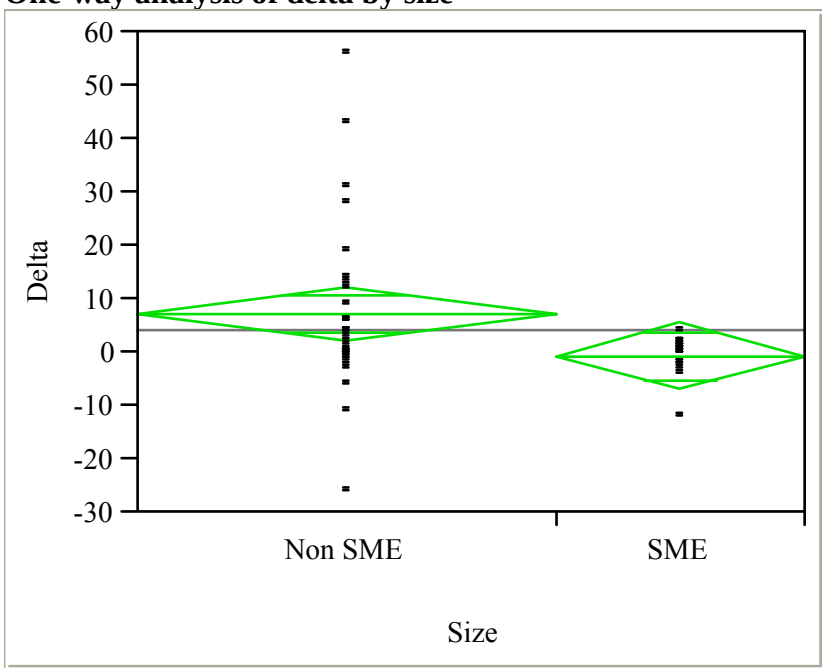


Source: Tables CS 3 to 16 in Statistical Report CS, available on www.efgcp.be/ICREL > Report

While unadjusted results for all types of commercially sponsored clinical trials showed a statistically significant increase of 29% from 2003 to 2007 with significantly more companies showing an increase than a decrease, the adjusted results showed a non-significant increase of 31.64%. The test was no longer significant because the change was negative in SMEs (see Figure 40) and this category was well represented in the population. The change was significantly dependent upon the size (SMEs or not) of respondents. A non-significant decrease (-0.53 CT/company) was observed in SMEs and a significant increase (+7.28 CT/company) was observed in non SMEs.

Figure 40: Change of total number of approved CS-CTs in 2007 with respect to 2003 in SMEs and non SMEs.

One-way analysis of delta by size



Source: Figure CS19A in Annex CS, available on www.efgcp.be/ICREL > Report

Comparable results were found in the sub-category "commercially sponsored clinical trials with medicinal products". This similarity was not surprising as the vast majority of clinical trials performed by commercial sponsors were performed with medicinal products. In relation to this the other sub-categories consisted of small numbers and thus relative changes seemed huge and outliers led to even higher changes in adjusted results than in unadjusted results. Nevertheless it can be concluded that there was a clear increase of commercially sponsored clinical trials of around 30% between 2003 and 2007. However, this increase was not seen in SMEs. The increases were seen in all categories but with diagnostic products. And the increase of commercially sponsored CTs with orphan drugs was clearly statistically significant. The duplication of commercially sponsored clinical trials with biotechnological products was probably reflecting the rapid development of that technology. Such an external reason for the increase of commercially sponsored non interventional / observational trials, however, especially seen in large companies, was not obvious.

How many non-approvals of a protocol by a Competent Authority or by an Ethics Committee in Europe, and uses of the appeal system were there per year in 2003 and 2004? (Question 5)

Question 5 aimed at receiving an impression of the level of non-approvals for protocols by competent authorities and ethics committees after the implementation of the CTD as well as of the availability of an appeal system in the different countries. Practically no non-approvals occurred before the implementation of the CTD in the EU. After the implementation in 2007 each company experienced approximately one non-approval by a competent authority and one by a lead ethics committee. The increase in 2007 was statistically significant in the case of the lead ethics committees and related to the number of non-approvals in 2003, however, not to the size of the company. The increase of protocol non-approvals by competent authorities was not statistically significant. The number of protocol non-approvals by local ethics committees was in the area of 1.4 per company and year in 2003 and increased to about 2.5 in 2007. However, this increase was not statistically significant and not related to the number of non-approvals in 2003 or the company size.

Only 19 companies answered the question whether there was an appeal system available or not for rejections from competent authority, lead or local ethics committee in EU countries. Only one company reported having used an appeal system in 2003 and two companies in 2007.

How many clinical trials with medicinal products did you sponsor, per phase, yearly in 2003 and 2007? (Question 6)

Information on the number of clinical trials performed in the Phases 1 to 4 was requested to identify a potential change in the types of trials performed in the EU in 2003 and 2007.

Table 55 provides an overview over the results:

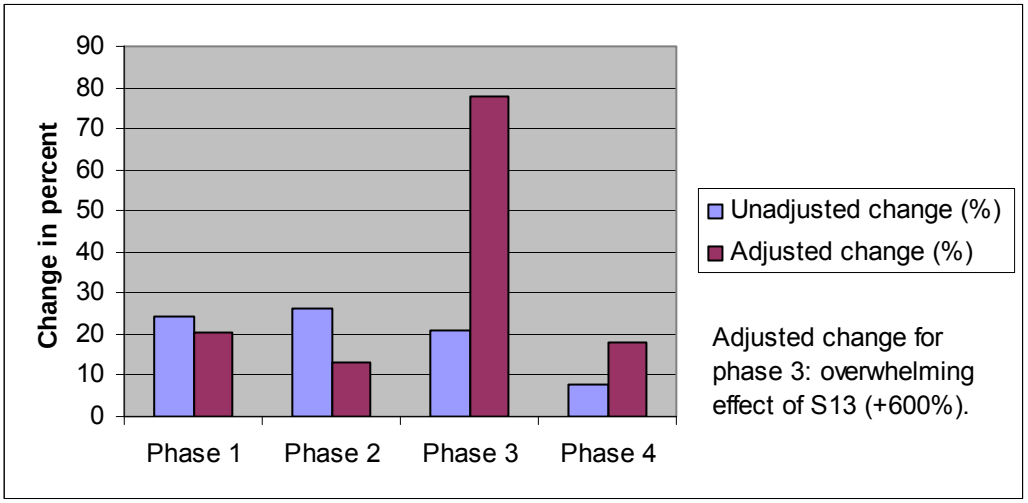
Table 55: Mean number of CS-CTs performed in Phases 1, 2, 3, and 4

Type of Category	2003	2007	Unadjusted change (%)	Adjusted change (%)
Phase 1	6.00	7.5	24.5	20.27
Phase 2	4.5	5.7	26.1	13.04
Phase 3	5.6	6.8	20.9	77.65
Phase 4	5.6	6.1	8.0	17.84

Source: Tables CS 25 to 32 in Statistical Report CS, available on www.efgcp.be/ICREL > Report

Figure 41 shows the unadjusted and adjusted changes in the types of clinical trial phases experienced by commercial sponsors between 2003 and 2007.

Figure 41: Unadjusted and adjusted changes between 2003 and 2007 in the phases of clinical trials performed by commercial sponsors



Source: Tables CS 25 to 32 in Statistical Report CS, available on www.efgcp.be/ICREL > Report

In the mean, every respondent company performed 6 Phase 1 trials in 2003; in 2007 the mean was 7.5. This increase of 24.5 for non-adjusted, respectively 20.3% for adjusted results was not statistically significant. SMEs reported a small, non significant decrease of Phase 1 trials in 2007.

Also in commercially sponsored Phase 2 trials, an increase of 26.1% respectively 13.04% (again statistically non significant) from 2003 to 2007 was detectable. SMEs and non-SMEs showed the same tendency.

Comparable increases in commercially sponsored Phase 3 trials from 2003 to 2007 were detected with an unadjusted increase of 20.9% and an adjusted increase of 77.65%, in both cases non significant. The magnitude of the increase in the adjusted results could be explained by the impact of a major outlier company in the "Beyond Top 100" stratum. However, there was a significantly higher number of companies with an increase in Phase 3 trials than with a decrease.

Also the increases in commercially sponsored Phase 4 trials of 8.0% and 17.84% for unadjusted and adjusted data, respectively, were not statistically significant. This trend was the same for SMEs and non-SMEs.

How many approved clinical trials with medicinal products, yearly in 2003 and 2007, were multi-national trials, national multi-centre trials, or mono-centre clinical trials? Please list the trials in the year their first Clinical trial authorisation was received in Europe. (Questions 7)

How many European centres and countries were involved in your clinical trials on medicinal products, initiated yearly in 2003 and 2007? Centres and countries can be counted several times if they were involved in several trials. (Question 8)

How many participants were recruited in your clinical trials in Europe, yearly in 2003 and 2007? (Question 9)

The harmonisation of clinical trial approval processes and requirements through the Clinical Trials Directive aimed at facilitating multi-national and multi-centre trials and at increasing recruitment. Questions 7 and 8 in the questionnaire focused on finding changes in the organisation of clinical trials, namely whether the clinical trials were placed in more or less sites and countries in 2003 and 2007. Question 9 explored changes in the number of recruited subjects in these sites.

Table 56 shows the results provided by the respondent companies.

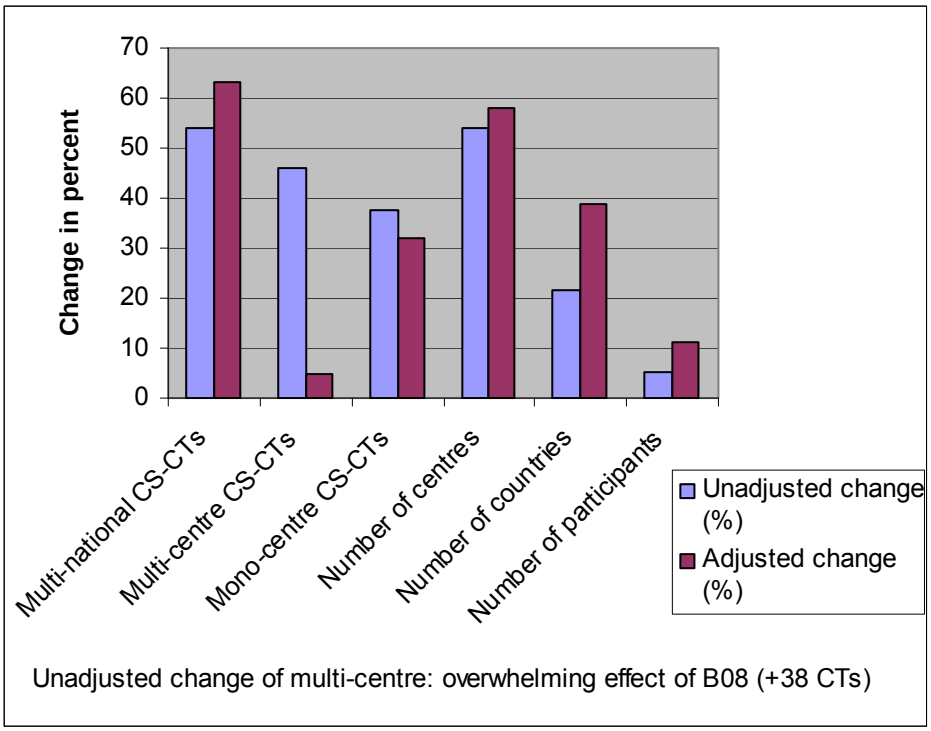
Table 56: Mean number of multi-national, multi-centre, and mono-centre CS-CTs in 2003 and 2007, number of involved sites, countries and recruited subjects

Centres/Subjects	2003	2007	Unadjusted change (%)	Adjusted change (%)
Multi-national CS-CTs	7.4	11.4	**53.9**	63.12
Multi-centre CS-CTs	3.2	4.7	46.0	4.62
Mono-centre CS-CTs	5.6	7.7	37.62	31.93
Number of centres	302.6	465.9	54.0	**57.84**
Number of countries	44	54	21.6	38.89
Number of participants	4.251	4.479	5.4	11.06

Results presented in italics were statistically significant
Source: Tables CS 33 to 44 in Statistical Report CS, available on www.efgcp.be/ICREL > Report

In Figure 42, the unadjusted and adjusted changes in number of involved countries and centres as well as number of participants from 2003 to 2007, listed in Table 56, are graphically presented.

Figure 42: Unadjusted and adjusted changes (2003 to 2007) in number of involved countries, centres and participants



Source: Tables CS 33 to 44 in Statistical Report CS, available on www.efgcp.be/ICREL > Report

In the average, the respondent companies increased their annual number of multi-national clinical trials from 7.4 trials in 2003 to 11.4 trials in 2007. This unadjusted mean change of 46% was highly significant and also the number of companies with increases was significantly higher than those with decreases. Yet, the adjusted increase of 63.12% was not statistically significant. While there was no difference between companies of different sizes, a significant positive relationship could be detected between the multi-national clinical trials activity in 2003 and the extent of change.

The increase of national multi-centre trials from in the average 3.2 trials in 2003 to 4.7 trials in 2007 per company was not statistically significant, neither when considering the unadjusted increase of 37.6% nor the adjusted increase of 4.62%. This trend was independent of company size and multi-centre trial activity in 2003. The difference in extend of change in unadjusted and adjusted results could be explained by a major outlier company. The unadjusted results should therefore be considered with caution.

Also the number of mono-centre trials increased from 2003 to 2007: from 5.6 trials per company in 2003 to 7.7 trials in 2007. This increase of 37.6% respectively 31.93% for unadjusted and adjusted results did, however, not reach the statistical significance level. Yet, the number of companies that reported an increase was significantly larger than the number of companies with decreases in mono-centre trials. Further look into the data revealed that the non-SMEs showed a significant increase, SMEs, in contrary a decrease (albeit not reaching the significance level). But this difference between SMEs and non-SMEs was significant.

Question 8 in the questionnaire asked for the number of investigational centres and countries involved in clinical trials in 2003 and 2007. Centres and countries could be counted several times if they were involved in several trials.

A strong increase was found in the number of centres per company and year: from 302.6 to 465.9 investigative centres. In contrast to the increase of 54.0% in unadjusted results the increase of 57.84% of the adjusted results reached statistical significance. This increase was independent of the company size and the number of sites in 2003.

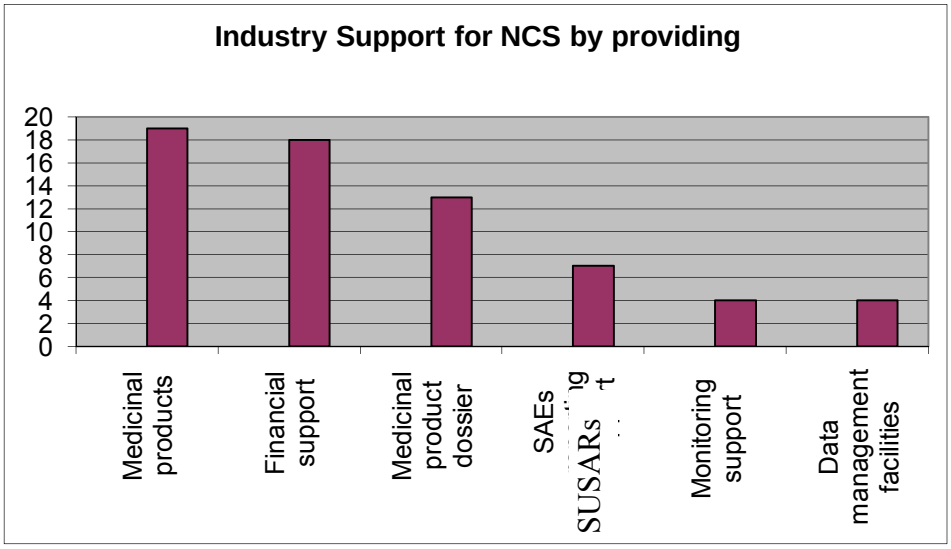
Also the mean number of countries involved in commercially sponsored trials increased from 44 to 54 centres for each company. This level of increase between 20 and 40% (21.6% for unadjusted results and 38.89% for adjusted results after exclusion of an outlier) was independent of the company size and not clearly linked to the number of countries involved in 2003.

Despite the increasing complexity of the clinical trials with more countries and centres involved the number of recruited subjects did not follow: the mean number of subjects in 2003 and 2007 recruited per company increased only from 4.251 to 4.479 subjects. This increases of 5.4% and 11.06%, respectively, for non-adjusted and adjusted results did not reach statistical significance. This trend was independent of company size or recruitment activity in 2003.

If applicable, how did you support trials sponsored by non-commercial institutions? (Question 10)

Question 10 aimed at exploring in which way Pharma companies supported investigator-initiated trials. Figure 43 presents the result:

Figure 43: Type of industry support for CTs sponsored by non-commercial institutions



Source: Figure CS 94 in Statistical Report CS, available on www.efgcp.be/ICREL > Report

Only approximately one third of the companies responding to the ICREL questionnaire seem to have supported non-commercially sponsored clinical trials. The majority of those who had experience with this approach provided study medication and financial support to the non-commercially sponsored trials. However, in about two thirds of these cases also the IMPD was made available to the academic sponsor. Only very few companies reported experience with providing expedited SUSAR reporting, monitoring or data management support.

What was the average time between the protocol finalisation and the inclusion of the first patient in an EU country? What was the average time between the moment when you released a (substantial) amendment and when it was implemented at the fist site in Europe, per year, in 2003 and 2007? (Question 11)

The harmonisation of study approval procedures and binding maximum approval time lines were implemented by the CTD to shorten the overall duration of clinical trials. This Question 11 was supposed to find out whether these reduced time lines really had an impact on crucial time lines in a clinical trial: the period from finalisation of the protocol to "First-patient-in" (FPI) and from release of a (substantial) amendment to its implementation at the first site. The term "Substantial" amendment was introduced by the CTD, thus creating a difference in terminology in 2003 and 2007 for this question.

Table 57 shows the results provided by the respondent companies.

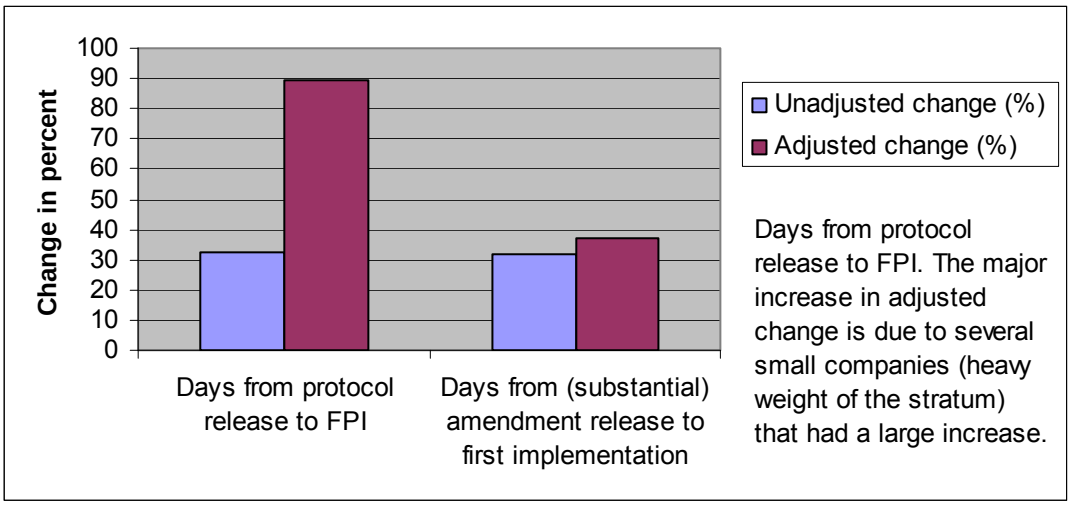
Table 57: Time lines from protocol finalisation to inclusion of first patient and from (substantial) amendment release to first implementation in 2003 and 2007

Time Periods	2003	2007	Unadjusted change (%)	Adjusted change (%)
Days from protocol release to FPI	115	152	**32.4**	**89.33**
Days from (substantial) amendment release to first implementation	40	53	31.7	37.13

Results presented in italics are statistically significant
Source: Tables CS 45 to 48 in Statistical Report CS, available on www.efgcp.be/ICREL > Report

Figure 44 presents the unadjusted and adjusted increases observed by commercial sponsors in the timelines for protocol initiation and substantial amendment implementation

Figure 44: Changes in timelines for protocol initiation and substantial amendment implementation

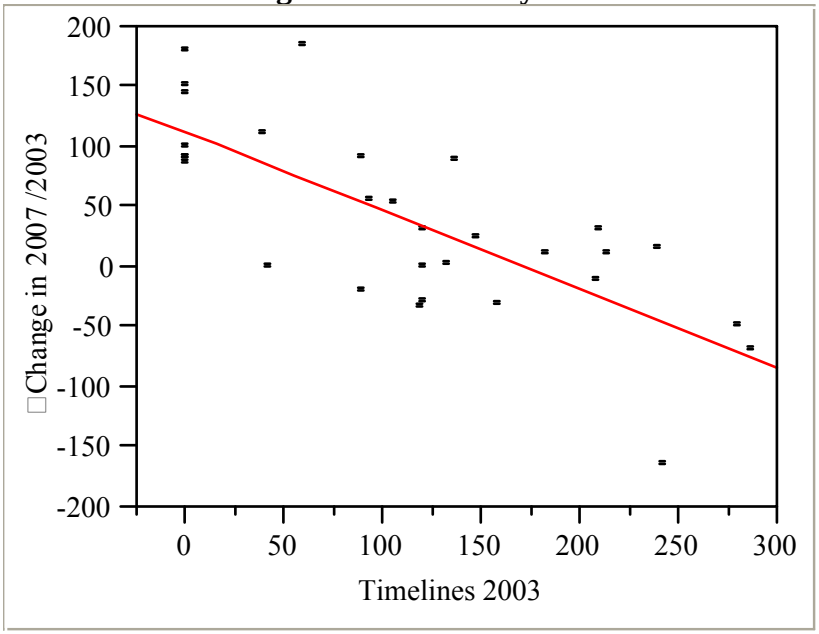


Source: Table CS 45 to 48 in Statistical Report CS, available on www.efgcp.be/ICREL > Report

The results were very surprising: the period from finalisation of the protocol to inclusion of the first patient was highly significantly prolonged from in the average 115 days in 2003 to 152 days in 2007. The unadjusted results increase of 32.4% and of the adjusted results increase of 89.33% were highly significant. However, while large companies increased their time lines only moderately,

SMEs faced drastic and significant increases in time lines in 2007. And – as presented in Figure 45 – a highly significant negative relationship was observed between the change in time lines from protocol finalisation to FPI and time lines in 2003: companies with short time lines in 2003 increased their time lines and companies with long time lines reduced their time lines.

Figure 45: Change in average time between protocol finalisation and inclusion of the first patient in 2007 as a linear function of 2003.
Bivariate fit of change in 2007 /2003 by time lines 2003



Source: Table CS 97 in Statistical Report CS, available on www.efgcp.be/ICREL > Report

Also the implementation of (substantial) amendments took longer in 2007 than in 2003: the mean time increased from 40 to 53 days, an increase of 31.7% and 37.13% for unadjusted and adjusted results, respectively. These increases were not statistically significant. However, also here a significant negative relationship was observed between the increase of the average time between (substantial) amendment release and implementation at the first site and time lines in 2003. Companies with short time lines in 2003 increased their time lines and companies with long time lines reduced their time lines. A difference between SMEs and non SMEs could not be detected.

In 2003 and 2007, how many full-time equivalents (as internal and external resources) worked on your following tasks? Clinical trial applications to Competent Authorities and Ethics Committees, incl. Investigational Medicinal Product Dossier preparation. Clinical trial coordination and monitoring. Pharmacovigilance tasks: SAE/SUSAR reports, Annual Safety Reports. Quality Assurance. (Question 12)

Question 12 was asked to identify the changes in workload created by clinical trials, measured by internal and outsourced full time equivalents working in the preparation and supervision of clinical trials, in pharmacovigilance and quality assurance in 2003 and 2007.

Table 58 shows the results provided by the respondent companies:

Table 58: Number of FTEs working on commercially sponsored CTAs and IMPDs, on CT coordination and monitoring as well as on Pharmacovigilance and Quality Assurance

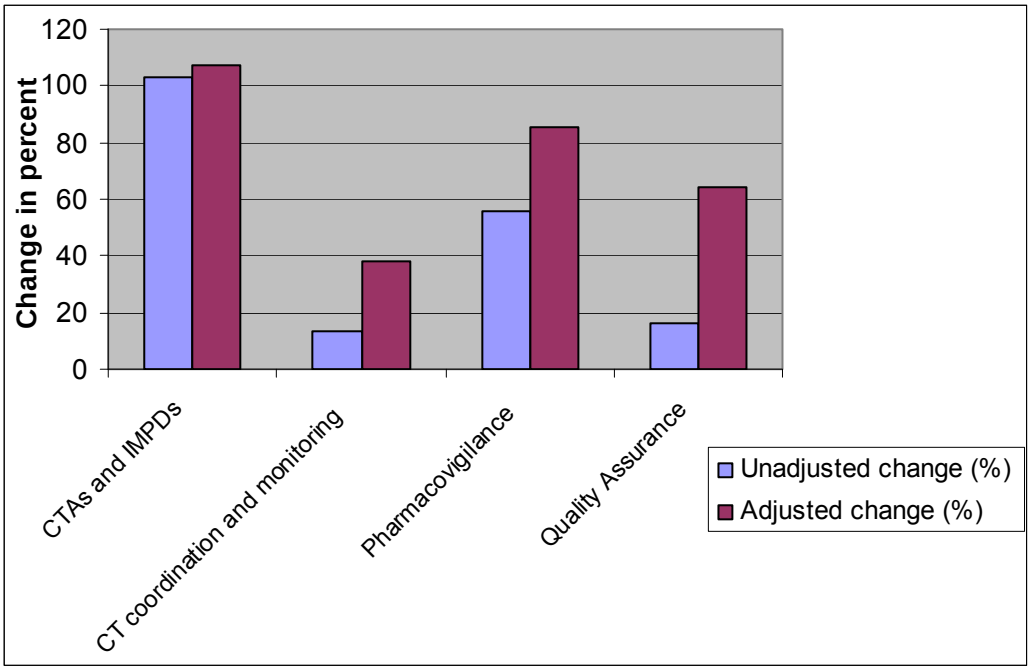
FTEs	2003	2007	Unadjusted change (%)	Adjusted change (%)
CTAs and IMPDs	1.9	3.9	103.2	107.25
CT coordination and monitoring	38.4	43.5	13.3	**38.12**
Pharmacovigilance	4.8	7.5	**55.9**	**85.75**
Quality Assurance	4.7	5.4	16.1	64.02

Results presented in italics are statistically significant

Source: Tables CS 49 to 56 in Statistical Report CS, available on www.efgcp.be/ICREL > Report

In Figure 46, the unadjusted and adjusted changes from 2003 to 2007 in FTEs required to perform the different clinical trial- related tasks in pharmaceutical companies are presented.

Figure 46: Increases in work forces for CT-related tasks in pharmaceutical companies



Source: Tables CS 49 to 56 in Statistical Report CS, available on www.efgcp.be/ICREL > Report

The number of staff working in the area of clinical trial applications and IMPD preparation obviously doubled in 2007 in comparison to 2003. The results for unadjusted and adjusted results did not reach statistical significance but the number of companies which experienced an increase is significantly higher than the number of companies with a decrease. Interesting is also the fact that there is a significant negative correlation between the staff level in 2003 and the change: those companies which had already a substantial staff number in this area in 2003 were able to cope with the additional workload created by the CTD. Companies with less staff obviously had to invest in additional staff for the clinical trial approval process.

The number of staff required for clinical trial coordination and monitoring significantly increased from an average of 38.4 to 43.5 FTEs, thus by 38.12% when considering the adjusted data. The unadjusted data showed a non-statistically significant increase of 13.3%. There was the same trend for large and small companies. When excluding the three companies that had not provided workload data from the companies they acquired there was a high significance in the unadjusted

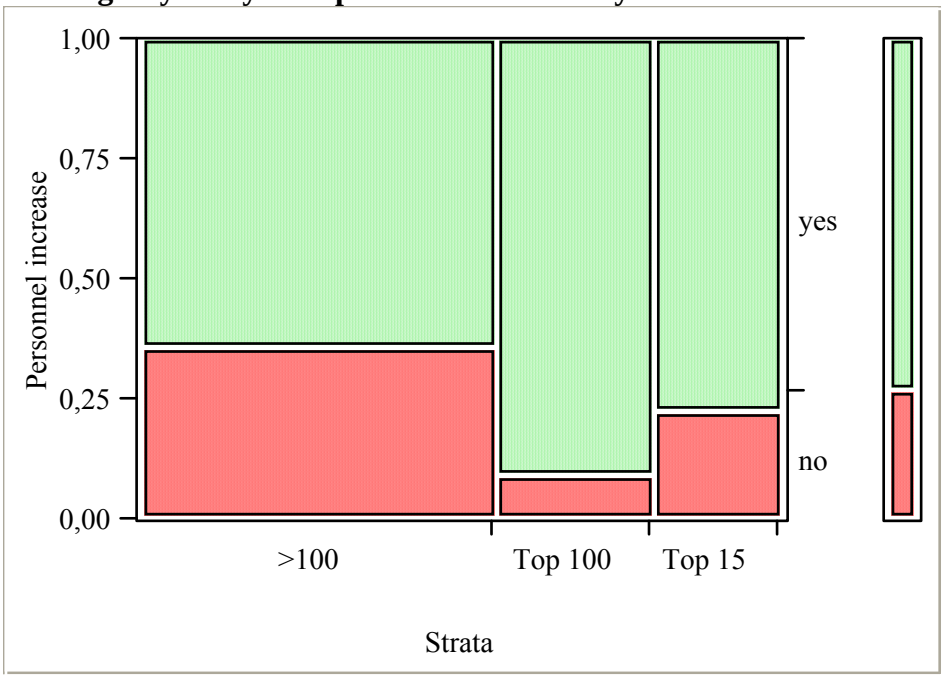
results in the number of companies which faced an increase versus those which faced a decrease. And the increase of the adjusted results became statistically significant with an increase of 37.72%. A highly significant increase in staff working in pharmacovigilance from in the average 4.8 to 7.5 FTEs, thus 37.6% for unadjusted results and 85.75% for adjusted results was observed. This trend was independent of the company size and the staff level in 2003. Obviously, the new legislation for safety reporting has not reduced the workload for commercial sponsors but significantly increased it by more than 50%.

In comparison to the increases of FTEs in other areas of the clinical trial management the increases in quality assurance staff from 4.7 FTEs in 2003 to 5.4 FTEs in 2007 was relatively modest and not statistically significant: 16.1% for unadjusted results and 64.02% for adjusted results. This increase was seen in large and small companies and was obviously independent of the level of QA staff in place before the implementation of the CTD. However, when excluding the three companies that had not given workload data from the companies they had acquired, there was a significantly larger number of companies that faced an increase than a decrease.

According to your experience, has the quantity of personnel per study increased between 2003 and 2007? (Question 13)

This question asked specifically in a qualitative way, whether the personnel required *per study* has increased between 2003 and 2007 in the experience of the respondent. The result is presented in Figure 47.

Figure 47: Increase of personnel involved in a clinical trial by stratum. Contingency analysis of personnel increase by strata. Mosaic Plot



Source: Figure CS119 in Statistical Report CS, available on www.efgcp.be/ICREL > Report

A large percentage of the respondents confirmed that there is more staff required to perform a clinical trial according to the new legislation than before 2003. The strongest agreement to this statement was found in the larger companies, especially those between ranks 16 and 100. However, these differences were not statistically significant.

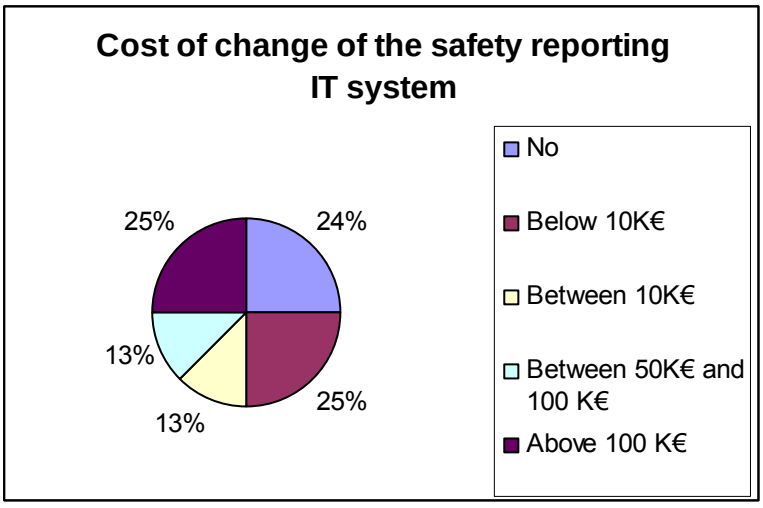
Did you have to adapt your expedited IT reporting system to the requirements of the Clinical Trials Directive? (Question 14)

What were yearly the overall subject indemnity insurance costs in 2003 and 2007? (Question 15)

With implementation of the CTD a new expedited safety data reporting system was introduced: EudraVigilance. While the process requires that sponsors provide this information to the national competent authorities and the CA of the country in which the SUSAR occurred is supposed to enter the SUSAR into the database located at the EMEA, However, the sponsor is obliged to prepare the information in a specific format, ideally electronically, so that the CA can easily enter the information into the database. In many cases this meant that companies had to adapt or establish their IT system to this requirement. The responses to this question are presented in Figure 48.

Only 24% of the companies reported that they did not need to invest into a new safety data system. 25% reported that they needed not to invest more than € 10,000 while another 25% of the respondents declared a need to invest more than € 100,000 into their new expedited safety data reporting system! Especially the largest companies had the biggest investment. The difference between small and large companies was statistically significant.

Figure 48: Distribution of cost of adapting an electronic SUSAR expedited reporting system



Source: Figure CS121 in Statistical Report CS, available on www.efgcp.be/ICREL > Report

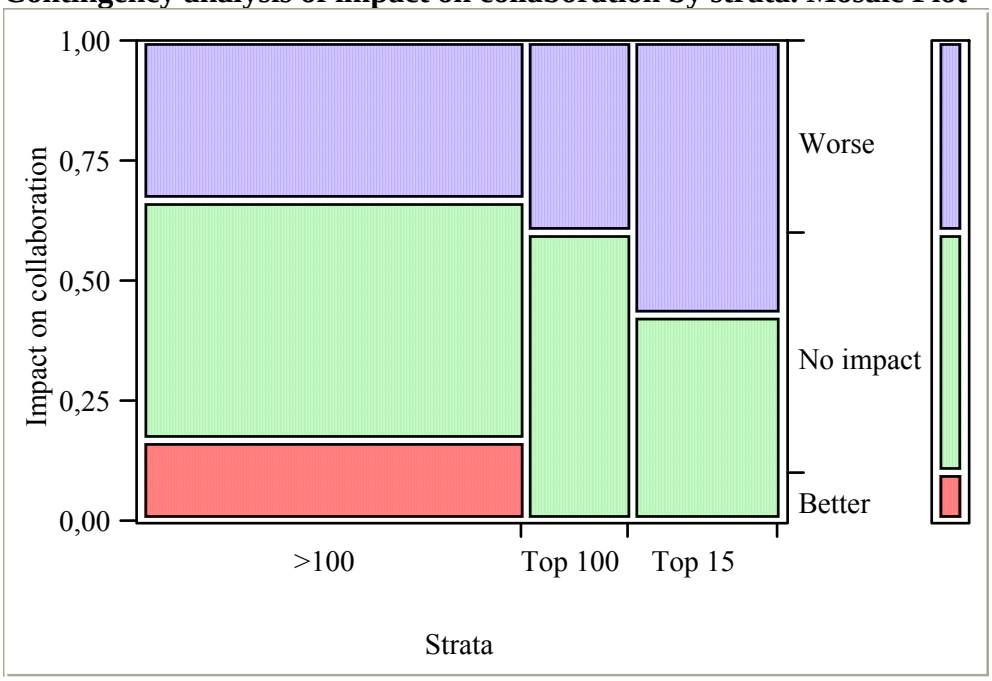
Coverage of subject indemnity costs had already been a sponsor requirement before the implementation of the CTS. However, the insurance industry has used the new situation to change their contractual conditions in many Member States by cancelling the existing group insurance conditions and replacing it by a risk-based per-study fee. In Question 15 we asked what the annual subject liability insurance costs were in 2003 and 2008. Obviously, this question was difficult to answer because only 20 companies could give us this information for 2003 and 2007. But the result was striking: the mean costs increased from € 103,390 in 2003 to € 489,035 in 2007. This was an increase of 373% in unadjusted results and of 814% in adjusted results. They both did not reach the significance level, probably due to the small sample size, but the number of companies that faced an increase was highly significantly greater than the number of companies which faced a decrease. The increase was independent of the company size.

According to your experience, has the Clinical Trials Directive's broader definition of sponsor tasks in the EU impacted your company's capacity to act as sponsor in national or in EU multi-national studies, and to participate in collaborative projects with academic institutions? (Question 16)

In Question 16 of the questionnaire we asked for the respondents' judgement on whether the CTD's broader definition of "sponsor" has helped them to act as a sponsor or not. The responses to this question were quite heterogeneous: about 50% of the respondents felt that the broadened sponsor definition had not impact on their ability to perform the sponsor role in national and multi-national studies and had no impact on their collaborative projects with academia. Especially the beyond 100 companies did not feel any impact. The Top 15 companies felt more frequently than the medium-sized and smaller companies that the CTD is more hindering their sponsor performance in multi-national trials and their collaboration with academia than that it helps.

Figure 49 shows this latter result concerning the impact of the CTD's broader sponsor definition on their collaboration with academia:

Figure 49: Relationship between the CTD's impact on collaborative projects and the stratum. Contingency analysis of impact on collaboration by strata. Mosaic Plot



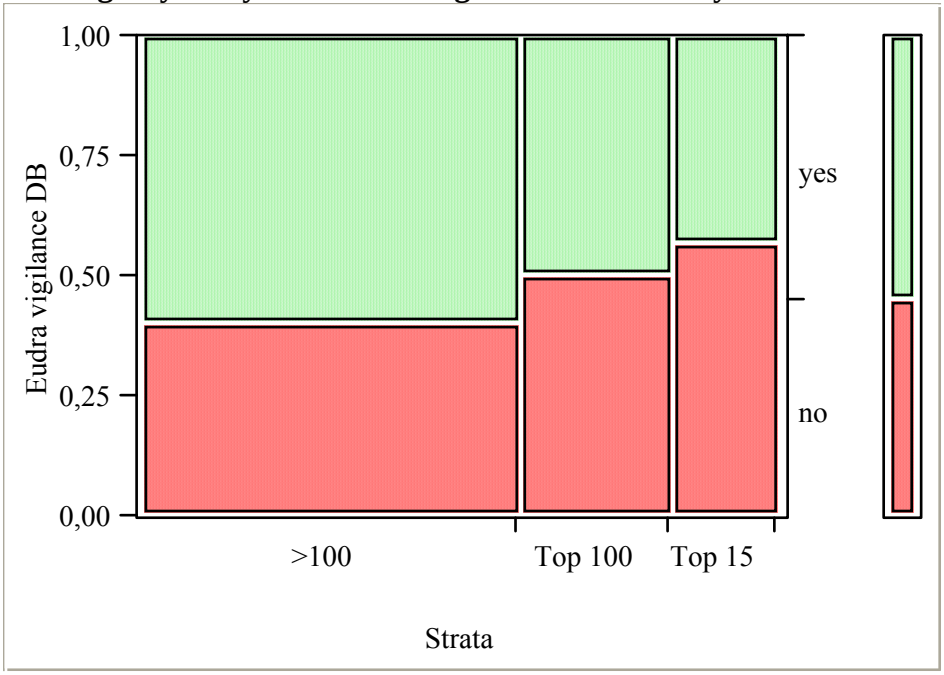
Source: Figure CS133 in Statistical Report CS, available on www.efgcp.be/ICREL > Report

In your experience, has the implementation of the EudraVigilance database for clinical trials helped increase the safety of participants in clinical trials in Europe? (Question 17)

With this last question the attempt was made to find out about the respondents' opinion on the impact of the newly implemented EudraVigilance database on the participants' safety.

As Figure 50 shows, there is quite some doubt in its protective capacities.

Figure 50: Impact of implementation of the EudraVigilance database on the safety of participants per stratum.
Contingency analysis of EudraVigilance data base by strata. Mosaic Plot



Source: Figure CS137 in Statistical Report CS, available on www.efgcp.be/ICREL > Report

57% of the Top15 companies, 50% of the Top100 and 40% of the "beyond Top 100" thought that the implementation of the EudraVigilance database did not increase the safety of study participants. The differences were not significant.

Open questions on Strengths, Weaknesses and Proposed Changes to the CTD

At the end of the questionnaire the respondents received an opportunity to express their opinion on strengths and weaknesses of the clinical trials legislation and to make suggestions for improvements. The main comments can be summarised in the following way (number of responses are provided in brackets):

Strengths (count)
- Predictable, fixed time lines (18)
- Consistency within EU – a first step to harmonisation (13)
- Harmonisation of procedures: similar requirements and documentation across EU (11)
- Clear framework bringing all MS to the same level (9)
- IMPD – common set-up of scientific documents (6)
- One consistent CT approval system across Europe – common application form (6)
- Parallel review by CA and EC (5)

Weaknesses (count)
- Lack of harmonisation of procedures between Member States (30)
  - Ethics Committees (12)
  - CAs (7)
  - SUSAR reporting and ASR (6)

- Burden in administration (12)
- Different CTA dossier requirements in different MS (12)
- Increase of substantial amendments due to unclear, too broad definition (10)
- Non-respect of time lines (8)

Proposed Changes (count)

- Single CTA in EU for multi-national CTs (9)
  - Central authorisation (5)
  - Mutual recognition (4)
- Regulation replacing national implications of CTD requirements (8)
- Simplification, harmonisation of procedures (7)
- Harmonisation of EC applications, time lines, decision criteria between MS (5)
- Single CTA dossier for multi-national CTs (4)
- Better definition of IMP (4)

Non-Commercial Sponsors

Statistical Methodology

Sampling process

In order to identify NCSs all over EU, the more reliable database would have been the EudraCT database. The access to it was denied and the questionnaire was therefore sent to 280 organisations recognized as non-commercial sponsors according to the NIH clinical trials repository "clinicaltrials.gov". The initial sample frame was not achieved because of the difficulty to identify contact in all selected NCS organisations. The reasons were time pressure, limited human resources and limitation also due to the great variety of languages used in the EU-27. Spontaneous participation was encouraged through broad advertising e.g. web sites, newsletters, and other types of publications.

The survey was open to NCSs from 1 June 2008 until 30 September 2008. 106 completed questionnaires were received from various European countries. 44% came from big organisations, 39% from medium and 12% from small organisations, according to the *a priori* stratification. Spontaneous participations were received from 11 organisations. After evaluation, 100 were considered as eligible, 6 not eligible. From those, 4 questionnaires were considered as non-eligible since they were from organisations stating that they were not sponsors of clinical trials, 2 questionnaires were submitted by organisations from a non-EU country: Switzerland. The overall response rate was of 38% but several countries were above average e.g. France, Belgium and UK with respectively 73%, 58% and 50% response rates.

Table 59: Response rate per country

Country	Sent	Answered	%
United Kingdom	36	18	50
France	22	16	73
Germany	43	13	30
Spain	62	12	19
Italy	39	12	31
Denmark	19	7	37
Belgium	12	7	58
The Netherlands	14	4	29
Austria	5	2	40
Finland	5	2	40
Greece	5	2	40
Poland	5	2	40
Ireland	4	2	50
Czech Rep.	2	2	100
Sweden	2	2	100
Switzerland	0	2	
Luxembourg	1	1	100
Bulgaria	1	0	0
Hungary	1	0	0

Country	Sent	Answered	%
Romania	1	0	0
Slovenia	1	0	0
Total	**280**	**106**	**38**

Source: Table NCS 6 in Statistical Report NCS, available on www.efgcp.be/ICREL > Report

Numerous reminders were sent to the 185 non-responding organisations. 36 organisations specified their main reason for non-responding. According to this small sample, the main reason for non-responding was that these organisations were wrongly identified as sponsor. The second and third reasons were the lack of time and the unavailability of data.

Table 60: Reason for non-responding

Reason	Organisation
Not sponsor	15
Do not have the time	11
Data not available	8
Not sponsor in Europe	2
Total	**36**

Source: Table NCS 8 in Statistical Report NCS, available on www.efgcp.be/ICREL > Report

Results

Results of the NCS questionnaire are presented question by question, in four sub-analyses (when applicable).

1. **Significant change between 2007-2003 (unadjusted and adjusted results)**

The unadjusted results will be presented first as they were directly based on the data collected in the survey while adjusted results gave more weight to under-represented categories (strata) and less weight to over-represented strata to balance observations according to their representation (weight) within the population. The adjusted results will be presented if they were significant or if the related unadjusted results showed significant changes. The full results of the analysis are available in the Appendix NCS

2. **Relationship between the change in 2007 and the *a priori* stratification**

Potential relationship was analysed between the changes in 2007 and the stratification according to the organisation size (big, medium and small).

3. **Relationship between the change in 2007 and the level of activity in 2003**

The absolute and the relative changes in 2007 will be discussed. The relative changes were computed by dividing the absolute change in 2007 by the baseline in 2003.

4. **Relationship between the change in 2007 and the overall level of activity in 2003**

A classification based on the overall level of activity in 2003 was implemented. Two criteria were used: the total number of approved clinical studies and the total number of centres that were involved in 2003. Five classes of overall activity level were therefore defined (the highest possible level of activity was retained for each institution):

- Level 1: Very active in 2003: > 45 studies (last decile) **or** > 125 centres (last decile)
- Level 2: Active in 2003: > 14 studies (last quartile) **or** > 50 centres (last quartile)

- Level 3: Moderately active in 2003: > 6 studies (median) **or** > 19 centres (median)
- Level 4: Slightly active in 2003: > 2 studies (first quartile) **or** > 3 centres (first quartile)
- Level 5: poorly active in 2003: ≤ 2 studies **and** ≤ 3 centres.

Areas of activity

The main areas of activities of the respondents were multi-disciplinary (43%) and oncology / haematology (42%). Organisations reporting multi-disciplinary areas of activities were supposed to be active in more than one of the areas of activities listed in the table below.

Table 61: Area of activity

	Frequency	%
Multi-disciplinary	46	43
Oncology / Haematology	45	42
Immunology and Infectious diseases	4	4
Other	4	4
Missing information	4	4
Gastroenterology	2	2
Psychiatry/ Neurology/ Pain	1	1
Total	**106**	**100**

Source: Figure NCS 1 in Statistical Report NCS, available on www.efgcp.be/ICREL > Report

How many Clinical Trial Applications (CTAs) on medicinal products did you submit to a Competent Authority and/or an Ethics Committee(s) in EU countries in 2007? (Question 1 in the Questionnaire to NCSs)

Data were available from 93 respondents. The number of submitted CTAs in 2007 ranged from 0 to 74, with a median of 4 CTAs per respondent. Respondents classified as big sponsor submitted on average more CTAs (Table NCS12, Appendix NCS).

Table 62: CTAs submitted in 2007 per NCS

Quantiles		CTA
100%	maximum	74
75%	quartile	8
50%	median	4
25%	quartile	1

Source: Figure NCS 2 in Statistical Report NCS, available on www.efgcp.be/ICREL > Report

How many of your clinical studies, as sponsor (medicinal products, or other) or as institution hosting investigator/sponsor or the coordinating investigator in non-commercial studies (medicinal products, medical devices, surgery, radiotherapy, diagnostic, observational studies, non-interventional clinical studies) were approved by a Competent Authority and/or received a favourable opinion from Ethics Committee(s) in Europe, for the years 2003 and 2007? (Question 2)

The number of available matched data was low and corresponded to less than 50% of the respondents except regarding the number of trials on medicinal products (75%). The available data

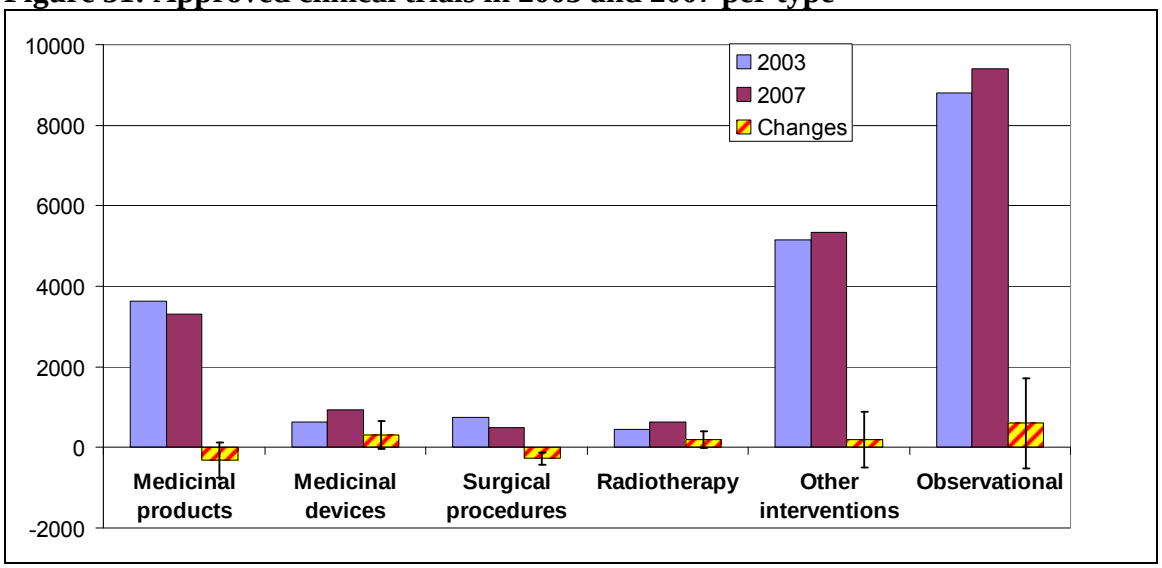
was very heterogeneous and therefore the standard errors were large. Depending on the type of trial, increases or decreases of the total numbers of trials were reported but none of those changes were significant according to unadjusted results. Similarly, the adjusted results were non significant with the exception of CTs on medical devices for which an increase of +21.34% was observed but at the limit of significance (p = 0.043). All types of trials were also pooled together but there were no significant changes according to both unadjusted and adjusted results.

Table 63: Approved clinical trials in 2003 and 2007 per type

Unadjusted data	Matched data	2003	2007	Change	%	SE
Medicinal products	79	3625	3309	-316	-9%	442
Medical devices	35	633	941	308	49%	348
Surgical procedures	34	755	482	-273	-36%	151
Radiotherapy	39	438	639	201	46%	209
Other interventions	42	5145	5331	186	4%	691
Observational	43	8796	9393	597	7%	1120

Source: Tables NCS 15, 21, 26, 30, 34, 38 in Statistical Report NCS, available on www.efgcp.be/ICREL > Report

Figure 51: Approved clinical trials in 2003 and 2007 per type



Source: Tables NCS 15, 21, 26, 30, 34, 38 in Statistical Report NCS, available on www.efgcp.be/ICREL > Report

A relation was observed for the CTs on medicinal products between the magnitude and the sign of change in 2007 and the strata. The mean change over time was not the same (not homogeneous) across strata (countries and size of institutions).

A highly significant negative relationship appeared between the **level of activity in 2003** and the magnitude of the absolute changes of CTs on medicinal product (p <0.0001): the larger the number of CTs in 2003, the larger the decrease in 2007. This observation was also valid for the CTs on surgery (p < 0.0001), CTs on radiotherapy (p = 0.0371) but it was not significant for the other types of CTs. To study the relation between relative changes in 2007 and the number of CTs in 2003 remained not possible since there were too few data.

The analysis of the relationship between the changes in the number of CTs and the **overall level of activity in 2003** (1 = highly active, 5 = very small activity) showed the change in the number of CTs on medicinal product to be significantly related to the activity level (p = 0.0018): the most

active institutions in 2003 were associated with decreases in the number of CTs for medicinal products approved in 2007. On the other hand, the less active institutions in 2003 showed an increase of the number of CTs with medicinal products in 2007. The analysis didn't show any relationship for the other types of CTs.

Focus on specific categories of clinical trials on medicinal products (Question 2)

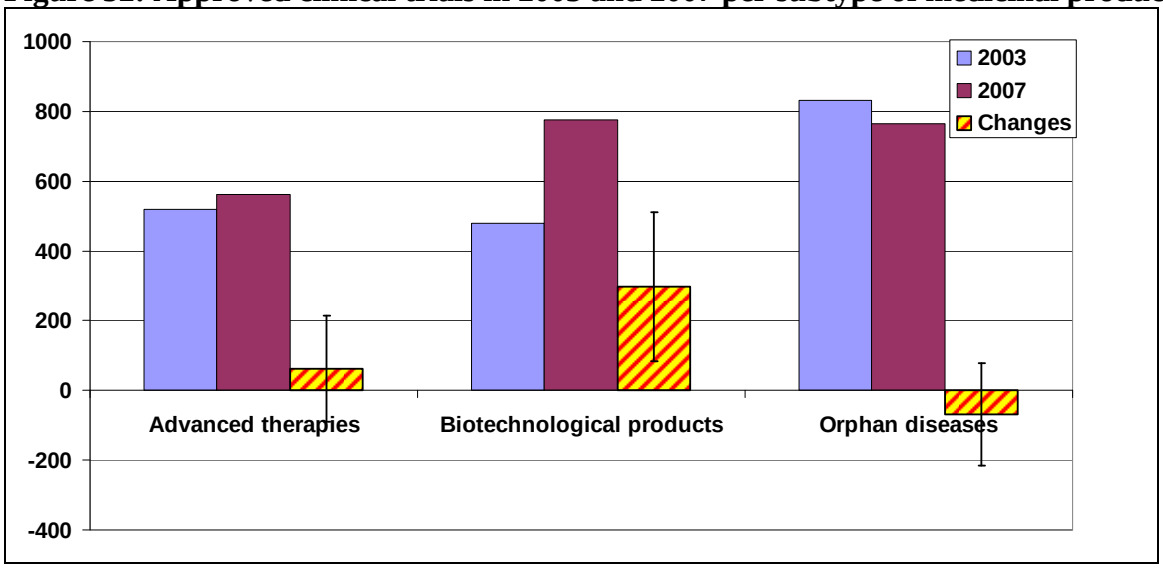
The number of available matched data was low and corresponded to less than 50% of the respondents. The available data were very heterogeneous and therefore the standard errors were large. Depending on the type of trial, increases or decreases of the numbers of subtypes of medicinal products trials were reported but none of those changes were significant according to both non-adjusted and adjusted results. In addition, the pooling of the number of CTs on orphan drugs, advanced therapy and biotechnological products led to a non significant increase.

Table 64: Approved clinical trials in 2003 and 2007 per subtype of medicinal products

Unadjusted data	Matched data	2003	2007	Change	%	SE
Advanced therapies	44	520	563	63	12%	152
Biotechnological products	42	479	776	297	62%	213
Orphan diseases	42	833	764	-69	-8%	146

Source: Tables NCS 46, 50, 54 in Statistical Report NCS, available on www.efgcp.be/ICREL > Report

Figure 52: Approved clinical trials in 2003 and 2007 per subtype of medicinal products



Source: Tables NCS 46, 50, 54 in Statistical Report NCS, available on www.efgcp.be/ICREL > Report

No relationship between the change in 2007 and the stratification, the activity in 2003, and the overall level of activity in 2003 was shown.

How many approved clinical trials (multi-national trials, national multi-centre trials, mono-centre trials) on medicinal products did you sponsor in Europe, for the years 2003 and 2007? (Question 3)

The number of available matched data was low and corresponded to less than 50% of the respondents except the number of national multi-centre CTs (59% of the respondents). The

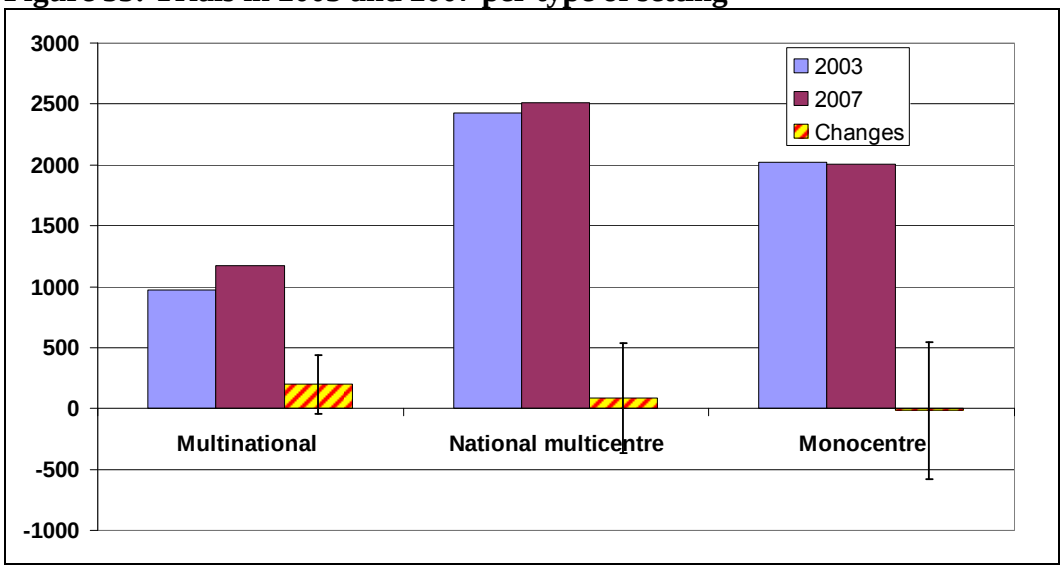
available data were very heterogeneous and therefore the standard errors were large. Depending on the type of trial, increases or decreases of the total numbers of trials were reported but none of those changes were significant according to both unadjusted and adjusted results.

Table 65: Approved clinical trials in 2003 and 2007 per type of setting

Unadjusted data	Matched data	2003	2007	Change	%	SE
Multi-national	50	984	1167	183	19%	239
National multi-centre	63	2455	2544	89	4%	456
Mono-centre	47	2049	2034	-15	-1%	561

Source: Tables NCS 61, 65, 69 in Statistical Report NCS, available on www.efgcp.be/ICREL > Report

Figure 53: Trials in 2003 and 2007 per type of setting



Source: Tables NCS 61, 65, 69 in Statistical Report NCS, available on www.efgcp.be/ICREL > Report

No relationship between the change in 2007 and the **stratification** according to the NCS size was shown.

Significant relationships between the **number of CTs in 2003** and the magnitude of the absolute change in 2007 were observed in multi-national (p = 0.0024), national multi-centre CTs (p = 0.0029) and mono-centre CTs (p = 0.0001): the most active NCSs in 2003 tended to report a larger decrease in number of CTs approved in 2007. Regarding the relative changes in 2007, no relationship was observed with regard to multi-national trials but significant relationship was observed for the national multi-centre (p = 0.0097) and mono-centre CTs (p = 0.0071): the larger the number of CTs approved in 2003, the larger the relative decrease or the smaller the number of CTs in 2003, the larger the relative increase. The relative changes had to be considered with caution since numerous institutions with no CT in 2003 were discarded in order to avoid the undetermined relative change (0/0) or infinite relative change (number/0).

The relationship between the change in the number of CTs approved in 2007 and the **overall level of activity** in 2003 (1 = highly active, 5 = very small activity) was significant for multi-national CTs (p = 0.048) and national multi-centre CTs (p = 0.0259): the most active institutions in 2003 tended to report larger decrease (or smaller increase) in 2007. No relationship was observed with respect to the mono-centre CTs.

How many European centres and countries were involved in your clinical trials on medicinal products, initiated in 2003 and 2007? (Question 4)

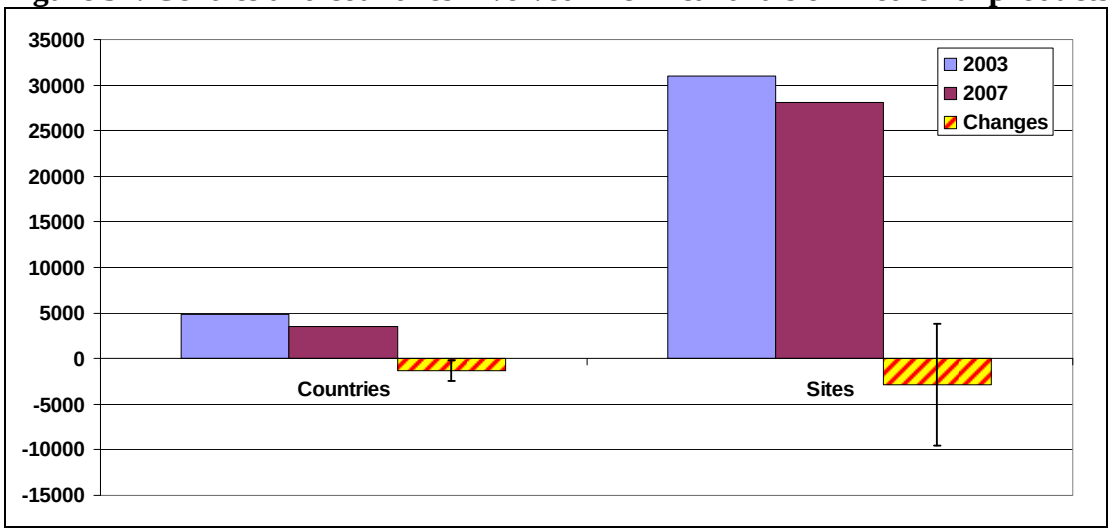
Matched data were available for at least 60% of the respondents. The available data were very heterogeneous. A decrease in the number of countries and sites involved in clinical trials on medicinal products was observed. None of the changes were significant according to non-adjusted and adjusted results. Centres and countries were counted several times when involved in different trials.

Table 66: Centres and countries involved in clinical trials on medicinal products

Unadjusted data	Matched data	2003	2007	Change	%	SE
Countries	70	4911	3605	-1306	-27%	1154
Sites	64	31349	28428	-2922	-9%	6757

Source: Tables NCS 73, 77 in Statistical Report NCS, available on www.efgcp.be/ICREL > Report

Figure 54: Centres and countries involved in clinical trials on medicinal products



Source: Tables NCS 73, 77 in Statistical Report NCS, available on www.efgcp.be/ICREL > Report

No relationship between the number of countries and sites in 2007 and the **stratification** according to NCS size and country was shown.

Significant relationships were observed between the **number of sites or countries involved in 2003** and the absolute changes in 2007 with regards to the number of involved sites ($p < 0.0001$) and the number of involved countries ($p < 0.0001$): the larger the number in 2003, the bigger the decrease in 2007. Similar relationships were shown with the relative changes with a significant negative monotonic relationship with respect to centres ($p = 0.0002$) and countries ($p < 0.0001$). This had to be taken with caution since the institutions reporting very few centres or countries in 2003 had a major leverage effect.

The analysis of the relationship between the change in the number of involved sites and countries and the **overall level** of activity in 2003 (1 = highly active, 5 = very small activity) showed that the classes with the largest overall activity in 2003 experienced the largest decrease in number of sites ($p<0.0001$) or in the number of involved countries ($p = 0.0062$).

How many patients were recruited in clinical studies in Europe, for the years 2003 and 2007? (Question 5)

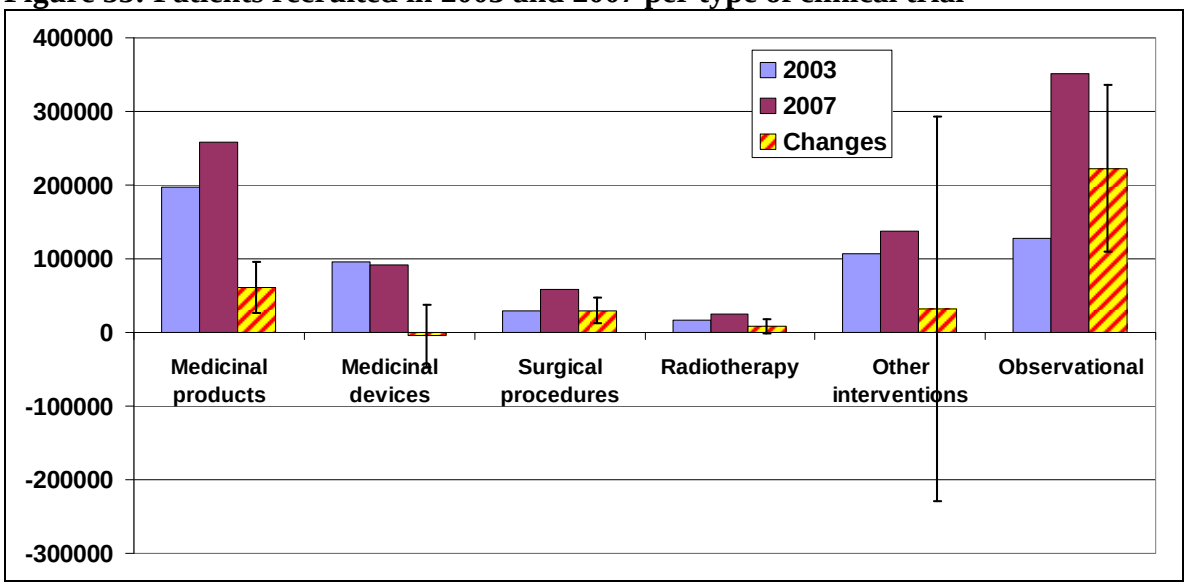
A very limited number of matched data was available and they were very heterogeneous. In most of the types of clinical trials, an increase was observed in the number of recruited patients. According to unadjusted and adjusted results, none of the changes was significant because of the large standard errors although the changes related to trials on medicinal products and observational studies were almost significant. Respondents were asked to provide figures for their ongoing and the newly authorised trials since it was not realistic to ask sponsors to differentiate their trials. In addition, the pooling of the numbers of patients recruited in all types of CTs led to a non significant increase of 15%.

Table 67: Patients recruited in 2003 and 2007 per type of clinical trial

Unadjusted data	Matched data	2003	2007	Change	%	SE
Medicinal products	56	199614	270828	61952	31%	35098
Medical devices	22	96822	92317	-4505	-5%	43127
Surgical procedures	24	29467	59609	30141	102%	17277
Radiotherapy	27	17444	25464	8019	46%	9690
Other interventions	33	107815	139641	31827	30%	261186
Observational	32	130033	355630	225597	173%	115133

Source: Tables NCS 81, 85, 89, 93, 97, 101 in Statistical Report NCS, available on www.efgcp.be/ICREL > Report

Figure 55: Patients recruited in 2003 and 2007 per type of clinical trial



Source: Tables NCS 81, 85, 89, 93, 97, 101 in Statistical Report NCS, available on www.efgcp.be/ICREL > Report

No relationship was observed between the change in 2007 and the stratification factor levels, the activity in 2003, and the overall level of activity.

What was the average time between the protocol finalisation and the inclusion of the first patient? What was the average time between the moment when you, as sponsor, released a (substantial) amendment and when it was implemented at the first site in Europe for the years 2003 and 2007? (Question 6)

A significant increase (p = 0.0391) of 1 month (34 days) was observed from the unadjusted results regarding the average period of time taken from the protocol finalisation until the first patient entry

(matched data available for 58% of the respondents). The adjusted results confirmed this figure and were also significant (+33%, p = 0.028).

A non-significant increase of the time needed for the amendment implementation (limited matched data availability) was observed from the unadjusted results; however the adjusted results showed a significant increase (p = 0.0236) of 23% (average per institution in 2003: 39 days).

Table 68: Timelines to 1st patient-in and amendment implementation

Unadjusted data	Matched data	Average/ organisation 2003 (day)	Change (%)	SE
1st patient in	61	144	+34 (24)	16
Amendment	40	41	+5.25 (13)	3.83

Source: Tables NCS 109, 113 in Statistical Report NCS, available on www.efgcp.be/ICREL > Report

No relationship was observed between the change in 2007 regarding the time needed for the 1st patient-in, the time needed for the implementation of amendment and the **stratification** according to NCS size.

The relationship between **the level of activity in 2003** in term of time lines and the absolute change in 2007 was not significant for the time needed for the 1st patient-in but it was for the time needed for the amendment implementation (p = 0.0157): the longer the average time in 2003, the larger the decrease in 2007. A significant linear negative relationship and significant negative monotonic relationship were observed between the relative change in 2007 and the time lines in 2003 for the time needed for the 1st patient-in (p = 0.0139) and the time for amendment implementation (p= 0.0167). The longer the time lines were in 2003, the larger was the relative decrease or the shorter the time lines were in 2003, the higher was the relative increase.

No relationship was observed between the time needed for the 1st patient-in, the time needed for the implementation of amendment and the **overall level of activity**.

How many full-time equivalents[22] (as internal and external resources) worked on the following tasks you sponsored for the years 2003 and 2007? (Question 7)

Matched data were available for 60% of the respondents regarding the regulatory and trial coordination tasks, 52% of the respondents for the pharmacovigilance and QA functions. The obtained data were quite homogeneous. According to unadjusted results, a significant general increase for all types of sponsor tasks was observed: for regulatory related tasks (+89%, p < 0.00001), trial coordination tasks (+60%, p < 0.00001), pharmacovigilance tasks (+88%, p < 0.0001) and especially quality assurance tasks (+115%, p = 0.00016).

The adjusted results corroborated those figures: a significant increase was observed for the regulatory related tasks (+98%, p < 0.00001), for the trial coordination tasks (+76%, p < 0.0001), for quality assurance related tasks (+77%, p = 0.005) but a non-significant increase for pharmacovigilance related tasks (+ 47%, p= 0.09).

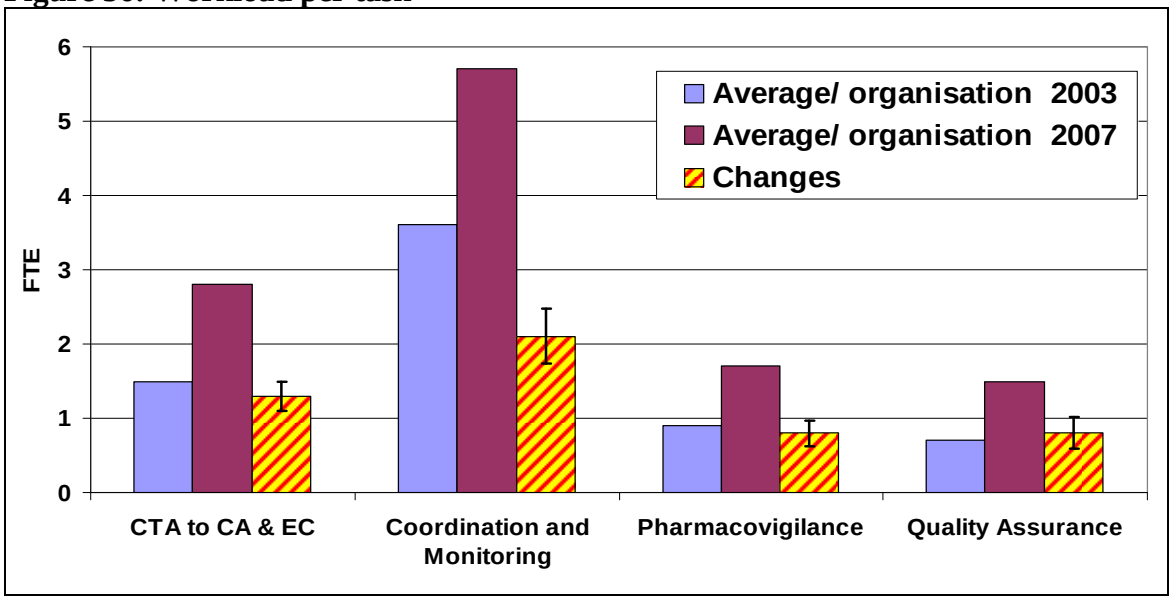
[22] **Full-time equivalent** (FTE): Tool to measure the workforce required in a project. One FTE is one full-time position or two half-time positions, etc. If a task requires 2.5 days per week to be realised, it will require one half-time employee or half the time of one full-time employee; this is 0.5 FTE. If a task requires three full-time people or six half-time people we talk about 3 FTEs.

Table 69: Workload per task

Unadjusted data	Matched data	Average / organisation 2003 (FTEs)	Change (%)	SE
Administrative tasks/CTA	68	1.5	+1.3 (89)	0.2
Coordination and Monitoring	63	3.6	+2.1 (60)	0.37
Pharmacovigilance	58	0.9	+0.8 (88)	0.17
Quality Assurance	55	0.8	+0.8 (115)	0.21

Source: Tables NCS 117, 121, 125, 129 in Statistical Report NCS, available on www.efgcp.be/ICREL > Report

Figure 56: Workload per task



Source: Tables NCS 117, 121, 125, 129 in Statistical Report NCS, available on www.efgcp.be/ICREL > Report

No relationship was observed between the change in 2007 regarding the workload and the **stratification** according to NCS' country and size.

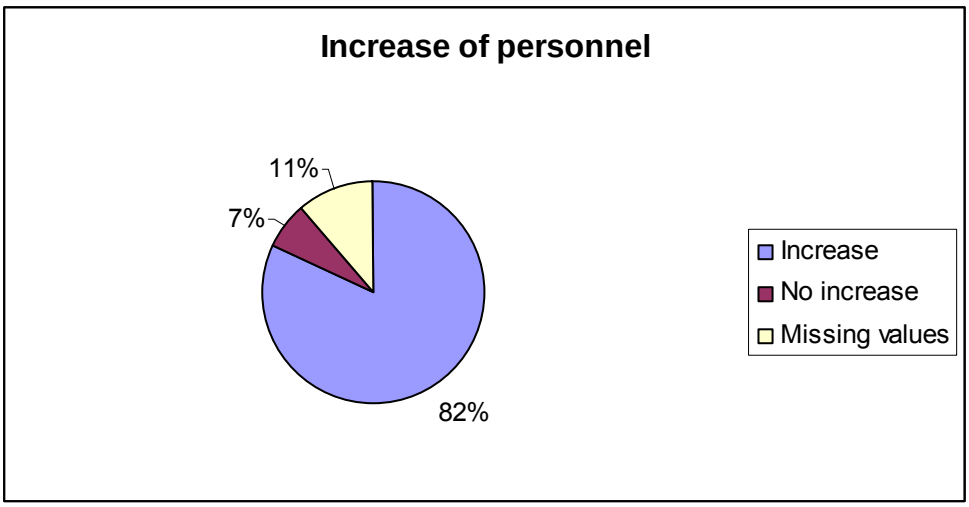
The relationship between the **level of activity in 2003** in term of FTE and the absolute changes in 2007 was significant for the regulatory related tasks ($p = 0.018$), and for the trial coordination tasks ($p = 0.04$): the increase in the workload in 2007 was a little larger for institutions having reported more FTEs in 2003. No relationship was observed for the pharmacovigilance tasks and quality assurance tasks. Significant relationship between relative changes in 2007 and the number of FTEs in 2003 was observed for the regulatory related tasks ($p = 0.0016$) and pharmacovigilance tasks ($p = 0.0161$): the institutions having reported less FTEs in 2003 reported bigger increases. No significant relationship was observed for trial coordination tasks and quality assurance tasks. Those relative changes had to be considered with caution since they were based on few data.

The analysis of the relationship between the change in the number of FTEs and the **overall level of activity in 2003** (1 = highly active, 5 = very small activity) showed a relation at the limit of significance ($p = 0.0511$) for the regulatory related tasks and for the trial coordination tasks ($p = 0.0034$): the institutions with the largest overall activity in 2003 tended to have the largest increase in term of FTEs. No relationship was seen for the pharmacovigilance tasks nor for the quality assurance tasks.

According to your experience, has the personnel required for preparation, management and supervision of each study increased between 2003 and 2007? (Question 8)

Data were available for 85 organisations. The answer was positive for 92% of respondents.

Figure 57: Perceived increase of personnel

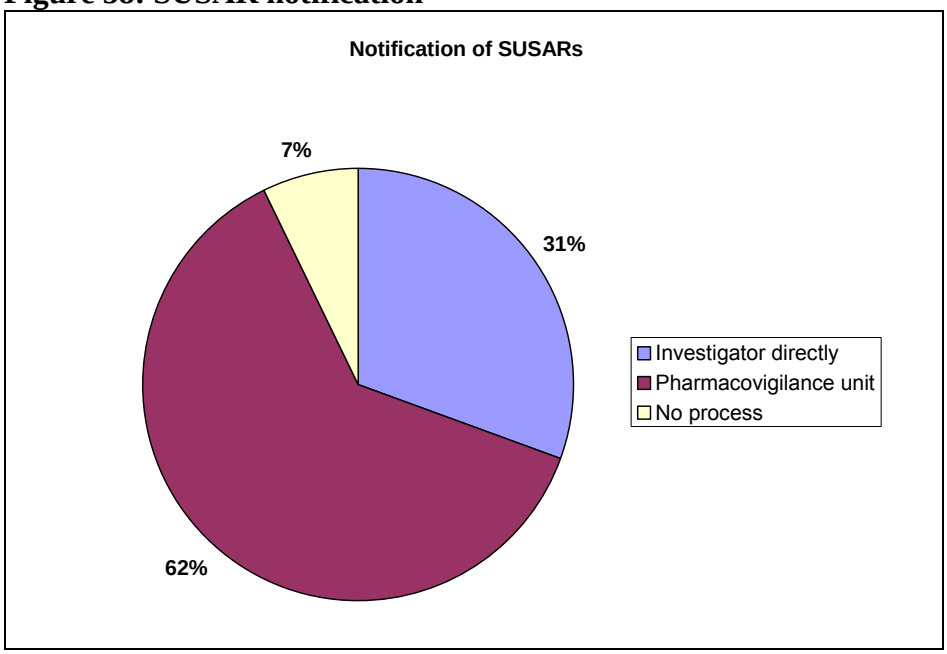


Source: Figure NCS 93 in Statistical Report NCS, available on www.efgcp.be/ICREL > Report

How do you report Suspected Unexpected Serious Adverse Reactions (SUSARs) to your Competent Authority? (Question 9)

Data were available for 98 organisations. The majority of respondents were managing SUSARs through a central pharmacovigilance unit.

Figure 58: SUSAR notification



Source: Figure NCS 94 in Statistical Report NCS, available on www.efgcp.be/ICREL > Report

What was the yearly overall subject indemnity insurance cost for clinical trials in Europe for the years 2003 and 2007? (Question 10)

There was limited availability of matched data and the available data were very heterogeneous. A non-significant increase (+20%) of the average per organisation of the yearly overall subject insurance costs was observed. The adjusted results were non significant.

No significant relationship was observed between the change over time and the stratification according to the size of NCSs and the overall activity.

Table 70: Subject indemnity insurance cost

	Matched data	Average / organisation 2003	Change (%)	SE
Non-Adjusted	49	36,698 €	+7,375 (20)	47,834

Source: Table NCS 136 in Statistical Report NCS, available on www.efgcp.be/ICREL > Report

What were the yearly costs of providing marketed IMPs and the devices used for their administration free of charge, for clinical trials in Europe, for the years 2003 and 2007? (Question 11)

There was very limited availability of matched data (18% of the respondents) and the available data were heterogeneous. A non-significant decrease (-34%) of the average per organisation of the IMP costs was observed from the unadjusted results. The adjusted results were non significant.

Table 71: Cost of IMPs and devices

	Matched data	Average/organisation 2003	Change (%)	SE
Non-Adjusted	19	309,054 €	-104,566 (34)	123,964

Source: Table NCS 140 in Statistical Report NCS, available on www.efgcp.be/ICREL > Report

Open question: What is your opinion on the impact of the European Union Clinical Trials Directive: strengths, weaknesses and suggested changes? (Question 12)

The top 10 of the answers regarding the perceived impact of the Clinical Trials Directive is given below. There was more feedback received regarding the weaknesses of the CTD and the proposed changes than regarding the strengths of the CTD. Overall, the CTD was perceived as having introduced a partial harmonisation of procedures but this positive effect was heavily counterbalanced by the general lack of harmonisation, the increase of the administrative burden and related costs, and the negative impact on academic sponsors. Respondents proposed several changes e.g. the simplification and the harmonisation of procedures, to simplify the requirements for non-commercial sponsors and to develop a risk-based approach reflecting the clinical trial hazards.

Strengths (count)

- Partial harmonisation (37)
- Better protection of patients' interests/safety (13)
- Increase the quality of research (10)
- GCP awareness and compliance (9)
- Predictable, fixed time lines (9)
- Enforcement of education of clinicians, EC members, etc. (7)
- More transparency of clinical trials (7)

- Central EMEA registration EudraCT database (7)
- More control over clinical trials (7)
- Higher reliability of CT results and data quality (7)

Weaknesses (count)
- Lack of harmonisation of procedures (36)
- Administrative burden (36)
- Not adapted to international Investigator-driven trials (33)
- Increase in time and costs (29)
- No risk-based approach (27)
- Lack of supportive infrastructure for NCS (15)
- Increase in workload (13)
- Lack of legal awareness/education (8)
- Single sponsorship (7)
- No proof that patients' safety has improved (5)
- On-site monitoring and inspections (5)
- Restrictive scope (5)

Proposed changes (count)
- Simplification/Harmonisation of procedures (26)
- Simplified requirements for non-commercial researchers (25)
- Risk-based approach (25)
- Financial support/ infrastructure (11)
- Multi-sponsorship (9)
- Better definition of terms/concepts (IMP, Substantial amendment, etc.) (9)
- No Free supply of IMP (7)
- Simplify and harmonise safety reporting requirements (6)
- Single CA application in EU for multinational CT (6)
- Unique European database of clinical trials, publicly available (5)

Non IMP Trials

Impact on clinical research other than clinical trials on medicinal products

Rationale

Clinical research other than clinical trials on medicinal products is a major part of the clinical research conducted by academic institutions. Although it remains outside the scope of the CTD, it may be affected by the changes in national legislations triggered by the implementation of the CTD. As national legislations are usually drafted by the Ministries of Health, their scope is often broader than the scope of the CTD, and they are in some countries even designed to protect participants in all the categories of clinical research. The objective of this Work Package was to provide metrics before and after the implementation of the CTD (number of studies, number of patients) for non-IMP studies.

This was assessed with the support of relevant stakeholders and the comparison was done between years 2003 and 2007. The targeted questions regarding clinical studies other than clinical trials were included in the questionnaires sent to non-commercial sponsors and to ethics committees but not to the competent authorities as in most countries such studies are not taken into account by competent authorities.
The common definitions of categories of clinical research other than clinical trials on medicinal products were those obtained from the survey developed by ECRIN:

- clinical trials on **medical devices**
- clinical trials on **surgical procedures**
- clinical trials on **radiotherapy**
- other (non therapeutic) interventional clinical studies, diagnostic procedures, prevention, incl. biomarkers genetic markers, imaging
- non-interventional /observational **studies**

Results

Number of clinical studies sponsored by non-commercial sponsors approved by competent authorities and/or that received a favourable opinion from ethics committees.

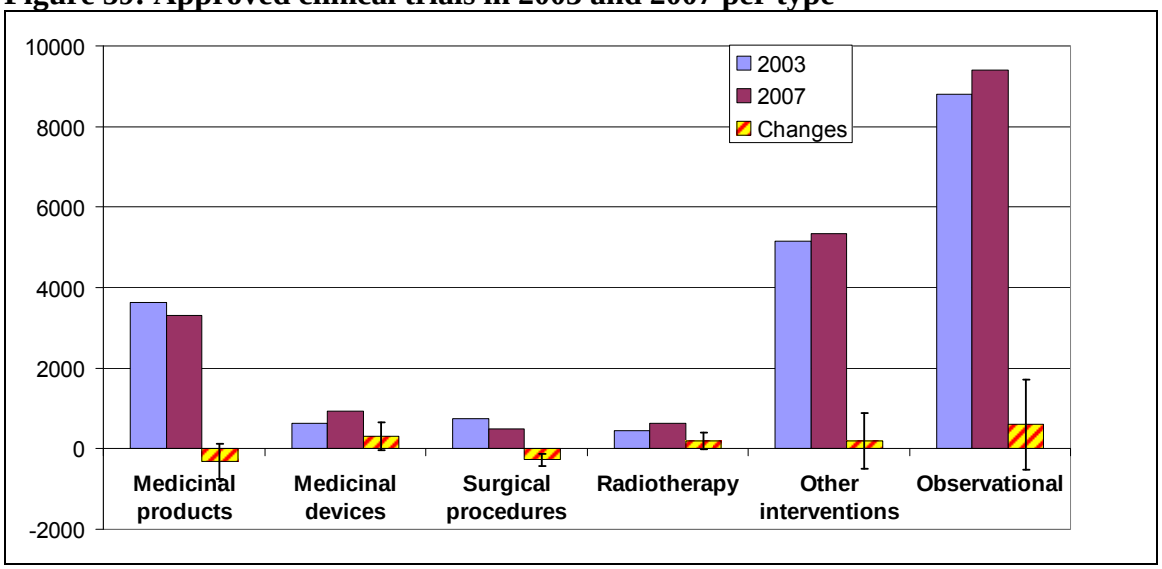
The results presented are those provided by non-commercial sponsors.

Table 72: Approved clinical trials in 2003 and 2007 per type

Unadjusted data	Matched data	2003	2007	Change	%	SE
Medicinal products	78	3803	3470	-333	-9%	453
Medical devices	34	641	910	269	42%	352
Surgical procedures	33	767	490	-277	-36%	153
Radiotherapy	38	444	647	203	46%	212
Other interventions	41	5212	5401	189	4%	700
Observational	43	8910	9515	605	7%	1135

Sources: Tables NCS 15, 21, 26, 30, 34, 38 in Statistical Report NCS, available on www.efgcp.be/ICREL > Report

Figure 59: Approved clinical trials in 2003 and 2007 per type



Sources: Tables NCS 15, 21, 26, 30, 34, 38 in Statistical Report NCS, available on www.efgcp.be/ICREL > Report

For the clinical studies other than clinical trials, the number of available data was low and corresponded to less than 50% of the respondents. The data were very heterogeneous and the standard errors were large. None of the changes observed were significant whether unadjusted or adjusted results were taken into account.

Number of patient recruited in clinical studies sponsored by non-commercial sponsors

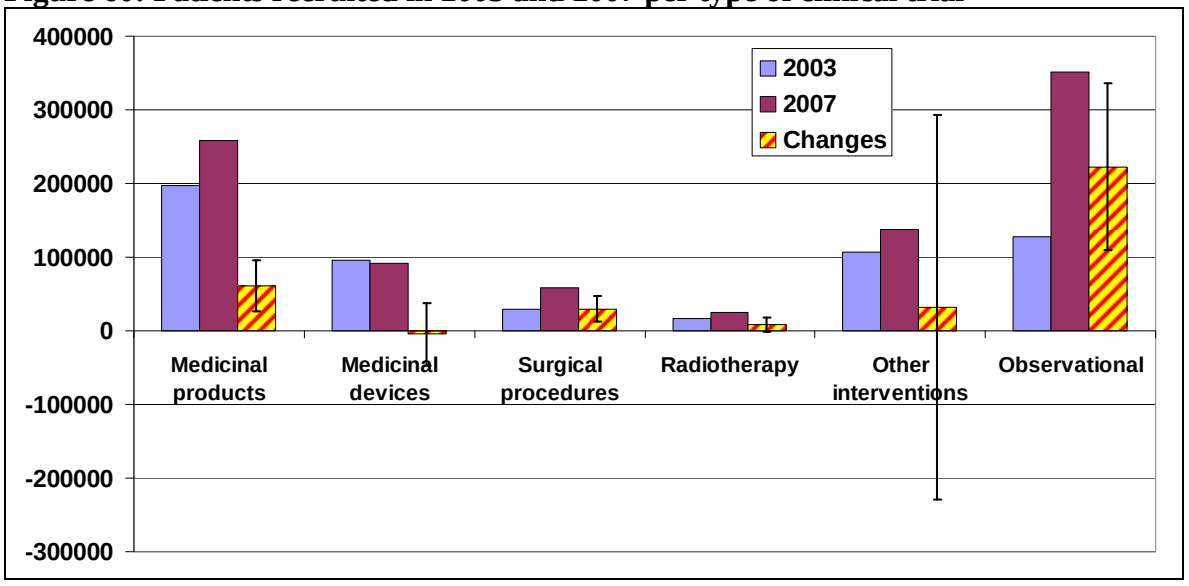
The results presented are those provided by non-commercial sponsors.

Table 73: Patients recruited in 2003 and 2007 per type of clinical trial

Unadjusted data	Matched data	2003	2007	Change	%	SE
Medicinal products	56	199614	270828	61952	31%	35098
Medicinal devices	22	96822	92317	-4505	-5%	43127
Surgical procedures	24	29467	59609	30141	102%	17277
Radiotherapy	27	17444	25464	8019	46%	9690
Other interventions	33	107815	139641	31827	30%	261186
Observational	32	130033	355630	225597	173%	115133

Sources: Tables NCS 81, 85, 89, 93, 97, 101 in Statistical Report NCS, available on www.efgcp.be/ICREL > Report

Figure 60: Patients recruited in 2003 and 2007 per type of clinical trial



Sources: Tables NCS 81, 85, 89, 93, 97, 101 in Statistical Report NCS, available on www.efgcp.be/ICREL > Report

Number of applications submitted to ethics committees

The results presented are those provided by the Ethics Committees.
Most of the responding ethics committees had competence for all categories of clinical research (see Figure 29: Categories of clinical research for which EC has competence) and received applications for clinical studies other than clinical trials on medicinal products.

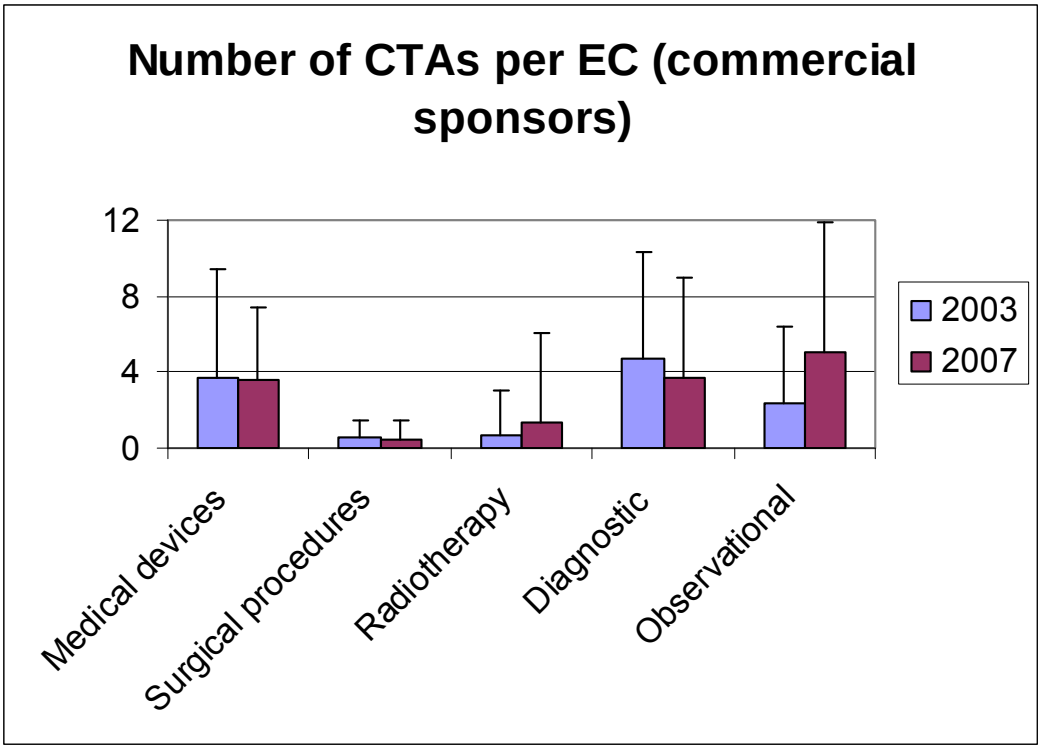
a) Number of applications for commercially sponsored studies submitted to ethics committees (source of data: ethics committees section)

Table 74: Commercially sponsored studies

Type of clinical research	Matched data	2003	2007	Change (%)
Clinical trials on medical devices	22	3.68 (SD= 5.71)	3.59 (SD=3.84)	-2.46
Clinical trials on surgical procedures	20	0.55(SD= 0.95)	0.45 (SD=1.05)	-18.18
Clinical trials on radiotherapy	18	0.67(SD=2.38)	1.33 (SD=4.69)	100
Other (non therapeutic) interventional clinical studies, diagnostic procedures, prevention, incl. biomarkers genetic markers, imaging	19	4.68(SD=5.66)	3.68 (SD=5.26)	-21.34
Non-interventional / observational studies	22	2.41 (SD=4.03)	5 (SD=6.85)	107.54

Source: Tables EC37, EC39, EC41, EC43, EC45 from Statistical Report EC available on www.efgcp.be/ICREL > Report

Figure 61: Number of commercial sponsor CTAs per Ethics Committee



Source: Tables EC37, EC39, EC41, EC43, EC45 from Statistical Report EC available on www.efgcp.be/ICREL > Report

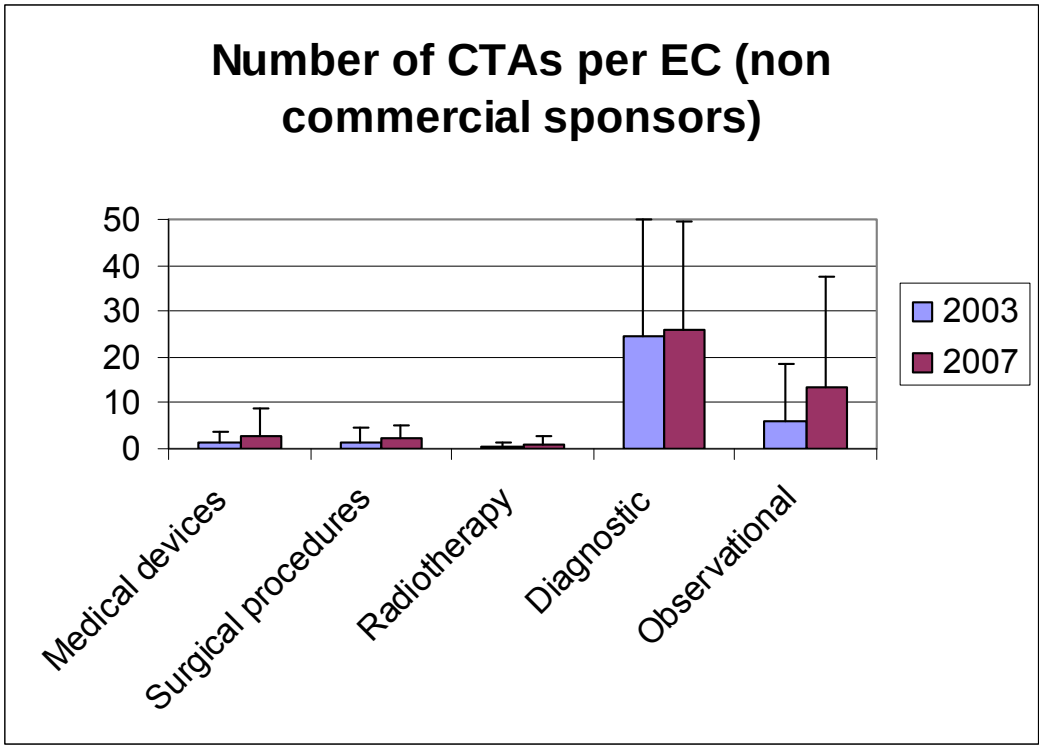
b) Number of applications for non-commercial sponsor-driven studies submitted to ethics committees (source of data: ethics committees)

Table 75: Non-commercial sponsor-driven studies

Type of clinical research	Matched data	2003	2007	Change (%)
Clinical trials on medical devices	19	1.32 (SD=2.16)	2.73 (SD=6.18)	108
Clinical trials on surgical procedures	18	1.33 (SD=3.11)	2.16 (SD=2.75)	62.5
Clinical trials on radiotherapy	15	0.6 (SD=0.99)	0.8 (SD=1.94)	33.3
Other (non therapeutic) interventional clinical studies, diagnostic procedures, prevention, incl. biomarkers genetic markers, imaging	23	24.61 (SD= 25.47)	26.13 (SD= 23.35)	6.18
Non-interventional / observational studies	20	6.25 (SD=12.3)	13.5 (SD=24.09)	116

Source: Tables EC51, EC 53, EC55, EC57, EC59 Statistical Report EC available on www.efgcp.be/ICREL > Report

Table 76: Number of non-commercial sponsor CTAs per Ethics Committee



Source: EC51, Tables EC 53, EC55, EC57, EC59 Statistical Report EC available on www.efgcp.be/ICREL > Report

Number of commercially sponsored clinical studies other than clinical trials on medicinal products approved by a competent authority and/or had received favourable opinion from ethics committees

Although the questionnaire sent to commercial sponsors focused on clinical trials on medicinal products, also information on diagnostic clinical studies and on non interventional / observational studies was collected.

Table 77: Mean number of commercial sponsored clinical studies other than clinical trials on medicinal products

Type of clinical research	2003	2007	Unadjusted change (%)	Adjusted change (%)
Diagnostic studies	0.59	0.55	-7.69	-25.48
Non interventional / observational studies	2.13	3.17	48.98	19.73

Source: Table CS 29 from Statistical Report CS available on www.efgcp.be/ICREL > Report

Main outlines

The assessments were based on only a few matched data. The standard errors were very high and the changes observed were non significant.

For non-commercial sponsors the trend was an increase in the total number of studies except for surgical procedures and an increase in the number of patients recruited for those categories of research but the results were non significant and very heterogeneous.

For the commercial sponsors, there was an increase in the total number of observational studies.

Discussion

The discussion of the survey results took place within the ICREL consortium as well as during the ICREL Results and Discussion Conference on 2 December 2008 in Brussels. The consortium partners – all experts in their field – are presenting their views in the following section of this Final Report.

Discussion Competent Authorities

Study limitations

The CAs survey was designed to describe and characterise the time-course profile of CTAs in the EU over a period (2000-2007). This was felt to be a valid method to evaluate whether the changes of the legal framework for the conduct of clinical trials in Europe and its subsequent implementation in the different member states had an impact (whatever the direction was, positive or negative) on the clinical research activity in the European Union. As any retrospective exercise, the study design presented some limitations that should be properly considered for a correct interpretation of the results provided.

The results were based on a survey questionnaire that was to be completed on a voluntary basis by EU CAs (plus 2 additional non-EU CAs presently integrated in the EU regulatory system: Norway and Iceland). As described in the results, most (all but 3) CAs responded to the survey request, however, a substantial intra- and inter-questionnaire variability was observed regarding the amount and completeness of the information provided. There could be a number of explanations for this fact:

- Firstly, the capability of the CAs to retrieve the requested information was different and depended on the availability of electronic databases and their information structure.
- Secondly, as in any retrospective exercise, the quality and quantity of the information gathered decreased in a backward direction. Consequently, information on all items became richer and probably more reliable over the last 4-5 years of the survey period (2003-2007). This became obvious by the number of countries providing information on each of the years, as well as by the level of questionnaire completion provided over time.
- Last but not least, the variability in the responses raised the question whether the scope of the questionnaire was not too ambitious in relation to the competent authorities' access to the information in the requested format; and their lack of resources to retrieve and report the information, especially for the earlier survey period, may have been a discouraging element for some of the participants.

Since the amount of information increased over time and to ensure optimal exploitation of information received on the time-course of clinical research activity in Europe, indexed data, based on matched analyses were calculated and presented to explain the main results obtained from the survey. Finally, in most of the analyses, years 2003 and 2007 were considered as particularly relevant to assess the changes in the clinical research performance indicators as 2003 was the last year with complete 12 months of information before implementation of the CTD in any member state and 2007 the year where practically all member states had gathered experience with the new systems.

Research performance

Despite the limitations of data availability described above, the received survey information clearly showed that the clinical research activity, assessed by the total number of CTAs in the EU, did not decline over the years investigated in the survey. This development was broadly in line with the development presented by Non-EU CAs used as external control. Overall, the number of CTAs per CA remained around 400 over the study period without major oscillations. Whether this would have been the same without the new legislation could not be determined as there were many other factors than the CTD that could have had an impact on the clinical research activity in the EU during that period. Data received from the EudraCT Database (see Annex IV), presenting total number of CTAs as of 2004, showed a strong increase from a low level in 2004 to 2005. This was to be expected as the new system could not reliably represent the clinical trial situation in Europe in its first 8 months of existence. From 2005 to 2007 a stronger increase in absolute CTA numbers was observed than visible in the indexed data representing information provided by the competent authorities.

Some CAs reported a peak of activity in the months before implementation of the CTD in their country, obviously a "preventive strategy" of pharmaceutical companies, worried about the potential negative impact of the CTD concerning administrative burden and unpredictable approval timelines under the new CTA system for their upcoming trials. BfArM in Germany presented such an observation in their clinical trials statistics on the BfArM webpage (see "CTA applications at BfArM and PEI," page 32).

Commercial Sponsors

The overall development of clinical research activity sponsored by pharmaceutical industry showed a slight but statistically significant upward trend of about 10% since 2003. The EudraCT data (see Figure EudraCT 2 in Annex IV) revealed that the slight increase seen in the total number of CTAs was primarily due to the increase in CTAs from commercially sponsored trials. No conclusion could be drawn on the cause for that increase as other factors than the CTD might have had an impact as well.

The development of commercially sponsored trials in the individual countries was very different. Some countries showed a more or less pronounced increase or decrease after 2003, others presented a jump in their commercial CTA approvals. This was particularly obvious in countries B and Y, two countries belonging to different levels of clinical research activity. Reasons for these trends could be the way the CTD was nationally implemented and/or other factors like the local research activity of some pharma companies as presented in "Is the randomized controlled drug trial in Europe lagging behind the USA?" (see page 25).

Despite the small amount of information available and the overall small numbers of these types of trials, an increase from 2003 to 2007 in trials with biotechnology products and orphan drugs could be detected in this survey. However, scientific and technological progress as well as new orphan drug legislation was likely to have had a greater impact than the CTD implementation.

Non-Commercial Sponsors

In contrast to several publications and presentations, no implosion of academic clinical research after implementation of the CTD could be detected in this survey. Indexed data showed only a minimal decrease, however, the relative change calculation revealed a decrease of nearly 26% comparing 2003 with 2007 while the EudraCT results (see Figure EudraCT 2 in Annex IV)

presented a slight steady increase from 2004 to 2007. However, when analysing the individual country developments it became obvious that some countries, especially country Y, faced strong decreases in their non-commercial clinical trials numbers. On the other hand, one country, "K", experienced a marked increase, supporting the impression that other factors than the CTD played a major role in these national situations.

Again, it is hard to imagine that a single factor may explain a complex reality, probably reflecting the heterogeneous nature of the EU. However, factors probably contributing to these findings were:

- **EU CTD** imposed a higher administrative burden on sponsors of CTs as compared to the pre-CTD era. One might discuss whether this increased burden effectively improved patients' protection and clinical research quality standards, but it is out of question that it increased the workload on the sponsor's side. It is also evident for the ICREL team that the ability to suffice these new requirements varied depending on the resources available at the sponsor's level, and this probably explained the less marked and more transient nature of the negative impact observed among CSs as compared to NCSs.
- Secondary legislation might explain the different impact observed among member states. Transposition of an EU Directive required retaining the key elements contained in the EU legislation, but left considerable room for interpretation at national level, especially in practical aspects. The ICREL surveys did not go into detailed evaluation of secondary legislation across Europe, but other organisations like ECRIN (see "Clinical research in Europe: national differences in legislative and regulatory frameworks" page 27) detected and presented major differences in the national legal conditions for clinical trials.
- **Other factors** as for instance research culture and tradition, perception of the relevance of GCP implementation, national programmes to promote independent research, strength and quality of research networks in each EU member state, may have played a role. None of these factors have been analysed by ICREL.

Non-approved CTAs

An effect over time of the number of non-approved CTAs was considered as an indicator of performance and an increase as an indirect consequence of the requirements introduced by the CTD for clinical trial approval. Non-approvals remained a relatively rare event over the surveyed years, however, the statistically significant increase of the mean of non-approvals per institution from 2003 to 2007 could be interpreted as a consequence of the fact that several countries switched from a notification to an approval process.

Very low practical experience seems to exist with appeal systems in those EU member states that have implemented this option for sponsors. In over 30% of the EU member states an appeal system seems not to exist.

Organisation of clinical trials

Information provided by the CAs on the organisation of clinical trials clearly demonstrated the increasing trend of sponsors since 2004 to organise their trials in several countries. Organisation as national multi-centre trials and as mono-centre trials decreased, however, ongoing since 2000 as shown by the indexed data of this survey. Thus, an impact of the CTD on this development seems unlikely. However, EudraCT data (see Figure EudraCT 3 in Annex IV) confirmed the survey findings by showing a stronger increase in multi-national than in mono-centre trials since 2004 but also revealed an interestingly strong, ongoing increase of trial organisation in non-EU countries. An impact of the CTD on this trend could not be excluded.

An indirect consequence of the increasingly multi-national organisation of clinical trials could be the strong increase of substantial amendments observed since 2005 as it is unlikely that with the increasing experience of sponsors with multi-national trials the level of quality and professional organisation of CTs – requiring substantial amendments – would be decreasing. Anecdotal and structured information collection, e.g. from BIA/EuropaBio (see page 35) and EFPIA-PHARMA (see page 37) confirm the complexity of multi-national trial organisation, further complicated by the fact that the definition of a "substantial" amendment varies between the different Member States.

Time lines

The information provided by CAs on the time lines for CTA approval was very inconsistent. Obviously, the definition of the time windows varied within the different countries. However, the data did show a slight trend towards decreasing timelines for the average CTA approval time per CA from 2003 (around 60 d) to 2007 (around 45 d). These data suggested that CAs have in general undertaken a considerable, successful effort to adhere to or even beat the maximum timeframe for CTA established by the CTD. An attempt to identify specific timelines for different trial phases and types of products as specified in the CTD xenogenic/somatic cell therapy failed as the CAs were obviously mostly not in a position to provide this level of detailed information.

Workload and Costs

A striking result of this survey was the statistically significant increase of FTEs required for scientific assessment and administrative tasks for CTAs. The strongest relative change occurred between 2003 and 2004 and thus a correlation with the CTD implementation appeared likely. However, there were differences between different member states in the level of staff increase. A number of CAs seemed to be able to handle the new CTD-related tasks with the available staff; one CA even reported a significant decrease of staff for scientific assessment since 2004.

The information on the number of expedited safety reports (SAEs, SUSARs) received by the different CAs was very heterogeneous. One CA (confirmed information!) reported up to 100fold higher numbers than the other CAs, however, ongoing since 2000 so that a systematic difference in counting had to be assumed. But also by discarding this CA and another outlier the increase of expedited safety reports between 2003 and 2007 was still above 100%. The staff numbers did not follow this development as the additional staff required for pharmacovigilance tasks remained below 20%. Interesting was also the finding of this survey that only 14 CAs started to enter reports into the EudraVigilance database in 2004 and 9 other CAs had not even started with data entry in 2007. Thus, currently, the CTD's intention to ensure EU-wide collection, handling and immediate action on safety information in clinical trials is not achieved.

Different countries choose different strategies to cover their increased budgets: while a number of CAs started to charge fees in 2004, 2005 or 2006, others maintained the same level as before the CTD implementation or raised the level only marginally. Some, however, increased their fees drastically aiming at complete cost coverage. There were also national differences in the fee levels and their increases for commercial and non-commercial sponsors, less so for SMEs and orphan drug trial sponsors, for CTAs and approval of substantial amendments. As the national fee increases occurred in most cases in close relation with the time of the national CTD implementation an impact of the CTD on the increased costs to sponsors for CTA and substantial amendment approval was very likely.

Comments from the ICREL Conference Break-out Group "Competent Authorities"

Reasons for the increase of CTA refusals after implementation of the CTD could be the increasing complexity of CTs as well as the fact that the overall number of CTAs increased. Further investigation was recommended on whether there was a country-specific trend. However, the small number of refusals reported did not allow for a meaningful evaluation.

The Group had the impression that the increase of substantial amendments was more linked to changes in protocol, administration and new sites and less to changes in the IMPD. It was agreed that not only the definition of "substantial amendment" needs urgent harmonisation but also the requests for notification or authorisation among the member states.

Own experience within the Group revealed that the constitution of the timelines for CTAs presented in the surveys were not transparent and often included clock stops, validation periods, waiting periods for other approvals like ethics committee opinion, hospital administration review, etc. It was recommended to improve the transparency.

The Group also recommended working towards common dossier content, a mutual recognition of the CTAs as well as clarification, transparency and harmonisation of SUSAR reporting requirements. Special support for NCSs was encouraged, like better information to NCS applicants and training. The division between commercial and non-commercial trials was criticised. A risk-based approach including a simplified CTA procedure for CTs with marketed drugs was recommended instead. Finally the Group proposed that EudraCT should be widened to a registry for all types of trials – both non-drug trials and trials in third countries.

Discussion Ethics Committees

This survey was the result of previous discussions and initiatives (VISEAR) focusing on the ethical review procedure[23]. Its objective was to provide facts and figures on the situation of EU ethics committees in 2003 and 2007, thus before and after the implementation of the CTD, and to collect information on clinical research activities not falling under the CTD but requiring a favourable opinion according to GCP requirements. The following discussion will focus on survey results and issues of particular relevance to the structure and tasks of ethics committees.

Low number of respondents

Despite considerable efforts and contacting ECs 4-5 times between June and September 2008, the number of respondents was quite small. Finally, 708 questionnaires were sent, but only 64 responses originating from 18 countries were obtained.

The very low number was not surprising, but rather representative for the nature and structure of European ECs. Ethics Committees are – due to their origin in 1975 as institutions of "peer review" – organised on a voluntary basis without any or with only minimal office staff. So the search for data, which is in many ECs not routinely assessed, is a time consuming burden. There are several reasons for this: Due to the heterogeneous nature of ECs in Europe – every EU Member State has different legislation regarding ECs and clinical research - there is no unanimous definition of clinical research. What is, in one country, defined as project evaluation of a medical device, might

[23] Druml C, Singer EA, Wolzt M, Report of the 1st meeting of the "Vienna Initiative to Save Academic Research (VISEAR)", Wiener Klinische Wochenschrift 118/5-6 (Suppl)1-12, Apr. 2006; 118:183-91

be in another country assessed as project evaluation of a medicinal product. Another reason is that as only very few ECs have personnel, every additional task – additional to the review procedures – is an additional workload and burden. Completing the questionnaire required several hours of data collection if the data were not already assessed in a specific database. Obviously, only a very limited number of ECs has personnel and money to establish statistics and a database. Furthermore, the legislation of the different EU Member States does not require a yearly report of the work of ECs, so the requested data were not readily available.

Another problem was that some ECs did not want to disclose information. They considered the information requested as "confidential" and thus did not complete the questionnaire.

Positive opinions

In the average ethics committees had to review significantly more projects in 2007 than in 2003. Especially the larger ECs faced a strong increase with the related higher workload and had to organise themselves accordingly. This finding of a stronger increase of non-commercial trials in comparison to commercial trials, which was in contrast to the findings from the competent authorities, could be explained by the fact that the ECs reported a change of the type of trials over the years – away from the standard drug trial to more trials on medical devices and non-interventional/observational studies. Non-commercially sponsored trials require different knowledge and expertise of the EC members and often more advice and support for the applicant, adding to the additional workload.

Negative opinions

There were only a very small number of negative opinions reported: approximately 3 negative opinions or votes per year per EC, with a small but non-significant increase from 2003 to 2007.

ECs were established as institutions of "peer review" and furthermore to give an opinion; they are institutions established to give advice. ECs' primary goal is to see that an application can be improved and thus finally approved. The aim is to strive for scientifically and ethically acceptable clinical research protocols of the highest standard and suitable informed consent documents and not for a high number of refusals. So, in the end, even protocols which were originally submitted in an imperfect way might be improved and finally accepted. This is a "commonly accepted conduct" within ECs worldwide.

Substantial amendments

The survey identified a huge increase in the number of substantial amendments. The number almost doubled in 2007 (+92.91%) compared to 2003.

As the definition of "substantial amendment" is not clear and not agreed between Member States sponsors tend to submit every amendment as "substantial amendment" in order to be on the safe side. This problem needs urgent resolution.

SUSAR reporting

Reporting of SUSARs to ECs turned out to be a major burden for ECs. The number of expedited safety reports in 2007 was almost three times higher than in 2003 (+183%). A lot of resources in ECs are bound with formally handling the reports from all over the world. As all ECs involved in a multi-national trial receive the same information a lot of unnecessary doubling of efforts occurs. In addition, the responsibilities in safety evaluation between ECs and competent authorities are not clearly defined. Therefore, the entire additional burden to ECs does not help to increase the trial participants' safety or the quality of the study.

FTEs per EC

To cope with the additional workload, there was a significant increase in the number of persons employed by ECs for scientific and ethical assessment, administration and pharmacovigilance from 2003 to 2007. However, these increases had to be interpreted with caution.

Firstly, absolute numbers were still quite small: 5-6 FTEs per EC for scientific, ethical assessment and 1-2 FTEs for administrative and pharmacovigilance tasks.

Secondly, there was a potential misunderstanding on the respondents' side: some obviously counted EC members as FTEs, although they were not employed by the EC, but were actually doing the work. In very small ECs the chairperson is also doing the administrative work but was counted as employee.

Historically seen, ECs started as small committees within a hospital or within an academic institution. So the chairperson was usually the head of a department who handled the administrative work him- or herself, maybe with the help of his/her secretary. Traditionally and until today, EC members are not paid and the function of chairperson is considered an "honour" without any remuneration. Only some ECs developed into big committees with a structured office. Obviously, some respondents used different approaches to describe their organisation in the restricted frame of this survey questionnaire and thus very heterogeneous answers concerning EC members and personnel doing the administrative work was received.

External review

Interestingly, only 55% of responding ECs had an external review process in place. This is surprising, as clinical trials are getting more complex with the additional challenges of advanced therapies, gene therapies etc. But not all areas of expertise can be covered by the EC members. Although the legislation requires that "expertise" has to be acquired from outside the EC if not existing within, there is still not enough guidance to regulate this aspect as the results of this survey showed. This is a major pitfall of the review system: it is not required that EC members are trained initially and continuously in regard to the laws and regulations of clinical research as well as in regard to the methodology. So the conclusion would be that expertise is expected to be lacking in many ECs[24].

Fees

The fees for commercial sponsors rose significantly by approximately 74%, whereas fees for non-commercial sponsors only rose non-significantly by approx. 18%.

However, these fees were charged by lead/central ECs issuing a "single opinion" in 2007; and a "single opinion" system was not in place in many countries in 2003. Therefore, the figures from 2003 and 2007 were not easy to compare.

Although, there was also a significant increase in the fees for local ECs as well, the absolute amounts (Euros to be paid) were considerably lower.

[24] Davies H, Wells F, Druml C. How can we provide effective training for research ethics committee members? A European assessment. J Med Ethics. 2008 Apr;34(4):301-2.).

Transparency of study results

Compared to the number of approved trials the number of final study reports received per EC after implementation of the CTD was still very low and not changing over time. This means that still today, if study results are not published in a scientific journal, they are not available to the public. Further guidance is needed to ensure that ECs receive study reports in order to obtain information on patients' safety attained and how investigators performed their task.

Patient safety, patient protection

Although the number of ECs without patient representatives decreased from 2003 to 2007, there are still many ethics committees which do not have any patient representatives as members.

Although the following question has not been covered by this survey, one of the important issues and a matter of heterogeneity within Europe is the inclusion of temporarily incapacitated patients in clinical trials.

For the inclusion of vulnerable populations in clinical trials there are still very different conditions between countries within the EC. Some countries, for instance, have laws that allow a waiver of informed consent for temporarily incapacitated adults, whereas there is no such legislation in other countries.

The EU legislation has not considered the particular needs of intensive care and emergency research, thus resulting in a heterogeneous system in Europe, hindering multicentre research projects. Guidance is needed to avoid a selection bias within multinational research projects. Furthermore legislation should be harmonised in order to guarantee that the ethical principle of justice is observed[25].

However, the situation of paediatric clinical research has improved due to the recent EU legislation. As far as the consideration of other vulnerable groups in clinical research is concerned, the involvement of patient representatives needs further evaluation.

Impact of the legislation on ethical review and the activity of ethics committees

The average number of meetings per EC participating in this survey did not change over time, nor did the average length of the meetings. However, it has to taken into consideration that the preparation time for the increased number of protocols for the EC meetings was not investigated in this survey.

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[25] Lemaire F, Bion J, Blanco J, Damas P, Druml C et al. (ESICM Task Force on Legislation Affecting Clinical Research in the Critically Ill Patient) The European Union Directive on Clinical Research: present status of implementation in EU member states' legislation with regard to the incompetent patient.Intensive Care Med 2005 Feb 15.
- Liddell K, Chamberlain D, Menon DK, Bion J, Kompanje EJ, Lemaire F, Druml C, Vrhovac B, Wiedermann CJ, Sterz F. The European Clinical Trials Directive revisited: the VISEAR recommendations. Resuscitation. 2006 Apr;69(1):9-14.
- Liddell K, Kompanje EJ, Lemaire F, Vrhovac B, Menon DK, Bion J, Chamberlain D, Wiedermann CJ, Druml C: Working Group of the Vienna Initiative to Save European Academic Research. Recommendations in relation to the EU Clinical Trials Directive and medical research involving incapacitated adults. Wien Klin Wochenschr.2006 Apr;118 (5-6):183-91.
- Druml C, Singer EA, Wolzt M, Report of the 1st meeting of the "Vienna Initiative to Save Academic Research (VISEAR)", Wiener Klinische Wochenschrift 118/5-6 (Suppl)1-12, Apr. 2006.
- Liddell K, Bion J, Chamberlain D, Druml C, Kompanje EJ, Lemaire F, Menon DK, Vrhovac, Wiedermann CJ. Medical Research Involving Incapacitated Adults: Implications of the EU Clinical Trials Directive 2001/20/EC. Med Law Rev. 2006 Aug 23.

Communication

All respondents to this survey that were not entitled to give a "single opinion" considered the procedure to reach a "single opinion" difficult. This was probably due to the fact that the communication system between central/lead EC and local EC is not harmonised and the national differences are huge. It is often not clear for the local EC what they are expected to assess, e.g. only the suitability of the local investigator and site or all other additional documents provided to them.

In addition, the information transfer between ECs and CAs is also not regulated and obviously functions better if the persons involved expect a benefit for their work by improving personal communication.

Comments from the ICREL Conference Break-out Group "Ethics Committees"

The discussion of this Break-out Group focused on the need for initial and ongoing mandatory education for ethics committee members as a pre-requisite to cope with the additional requirements of the new system. A harmonised approach to accreditation of ethics committees, acceptance of audits and inspections should be considered among the Member States.

The Group was concerned about the lack of harmonisation of the ethical review process in Europe and the resulting potential differences in patient safety protection.

Several EC members complained about the fact that information on other trials is not easily available and requested public access to CT databases and registries.

There was broad agreement that the current SUSAR reporting system to ethics committees is not helpful and only a huge burden and should therefore be revised.

Discussion Commercial Sponsors

Despite the fact that the respondent rate was much lower than expected and the sampling could not be performed in a random stratified way the received data from very large, large, medium-sized/small companies and SMEs showed several very interesting trends which partly even reached a statistical significance level.

Commercial research activity

Overall, the commercially sponsored clinical trials activity rose by more than 30% between 2003 and 2007. The more detailed analysis, however, showed that this was not the case for SMEs: this group showed even a trend towards a small decrease. Obviously, the CTD was not able to support an increase of the clinical trial activity in this category of particular interest to the European economy.

The information received was dominated by results on trials with investigational medicinal products but also the sub-categories showed interesting changes: there was a significant increase of over 100% in clinical trials with biotechnology products and of about 140% in trials with orphan drugs. These increases can not only be explained with an impact of the CTD. Many more biotechnological drug candidates were identified and developed between 2003 and 2007 and the impact of the orphan drug legislation certainly had a positive impact on Pharma industry's interest in orphan indications. There was too few information on clinical trials with advanced therapies available to be able to

detect already a trend. It is obvious, however, that the number of clinical trials with diagnostic products has decreased which may be caused by the CTD requirements but which may also be a reflection of the limited success of biomarker development during the investigated period.

The observed increase of non-interventional/observational commercially sponsored studies may be a result of an attempt to answer scientific questions with study designs for which the CTD does not apply; but between 2003 and 2007 there was also an increase in the request for safety information after marketing authorisation which by definition can be very well generated through observational studies.

Non-approvals

Non-approvals of clinical trials by competent authorities, lead and local ethics committees was and is a rare event in all type of companies. But of course, due to the fact that a trial approval process exists now in all EU Member States non-approval occurred now more frequently than in the past. The more frequent provision of a negative opinion by ethics committees could be a hint for a more professional ethical review process enforced by the CTD. Too few companies had experience with using an appeal system to be able to detect a trend.

Clinical trial organisation and phases

The increase of the clinical trials activity between 2003 and 2007 was based on an increase in all 4 phases, however, the increase in phase 4 trials was less pronounced. SMEs showed even a decrease in phase 1 trials. This was in line with their decrease in overall clinical trial activity because a lot of them are still in the phase 1 stage of drug development.

A significant number of companies increased their number of multi-national trials between 2003 and 2007, especially those who had already in 2003 a relevant number of their trials organised as multi-national trials. Their available infrastructure obviously allowed more easily their multi-national expansion. Proportionally, the number of national multi-centre trials did not change from 2003 to 2007: only a third of the multi-centre trials were organised in a single country.

Especially non-SME companies increased the number of their mono-centre trials by approximately 30% from 2003 to 2007. It has to be taken into consideration that primarily phase 1 trials are organized as mono-centre trials.

Subject recruitment

The most critical element for time lines and budget of a clinical trial is the recruitment of patients. This survey showed that commercial sponsors could not increase their recruitment rates despite an increase of involved countries by about 30% and of involved centres by nearly 60%. This means de facto that companies had to increase their number of sites because less sites were able to provide the expected number of patients. The reasons for this development are further explored in the section on non-commercially sponsored trials.

Time lines

A major objective of the CTD was the reduction of the study preparation period by implementing defined maximum time lines for study approval by competent authorities and ethics committees. This survey showed that this objective was clearly missed for pharmaceutical companies, especially for SMEs. Larger companies with already established know-how and resources for the preparation

of multi-national trials faced a less significant increase in time lines than the small companies. Only those companies with long time lines in 2003 were able to shorten their time lines to some degree.

A very time consuming process is the implementation of substantial amendments. Under the new legislation the commercial sponsors' time lines for amendment implementation increased by approximately 30%. Taking into consideration that the number of substantial amendments has strongly increased after CTD implementation it must be concluded that this process has also become much more complex, resource and time consuming than before implementation of the CTD.

Workload

A very clear result of this survey was the need for more staff to cope with the CTD requirements in preparation and execution of clinical trials: the vast majority of companies responded that they need more personnel than before to prepare and perform clinical trials. In particular the number of FTEs required to handle the study approval process has practically doubled in the average; small companies faced an even stronger increase because companies with a larger staff in place in 2003 needed less additional resources. But also trial management tasks requested considerably more FTEs (38%) in companies of all sizes. This can partly be explained with the increased number of sites and countries involved in a particular trial and the overall clinical development process in pharmaceutical industry.

With the implementation of the SUSAR definition, the new legislation aimed at reducing the workload of expedited safety reporting. However, according to the results of this survey the contrary was achieved: the required number of FTEs in pharmaceutical companies increased by 85%! This is a clear evidence for the fact that the new expedited reporting process is more complex than the former. In addition, 75% of the companies had to invest in the establishment of a new IT platform for safety data collection and reporting, 25% of them in a magnitude of over € 100,000. However, despite this considerable investment in resources and technology only half of the respondents were of the opinion that this new process has increased the safety of study participants.
As commercial sponsors had quality assurance in place since implementation of Good Clinical Practice in the early 90ies, the need for additional QA staff after implementation of the CTD was in the average limited, however, also here more companies needed to increase their staff in this area than those who decided to decrease it.

Increased sponsor responsibilities

The responding Pharma companies did not have a strong opinion on whether the CTD has helped them to perform their sponsor responsibilities or not: half of them felt no impact. And they did not feel that the CTD helped them in their interaction with academia and investigator-initiated trials. In fact, only a third of the respondents reported any interaction with IITs, mostly in form of provision of study medication and the related IMPD. Hardly any company supported non-commercial trials with assistance in data management or expedited SUSAR reporting. Thus, also another objective of the CTD, the fostering of the collaboration between industry and academia by clarifying responsibilities and harmonizing the quality requirements, has not really been achieved.

Insurance

The CTD just confirmed the need for adequate subject indemnity insurance coverage requested by GCP. However, since implementation of the CTD the insurance fees dramatically increased for commercial sponsors by over 800%. This was due to the decision of the insurance providers to change their contracts with sponsors from a general annual fee to a risk-based per study fee. This

additional cost driver in the clinical trial process should be proactively managed by pharmaceutical industry through re-negotiation of the contractual conditions for clinical trials with re-insurers or through finding alternative indemnity coverage models for their clinical trials.

Comments from the ICREL Conference Break-out Group "Commercial Sponsors"

This Break-out Group was critical about the low number of respondents and complained about the lack of commitment from industry to the need for maintaining statistics on the own performance. The decision that the ICREL project did not seek information from CROs due to the danger of double-counting of clinical trials when information was requested from sponsors and their service-providers was questioned. There were also complaints about the fact that this survey did not measure the impact of the CTD on quality.

The discussion revealed concerns about the fact that a third of all trials include already today sites in non-EU countries and that a complete category of trials like bioequivalence trials have been moved outside the EU. It was felt that there is a need to better understand the reasons and consequences of these shifts.

A final recommendation was to substantially reduce the complexity of the clinical trial authorisation process to reduce the trial preparation time and duplication of efforts of all stakeholders.

Discussion Non-Commercial Sponsors

Response to the survey

The observed response rate was lower than expected especially for the small NCSs. Retrieving the data requested in the questionnaire could have represented a significant challenge especially for small organisations. The way data were stored and the available workforce at the institutions could have been deciding factors with respect to an institution's participation in the survey. Difficulties in retrieving the requested data seemed to be the most relevant explanation regarding the high number of missing data and therefore the low number of matched data allowing for sound comparison of the CTD before and after its implementation.

As for the 15 organisations which reported not being a sponsor as the main reason for not participating in the survey, a possible explanation could be the inaccuracy of the information contained in the clinicaltrials.gov database, especially concerning trials sponsored by organisations outside the US.

There was some disparity in terms of response-rate amongst the countries; this may be explained by the difficulties in identifying the right contact person in the institution due to the lack of clarity of the information posted on the organisation's website and to the language barrier which is a real issue in the EU-27. Sometimes, there was a lack of cooperation from the contacted person by not forwarding the survey to the appropriate colleague. The duration of the ICREL project was one year, which was very short, and the available funding was limited and did not allow for appointing sufficient workforces needed for such task.

Areas of activity

It was not surprising that the majority of responding NCSs were multi-disciplinary or reported oncology/ haematology as the main area of activities, since most of the large NCSs are important multi-disciplinary organisations. It is widely reported that the majority of the clinical research in Europe is performed in the field of oncology/ haematology e.g. 24% of CTAs in France[26] in 2007 and 28% for 2006 in Italy[27] (56% of academic trials). For comparison, the second most frequent area of activity is "nervous system" in France with 19% of CTAs and "cardiovascular" in Italy with 11%. Another reason is that the oncology clinical research groups are known to have the longest tradition of conducting multi-centre trials and, therefore, are able to participate to a greater extent in such survey. In addition, the oncology clinical research activities, which are often complex multi-centre and multi-disciplinary trials, e.g. combining chemotherapy with surgery and human tissues collection, have been heavily impacted by the implementation of the CTD and therefore raise sponsors' motivation to participate in this survey.

Volume of clinical research activities

The data did not show any significant changes regarding the number of clinical trials, patient recruitment, number of involved countries and sites, and the costs of insurance and IMP when compared before and after the implementation of the CTD. This could be explained by the low number of matched data obtained for those questions. In addition, the available data were very heterogeneous, and this reflects the complexity of the situation. In fact, various factors may account for the variation in the volume of clinical research from one year to the next which occurs at the organizational level: staff shortage, financial trouble, change of organisation's priorities, or at the macro level: the general economy which might cause variation in R&D investment by industry, or the availability of public and charity funding.

On the other hand, the analyses of the relationships between the level of activity of the respondents in 2003 and 2007 showed that the NCSs with higher levels of activity in 2003 in term of number of trials on medicinal products, the number of involved sites and countries were also the ones which experienced the largest decreases in 2007. This was significant for trials on medicinal products performed in multi-national, national multi-centre or mono-centre settings. This was confirmed by the analyses of the relative changes: the most active institutions in 2003 were experiencing proportionally larger decreases. In contrast, the less active institutions experienced larger relative increases. This was also supported by the analyses of the relationship between the changes in 2007 and the overall level of activity in 2003, which showed that the most active institutions in 2003 were associated with a larger decrease (or smaller increase) of their activity. On the contrary, the less active institutions in 2003 showed an increase in their number of CTs on medicinal products.

This was not surprising because the space for absolute decrease was on average small for the less active institutions and large for the most active ones. The largest non-commercial sponsors were impacted the most because they faced a more challenging situation adapting their structure and workforce in relation to their volume of clinical trials comprising large number of multi-national trials (implying to cope with multiple national legislations), whereas it was easier for the small NCSs dealing with a smaller number of CTs (mainly national multi-centre CTs) to adapt their capacities. Therefore the needed adjustment in their structure impacted large sponsors' capacity to perform CTs and therefore, the number of CTs they sponsored.

[26] Afssaps. Rapport d'activité 2008.
[27] Agenzia Italiana Del Farmaco. Bulletin Clinical Trials of Drugs in Italy. 2007.

Moreover, concerning the level of workload, the analysis of the relationship between the workload in 2003 and the absolute change in 2007 showed that the increase in the workload for regulatory and trial coordination tasks was slightly larger for institutions having reported more FTEs in 2003. The analyses of the relationship between the changes in terms of FTEs in 2007 and the overall level of activity in 2003 showed that the institutions with the higher number of FTEs tended to experience higher increases in regulatory and trial coordination tasks. According to the relative changes in 2007, the less active institutions in 2003 experienced proportionally larger increases in terms of FTEs.

This reflected the reality according to which sponsors had to increase their capacity facing the increasing workload. The majority of sponsors experienced an increase in their workload (absolute changes) but, proportionally, the small sponsors experienced a larger increase in their workload. The later could appear as contradictory to the arguments above. It has to be kept in mind that small sponsor workload corresponds to small figures compared to the large sponsors. Therefore, important relative increase in the small sponsor workload will correspond to small absolute changes which will request less adaptation than the large changes observed with the large sponsors. Concretely, it is easier extending e.g. the half time of a regulatory manager working in a small sponsor organisation to a full time (relative change of 50%) than recruiting e.g. two additional persons in addition to the existing team of six regulatory managers (relative change of 33%) working in a large sponsor organisation.

The relative changes had to be considered with caution since they were based on fewer data than the exact changes, but they were important for limiting the risk of trivial observation: e.g. most active NCSs in 2003 were likely to lose more CTs than less active NCSs which could not lose more than what they had in 2003.

The data supported claims that the implementation of the CTD increased the administrative requirements and therefore the costs and the length of the clinical trial approval process. In fact, the significant increase of at least 34 days (24%) for the average time between protocol finalisation and inclusion of the first patient now to 144 days bolstered this claim. In addition, the time lines for amendment implementation increased significantly by 9 days (23%) according to the adjusted data.

In addition, the data showed a marked increase of the workload and therefore the costs related to the sponsor's tasks such as in administration related to the regulatory process with an increase of at least 89%, trial coordination and monitoring, +60%, pharmacovigilance, +88% and quality assurance, +155%. The increase in pharmacovigilance-related tasks in the unadjusted results was not any more significant than in the adjusted results. This was likely due to the weight given to the small NCSs in the adjusted results. One possible explanation might be that small sponsors were asking their investigators to report the safety alerts directly to the Ethics Committees and Competent Authorities.

This general increase was also reflected in the data collected from the other stakeholders who reported a significant more than 130% increase in the number of SUSARs, the number of substantial amendments received by the CA (+153%) and by the EC (more than 64%). Moreover, the average costs of CTAs raised significantly (+236%) according to the Competent Authorities data. Those data showed that the costs rose significantly for conducting a comparable number of trials according to the Competent Authorities data (non-significant 26% decrease). Those data highlighted the intense adaptation of NCSs for coping with the evolving regulatory environment.

The findings were similar to data published in numerous articles, e.g. Hearn and colleagues[28]. The authors investigated the impact of the CTD on eight clinical trials units in UK. Results showed that costs have doubled, the start of the trials was delayed and starting and conducting trials was much more difficult than before. As for the clinical research activity, Moulton[29] reported a decrease of 25% in submissions in Sweden; 40% in Ireland with a drop of 60% from non-commercial sponsors. And the same was found by the Cancer Research UK (CRUK) where the number of CTAs was down by approximately 50%. The European Organisation for Research and Treatment of Cancer[30] faced the same situation: from 23 new studies in 2003 to 10 in 2007 (see "The Experience of the European Organisation for Research and Treatment of Cancer" in Annex VI). Unfortunately, the FP6 CLINT survey results are being submitted for publication, and therefore, were not available for this final report.

From the answers to the open question, respondents perceived the CTD as having introduced some harmonisation but were at the same time viewed to be the source of a problematic heterogeneity of requirements from the Competent Authorities. The increased administrative burden and the related costs were clearly expressed by the respondents. Their proposals for improving the CTD were consistent since the majority call for a simplification and harmonisation of the requirements, the risk-based approach and also that NCS specificity should be taken into account and NCSs have to be supported through funding and infrastructure.

Several respondents proposed to end the request for free supply of the IMP to be provided by non-commercial sponsors. This request should be put in context: there is a need to differentiate between the "true IMP", drugs not available on the market, and "false IMP", drugs already on the market but whose use is foreseen as standard treatment in the clinical trial protocol or they will be used for a new indication. Because of the lack of harmonisation between national CA interpretations of what is an IMP, the "false IMP" may sometimes be considered as a "true IMP" by some national CAs. "True IMPs" are usually provided by the sponsor free of charge to the participating clinical sites since this is the only way to make unregistered drugs available with the support of the industry. It becomes problematic when the NCS has to provide, at its own expense, marketed drugs in the context of, for example, treatment strategy studies (which represent the majority of academic clinical trials) because the industry has no commercial interest in the study. With the implementation of the CTD, NCSs are more frequently faced with the situation of "false IMP" which is detrimental because of the related financial issues. This is particularly true for studies aiming at reducing number of drugs or duration of treatment.

The survey conducted by FECS[31] designed to analyse the provisions implemented in national laws to address the main concerns of academic research, highlighted significant differences in the implementation of the CTD across Europe, a huge unanimity regarding the negative impacts on academic research and the absence of benefit from the CTD compared to the previous GCP.

[28] Hearn J, Sullivan R, The impact of the 'Clinical Trials' directive on the cost and conduct of non-commercial cancer trials in the UK. Eur. J. Cancer 43:8-13, 2007.
[29] Moulton B, Two years later: the impact of the EU CTD. Why research in Europe has declined since the implementation of the Clinical Trials Directive. Applied Clinical Trials. August 1, 2006.
[30] van Vyve D, Meunier F, Facing the Challenges of the European Clinical Trials Directive: the European Organisation for Research and Treatment of Cancer perspective, *European Oncology*, 2008; 4; 1.
[31] Federation of European Cancer Societies. Survey on the impact of the directive on academic research, 2005.

Those findings were consistent with the different factors which have been identified by several authors[32,33,34,35] as bottlenecks to the European academic clinical research activity:

1. the free supply of IMP (in some countries[36], even standard treatment is considered as IMP);
2. the obligation for the sponsor to contract an insurance with different national coverage, ceiling and type of policy;
3. the single sponsorship model where the legal liability lies on one single person;
4. the requirement for on-site monitoring;
5. the national binary procedure involving national competent authorities and Ethics Committees for a clinical trial to be authorised, amended, ended;
6. cumbersome safety reporting;
7. the single Ethics Committee opinion, still involving local Ethics Committees in some EU Member States[37];
8. the broad definition of substantial amendment;
9. the fees for the assessment of the clinical trial by the Competent Authorities and Ethics Committees;
10. the 27 legal frameworks implementing the EU CTD into national Member States' legislation.

Non-commercial sponsors felt most impacted by the CTD since they had simultaneously to deal with dramatic increases in their operating costs. The risk-driven approach adapting the legal requirements according to the risks presented by the clinical trials is clearly warranted. This is especially important for NCSs which are conducting a number of trials testing marketed drugs or using standard treatment strategy as comparator. Simplified and harmonised requirements and sound risk based-approach are clear avenues for improving the CTD since it would alleviate some of the burden caused in its implementation. It was claimed that the CTD contributes to a better patient protection and increase the quality of data but this is not reflected by the data of this survey since only a few of the respondents mentioned it as a strength of the CTD. Admittedly, this survey was not designed for adequately capturing variables linked to the quality of research and patient safety.

Comments from the ICREL Conference Break-out Group "Non-Commercial Sponsors"

In this Break-out-Group the difficulties of the sponsor role were discussed. Academic investigators had, in many instances, problems clarifying, in their institution, who should be the official sponsor and how to distribute/delegate the responsibilities. National academic institutions can not take sponsor responsibilities for investigators in other countries and thus can not literally fulfil the CTD requirement for *one* sponsor per CT in the EU. The Group recommended clarification of the possibilities for co-sponsorship in non-commercial trials.

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[32] Moulton B, Two years later: the impact of the EU Directive. Why Research in Europe has declined since the implementation of the Clinical Trials Directive. Applied Clinical Trials, Aug 1, 2006.
[33] van Vyve D, Meunier F, Facing the Challenges of the European Clinical Trials Directive: the European Organisation for Research and Treatment of Cancer perspective, European Oncology, 2008; 4; 1.
[34] BIA - EuropaBio White paper, Promoting consistency of implementation and interpretation of the Clinical Trials Directive across EU member States. October 2006.
[35] Hartmann M, Hartmann-Vareilles F, The Clinical Trials Directive: How Is It Affecting Europe's Noncommercial Research? PLOS Clin Trial 1(2): e13. doi:10.1371/journal.pctr.0010013.
[36] Austria, Denmark, Germany, Hungary, Poland
[37] Austria, Belgium, Czech Republic, Germany, Italy, Lithuania, Slovakia, The Netherlands, The United Kingdom Spain,

The ICREL results raised discussions on the changes in phase and type of trials performed by non-commercial sponsors before and after implementation of the CTD. It was recommended to analyse the results on national levels to identify the impact of the differences in implementation of the CTD.

The Group recommended to simplify the CT authorisation and performance process and to have a single CTA in Europe achievable with shortened timelines. The level of required documentation and bureaucracy should be based on the level of risk defined for a particular CT and this "risk" level should also be the basis for the insurance fee calculation. As the funding conditions are nationally very different in the EU, it was recommended to establish a pan-European funding organisation comparable to the US "NIH."

Global discussion

In order to provide most actual data, the ICREL project collected data within 4 months from all four stakeholder groups. Despite major efforts to encourage the completion of the 4 surveys by commercial and non-commercial sponsors, competent authorities and ethics committees the response was limited. According to the feedback received this was mostly due to lack of resources for data compilation, non-availability of the required information or too many changes in an organisation or professional activity to allow for any comparison in 2003 and 2007. Nevertheless, ICREL was able to provide pan-European metrics on important developments otherwise postulated or observed in a limited frame. The statistical approach aimed at stratification in different respondent categories, at the most comprehensive and transparent evaluation of the data based on matched data with adjusted and unadjusted results wherever possible and describing all information collected. The limitation of this project was the residual uncertainty regarding the large number of non-respondents and no reliable adjustment could be done to this fact.

The rate and quality of responses was highly variable between stakeholders, with a very good contribution from competent authorities, a fair response rate in non-commercial sponsors, a lower response rate in commercial sponsors, and a poor involvement of most ethics committees.

Taken together, data from the various stakeholder groups helped delineate some salient features of the changes observed over the 2003 to 2007 period. However, these data could not demonstrate that the observed changes, although contemporary to the implementation of the Directive in the EU Member States, were direct or indirect consequences of the Directive 2001/20/EC.. The few available data obtained from non-EU European countries could not be regarded as an external validation, not only because of these countries' size but also because their legislation is comparable to the EU one. In turn comparison of trends over the period (between sponsors, between countries, between categories of studies) may help identify possible causes for the observed changes.

The ICREL data suggested that large pharmaceutical companies seem less affected than SMEs and non-commercial sponsors by the new legislation: the number of CTAs increased for commercial sponsors, not for non-commercial sponsors. Among commercial sponsors, the features for SMEs appeared closer to non-commercial sponsors than to large pharmaceutical companies, with no increase in their clinical trials activity. In commercial sponsors, the increase was lower for interventional phase 4 studies than for other phases, whereas there was an increase in observational studies - this could be interpreted as a shift in study design to escape the requirements of the Directive.

Regarding non-commercial sponsors, changes in the clinical trials activity may have differently affected institutions depending on their level of activity, with a stronger impact in terms of number of studies and of FTEs on sponsors with a higher activity. Changes in non-commercial trials activity also varied from one country to another, with a slight increase in some countries and a slight decrease in others. Only one country showed a major decrease (about -50%) in non-commercial trials activity over the period. This could possibly be interpreted in light of the reluctance of public institutions to endorse the sponsor's responsibility as defined by the Directive, and requiring a third review and approval process.

One of the major consequences of the implementation of the CTD identified in this project was an increase in workload and associated FTEs in all the stakeholders: a major increase at the competent authorities, a less apparent increase at the ethics committees (although the management of SUSARs was a major concern), a moderate increase in commercial sponsors, and a major increase at the non-commercial sponsors (and SMEs). There was also an increase in fees to competent authorities and to ethics committees, whose amplitude was far higher for commercial than for non-commercial sponsors. The cost of insurance dramatically increased for commercial sponsors, not for non-commercial sponsors.

In spite of this increase in cost and workload, and in spite of a reduction in time for review by the individual competent authorities and of the single opinion by ethics committee, the time interval between protocol finalisation and the first inclusion of patients has considerably increased, possibly due to the complexity of the preparation of the application dossier upstream to submission, to the contracting between sponsor and hospital downstream, an/or to poor synchronisation between the submission to multiple competent authorities and ethics committees for multi-national studies.

This increase in cost and workload should be interpreted in light of the improvement of data quality and participants' protection, as this was one of the objectives of the Directive. This survey only gave qualitative assessment of the increase in the quality of data and the protection of participants - and a majority of responders did not see any significant improvement. However, collecting metrics allowing comparison of the quality of studies and of the protection and safety of participants would help further delineate the usefulness of these additional costs.

Conclusions and Recommendations

Conclusions Competent Authorities

As for the data of the ICREL survey among Competent Authorities the following conclusions could be drawn:

1. The vast majority (25 out of 28) of EU CAs participated in the survey. Two non-EU CAs from countries integrated within the EU regulatory system accepted to participate and provided responses.
2. Content and quality of the responses were time dependent and varied greatly among CAs, probably subsequent to a variable capability of retrieving reliable data.
3. An impact on clinical research activity in the EU derived from the CTD implementation was apparent, though could not be readily confirmed from the available data.
4. No negative impact of the CTD on commercial sponsors could be detected. The number of CTAs submitted by commercial sponsors increased slightly (+11%) between 2003 and 2007.
5. Overall, a slight potential negative impact of the CTD on non-commercial sponsors was detected represented by a relative change of -25% of CTAs between 2003 and 2007, however, while some countries faced strong or even dramatic decreases other countries experienced an increase of non-commercial CTAs.
6. The number of substantial amendments and SUSAR reports increased strongly after CTD implementation.
7. Average CTA timelines decreased after CTD implementation and were in 2007 with 49 days clearly below the 60 days limit.
8. The indisputably increased administrative burden imposed by the CTD on the evaluation process and supervision of CTAs was reflected by an increase in workforces and related costs which was paralleled by a raise in fees.

Conclusions Ethics Committees

1. Despite multiple contacts, the number of responding ECs was quite low.
2. The overall number of positive opinions increased by 23% between 2003 and 2007, with especially strong increases in CTs with medical devices and radiotherapy as well as non-interventional/observational studies.
3. A huge increase in workload for ECs was observed since the implementation of the CTD, evidenced by higher numbers of substantial amendments and SUSAR reports to ECs.
4. The number of negative opinions issued by lead or central ECs increased between 2003 and 2007 in line with the overall increase of reviews. More than 25% of responding ECs did not have an appeal system in place in 2007 but in those ECs were an appeal system was in place it was significantly more frequently used than in 2003.
5. An increase in FTEs per EC was reported, however, the absolute numbers of employees per EC were still very low and often no clear differentiation was made between unpaid EC members and employees.

6. More than half of the ECs did not involve external reviewers in assessing applications despite the increasing complexity of the CTAs.
7. No differences could be detected in number of EC meetings and duration of review time per protocol between 2003 and 2007. However, the duration of the meetings increased slightly but significantly.
8. Fees charged by lead or central ECs to commercial sponsors, SMEs and orphan drug trial sponsors for review of protocol and substantial amendments increased significantly from 2003 to 2007 but the fee level was different for these categories. The fee for academic trials was much lower and increased only slightly. Non-lead ECs did not charge significantly lower fees than lead or central ECs.
9. The annual budget of ECs increased by 50% between 2003 and 2007.
10. In 2007 ECs received final report summaries for less than 20% of the reviewed protocols.
11. 60% of responding ECs had no patient representative in their membership.
12. Especially non-lead/central ECs consider the procedure to generate a single opinion to be difficult.

Conclusions Commercial Sponsors

1. The overall number of commercially sponsored clinical trials has increased by about 30%, driven by increases seen in large and medium-sized companies.
2. SMEs did not experience an increase but faced higher staff needs and related costs due to an increase in trial complexity.
3. Areas of relatively stronger increases were clinical trials with biotechnology products and in orphan indications.
4. Clinical trials were increasingly organised in more countries and more sites than before implementation of the CTD, however, the number of patients recruited did not increase accordingly.
5. There was no shift detectable in the responding companies in the type of trial phases performed in 2003 and 2007. However, generic companies did not participate in the survey because they reportedly do not perform their bioequivalence trials in Europe anymore.
6. Time lines for the overall protocol and substantial amendment approval process increased in commercially sponsored trials.
7. Need for staff increase for preparation and management of clinical trials as well as for pharmacovigilance tasks, need for investment required to adapt IT systems to the new safety reporting requirements, and an increase of subject indemnity insurance fees added to an overall increase in resources required for the performance of clinical trials in the new regulatory environment without a demonstrable impact on improved patient safety.
8. In the opinion of commercial sponsors the CTD has created a certain level of harmonisation of the clinical trials infrastructure in the EU but as this harmonisation has not been far reaching enough, the complexity of clinical trials has increased.

Conclusions Non-Commercial Sponsors

According to this survey's data, the major impact of the CTD on the NCS activities was reflected in a significant increase of the workload and timelines, i.e., an increase in the delay before the entry of the 1st patient. The CA data did not show significant changes in the overall number of clinical trials conducted by NCSs. Overall, the CTD was perceived as having introduced a partial harmonisation of procedures but this positive effect was heavily counterbalanced by the general lack of harmonisation, the increase of the administrative burden and related costs. NCSs called for simplified and harmonised requirements and sound risk based-approach.

A great heterogeneity was observed in the responses rates, the number of missing values, and the trends arising from the data collected from NCSs. These reflected the great heterogeneity of the NCS organisations, reaching from large research organisations and well organised structures to small structures with a lower level of cooperative and dedicated resources. The capacity of NCSs to log critical information needs to be improved.

This survey was not designed for qualitative assessment of the impact of the CTD on the performance of future studies. The following questions need to be addressed: has the CTD improved patient protection and safety? What is the impact of the CTD on the quality of science: do we guarantee progress for patients in a timely manner? Can the nature of investigator-driven trials be preserved when independence from industry is threatened by the increasing burden of conducting such kinds of activities?

A re-evaluation of the situation with respect to the implementation of the CTD and its impact would need to be performed over a 3 year time frame in order to take advantage of a more complete EudraCT database. The systematic comparison with the situation in non-EU territories, e.g. US, Canada and Japan, should also be included.

Global Conclusions and Recommendations

Through extensive collection of data from different stakeholders, from different countries, and for various categories of clinical research, ICREL provided metrics on the changes in clinical research activity in Europe observed in the period before and after implementation of the Directive 2001/20/EC. These data will provide a major contribution to the debate on the need for a possible revision of the current European legislative and regulatory framework for clinical research. ICREL provided strong arguments supporting some of the recommendations proposed by various stakeholders in scientific journals, at the EC-EMEA conference on the Directive (2007) and in the ESF *Forward looks on investigator-driven clinical trials* (2009). For instance a risk-based approach to regulation would result in a substantial reduction in workload and cost, particularly for academic institutions that run a number of low-risk studies using marketed drugs. Simplification of the Clinical Trial Authorisation process by the competent authorities through a single CTA for multi-national trials would reduce duplication of efforts and also save time, costs, and expertise. Harmonised practice in ethics committee requirements would facilitate and reduce the administrative burden of dossier submission, and changes in expedited SUSAR reporting to the ethics committees would alleviate their workload. Insurance coverage for clinical trials should be reconsidered at the EU level and adequate funding should be provided to institutions performing clinical trials to ensure capacity and expertise for all trial–related activities.

The legislative and regulatory framework for clinical research is one of the major determinants for the attractiveness of a given region for clinical research. Clinical research is a critical activity for science, developing knowledge on diseases and on their treatments. It is also critical for health, allowing development and optimal use of preventive, diagnostic and therapeutic strategies. It is a central activity for the health industry, allowing development of innovation and subsequent economic growth. It is also a source of employment and of revenues for investigational sites. From this perspective, ICREL may be regarded as a model for monitoring the attractiveness of the European Union for clinical research. For this reason, ICREL should now be extended over time for the monitoring of the EU legislation. This could be achieved through a similar survey proposed every 2nd year, in an updated and focused version, including metrics on the impact on the quality of studies and the protection of participants.

Annexes

I. Bibliography

Multi-stakeholder-related

International aspects

- Hiddo J. Lambers Heerspink, Mirjam J. Knol, Robert J.W. Tijssen, Thed N. Van Leeuwen, Diederick E. Grobbee & Dick de Zeeuw. Is the randomized controlled drug trial in Europe lagging behind the USA? British Journal of Clinical Pharmacology, DOI:10.1111/j.1365-2125.2008.03296.x.
- Thiers FA, Sinskey AJ, Berndt ER, Trends in the globalization of clinical trials. Nature Reviews Drug Discovery, 7:13-14, 2008.

Pan-European aspects

- Druml C, Singer EA, Wolzt M, Report of the 1st meeting of the "Vienna Initiative to Save Academic Research (VISEAR)", Wiener Klinische Wochenschrift 118/5-6 (Suppl)1-12, Apr. 2006.
- Editorial: Who's afraid of the European clinical trials Directive? Lancet 361:2167, 2003.
- ECRIN-TWG, Clinical research in Europe: national differences in legislative and regulatory frameworks. Deliverable 4, 2008, see www.ecrin.org.
- EFGCP Ethics Working Party, Subgroup on Ethics Committees Reviewing Investigational Medicinal Products within the European Union. The procedure for the ethical review of protocols for clinical research projects in the European Union. Int J. Pharm. Med, 2007, 21:1-113.
- The European Parliament and the Council, Directive 2001/20/EC of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. OJEC 1.5.2001, L 121/34-44.
- Hartmann M, Hartmann-Vareilles F, Outcome of the Clinical Trials Directive on clinical cancer research in Europe: a 3-years'-follow-up analysis. Poster. Eur J Cancer Supplements (2007) 5(4):107(abstract 700).
- Hiddo J. Lambers Heerspink, Daniela Dobre, Hans L. Hillege, 1 Diederick E. Grobbee2 & Dick de Zeeuw; for the Collaborative Study Group. Does the European Clinical Trials Directive really improve clinical trial approval time? British Journal of Clinical Pharmacology, DOI:10.1111/j.1365-2125.2008.03246.x.
- Hoey R., The Clinical Trials Directive: 3 years on. Lancet 369:1777-8 (2007)
- ICH Good Clinical Practice Guideline E6 (R1), 10 June 1996.
- Lemaire F. The Nuremberg doctors' trial: the 60th anniversary. Intensive Care Med. 2006, 32:2049-52.

- Lemaire F, Bion J, Blanco J, Damas P, Druml C et al. (ESICM Task Force on Legislation Affecting Clinical Research in the Critically Ill Patient) The European Union Directive on Clinical Research: present status of implementation in EU member states' legislation with regard to the incompetent patient. Intensive Care Med 2005 Feb 15.
- Liddell K, Bion J, Chamberlain D, Druml C, Kompanje EJ, Lemaire F, Menon DK, Vrhovac, Wiedermann CJ. Medical Research Involving Incapacitated Adults: Implications of the EU Clinical Trials Directive 2001/20/EC. Med Law Rev. 2006 Aug 23.
- Liddell K, Chamberlain D, Menon DK, Bion J, Kompanje EJ, Lemaire F, Druml C, Vrhovac B, Wiedermann CJ, Sterz F. The European Clinical Trials Directive revisited: the VISEAR recommendations. Resuscitation. 2006 Apr;69(1):9-14.
- Liddell K, Kompanje EJ, Lemaire F, Vrhovac B, Menon DK, Bion J, Chamberlain D, Wiedermann CJ, Druml C: Working Group of the Vienna Initiative to Save European Academic Research. Recommendations in relation to the EU Clinical Trials Directive and medical research involving incapacitated adults. Wien Klin Wochenschr.2006 Apr;118 (5-6):183-91.

Denmark

- Louise Berendt, Cecilia Hakansson, Karin Friis Bach, Kim Dalhoff, Per Buch Andreasen, Lene Grejs Petersen, Elin Andersen and Henrik Enghusen Poulsen, Effect of European Clinical Trials Directive on academic drug trials in Denmark: retrospective study of applications to the Danish Medicines Agency 1993-2006. BMJ published online 6 Dec 2007; doi: 101136/bmj. 39401.470648.BE.

France

- Jaillon P, Demarez JP, History of the Huriet-Sérusclat's law genesis (December, 1988): protection of patients in biomedical research. Med Sci (Paris). 2008, 24:323-7.

Competent authority-related

France

- Afssaps, Rapport d'activité 2008.

Germany

Bfarm, Processing statistics Bfarm, www.bfarm.de > drugs > statistics, updated 26 Feb. 2008.

Italy

- Agenzia Italiana del Farmaco, Bulletin Clinical Trials of Drugs in Italy, 2007 and 2008.

Ethics committee-related

Pan-European aspects

- The Procedure for the Ethical Review of Protocols for Clinical research Projects in the European Union, The European Forum for Good Clinical Practice (EFGCP) Ethics Working Party, Subgroup on Ethics Committees Reviewing Investigational Medicinal products within the

European Union. International Journal of Pharmaceutical Medicine vol.21, No. 1 (pp. 1-113) 2007. Annual Update on www.efgcp.be.

The Netherlands

- Nefarma, Clinical Trial Database (NCTD) Monitor, August 2008, *http://www.nefarma.nl/cms/publish/content/showpage.asp?pageid=1967*.

Commercial sponsor-related

Pan-European aspects

- BIA - EuropaBio White paper, Promoting consistency of implementation and interpretation of the Clinical Trials Directive across EU member States. October 2006.
- Results of the Joint EFPIA-PhARMA Survey on the Implementation of the Clinical Trial Directive in Europe. February 2006.

France

- Leem: Lassale C, Sibenaler C, Béhier JM, Plétan Y, Courcier S., France, an attractive country for international clinical research: 2008 survey. Therapie 63: 345-57 (2008).
- Soizic Courcier, Claire Sibenaler, Monique Couderc, Françoise Trinquet, Yannick Plétan, Catherine Lassale, et le groupe de travail "Attractivité de la France" du LEEM, A Survey on the Position of France in International Clinical Research as Assessed by Pharmaceutical Laboratories. Thérapie 2006 Sept.-Oct.: 61 (5): 407-418, DOI: 10.2515/thérapie: 2006070.

Germany

- Birgit Wolf, Ferdinand Hundt, Genehmigung klinischer Prüfungen in Deutschland. Pharm. Ind. 69, Nr. 12, 1421-1427 (2007).

Non-commercial sponsor-related

International aspects

- Johan PE Karlberg, Investigator Initiated Clinical Trials Characteristics. Clinical Trial Magnifier, Oct. 2008, Volume 1, Issue 10.

Pan-European aspects

- Bassand JP, Martin J, Ryden L, Simoons M: The need for resources for clinical research: the European Society of Cardiology calls for European, international collaboration. Lancet 2002; 360: 1866-69.
- Clumeck N, Katlama C. Call for network of Centres of Excellence in clinical research in Europe. Lancet 2004; 363: 901-02.
- Demotes-Mainard J, Ohmann C. European Clinical Research Infrastructures Network: promoting harmonisation and quality in European clinical research. Lancet 2005; 365, 107-108.

- Federation of European Cancer Societies, Survey on the impact of the directive on academic research, 2005.
- Hartmann M, Hartmann-Vareilles F, The Clinical Trials Directive: How Is It Affecting Europe's Noncommercial Research? PLOS Clinical Trials, June 2006, e13.
- Meunier F, Dubois N, Negrouk A, Rea LA, Saghatchian M, Turz T, Sullivan R, Law K, Tiner R, Throwing a wrench in the works ? Lancet Oncol. 4:717-9, 2003.
- Meunier F, Lacombe D: European Organisation for research and Treatment of cancer's point of view. Lancet 362:663, 2003.
- Moulton B, Save European research campaign. BMJ 328:286, 2004.
- Moulton B, Two years later: the impact of the EU Directive. Why Research in Europe has declined since the implementation of the Clinical Trials Directive. Applied Clinical Trials, Aug 1, 2006.
- Schölmerich J, Billig H, Bouillon R, Makarow M, Højgaard L, Moquin-Pattey C, ESF-EMRC Forward Looks on Investigator-driven Clinical Trials. March 2009 ISBN: 2-912049-95-4.
- van Vyve D, Meunier F. Facing the Challenges of the European Clinical Trials Directive: the European Organisation for Research and Treatment of Cancer perspective, European Oncology, 2008; 4; 1.

France

- Demotes-Mainard J, Chêne G, Libersa C, Pignon JP. Clinical research infrastructures and networks in France: report on the French ECRIN workshop. Thérapie, 60:183-199, 2005.

United Kingdom

- Bell J. Resuscitating clinical research in the United Kingdom. BMJ 2003; 327: 1041-43.
- Hearn J, Sullivan R., The impact of the 'Clinical Trials' directive on the cost and conduct of non-commercial cancer trials in the UK. Eur. J. Cancer 43:8-13, 2007.
- Morice AH., The death of academic clinical trials. Lancet 361:1568 (2003).

II. List of tables

III. List of figures

IV. EudraCT data

Methodology

Following the implementation of the Directive 2001/20/EC, an EMEA-based database for study identification (EudraCT) was created on the 1 May 2004. The information stored in EudraCT are the total of clinical trials applications (CTA) with subtotals for the type of sponsor (commercial or non-commercial) and the type of trial (single site, multiple site, multi-member states or third countries).

All the data presented in this Annex are the total clinical trials applications and since one trial may involve more than one member state, the actual number of distinct trials is less than the number of CTAs.

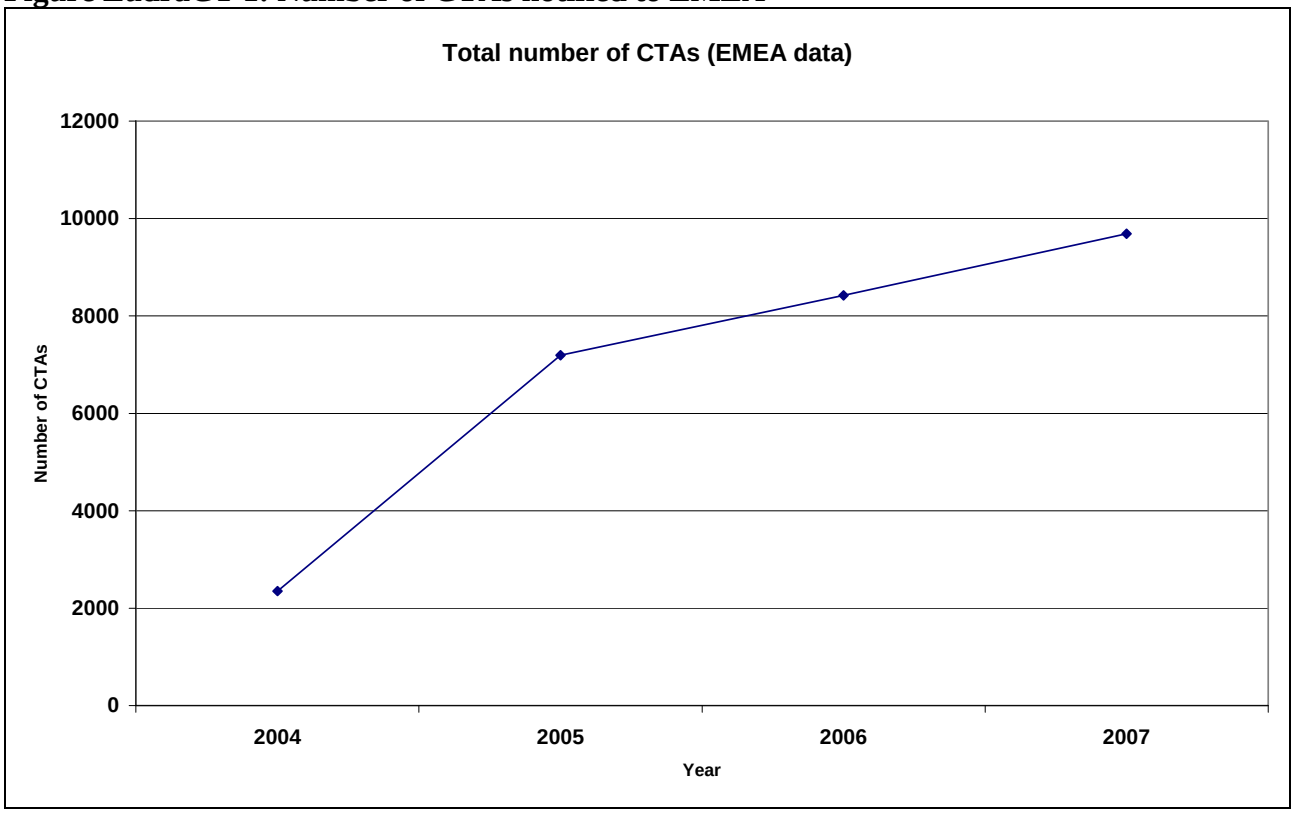
Provision of data from the EudraCT data base for this report was only possible in an anonymous way. Thus the individual curves could not be allocated to particular countries. However, the messages provided were very relevant for the understanding of clinical trial activities in Europe since 2004.

Results

Total number of Clinical Trials Applications notified to EMEA from 2004 to 2007

Data for 2004 were adjusted for covering 12 months. Adjustment assumed a uniform distribution over time; the time series was too short to apply a non parametric approach.

Figure EudraCT 1: Number of CTAs notified to EMEA

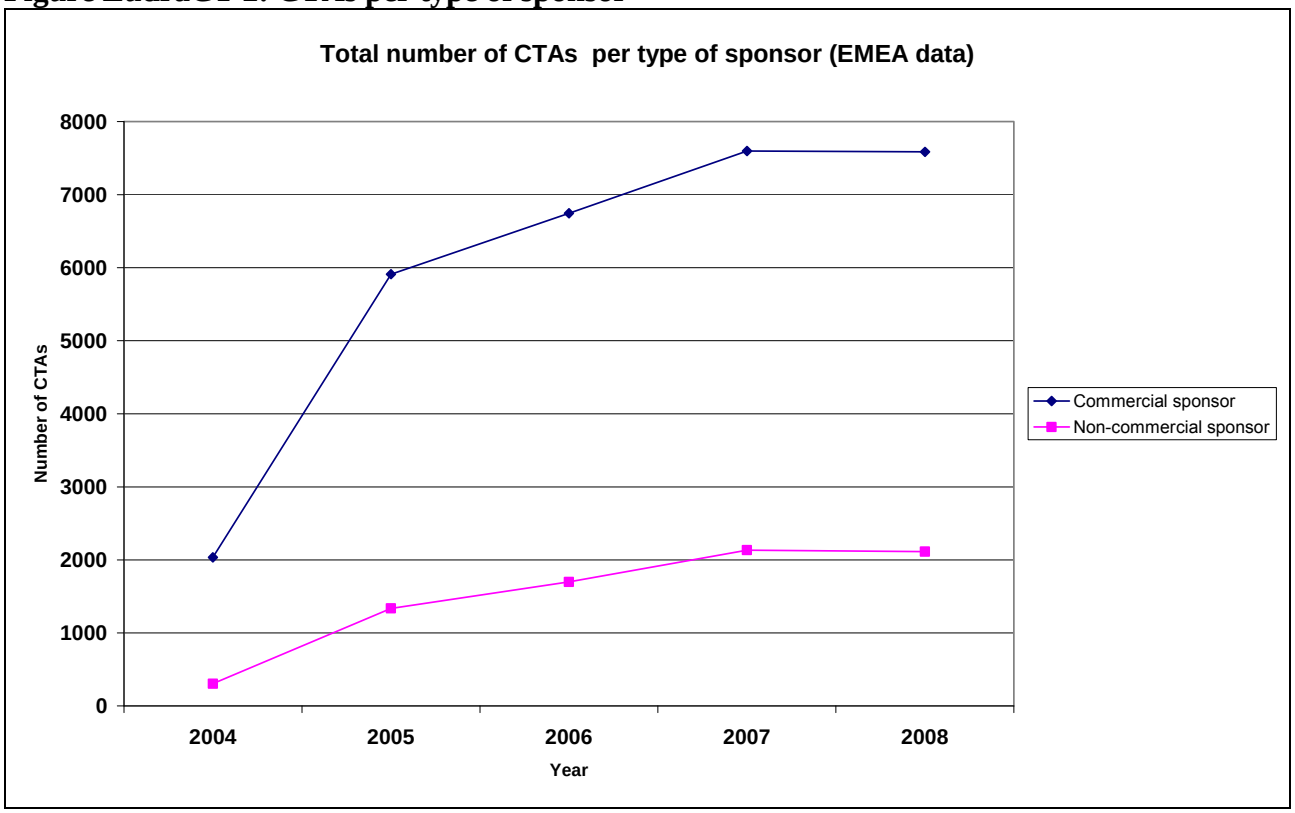


The total number of CTAs increased from 2004 and 2007. Regarding the trend, the data were not compatible with a decreasing trend but compatible with a non-linear increasing trend.

Total number of Clinical Trials Applications notified to EMEA per type of sponsor

Data for 2004 were adjusted for covering 12 months.

Figure EudraCT 2: CTAs per type of sponsor

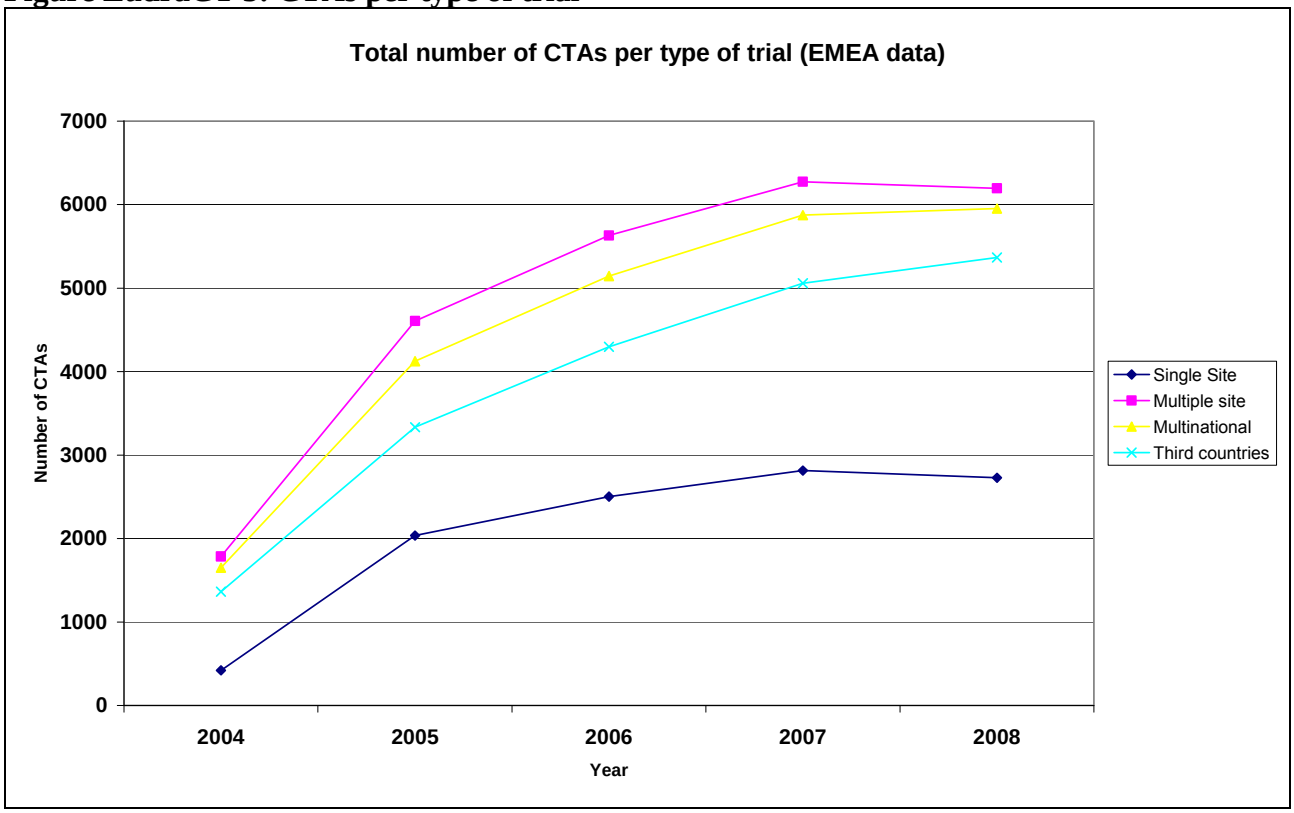


The increase in the number of CTAs was larger for commercial sponsors but the percentage of increase of the number of CTAs was consistently larger for non-commercial sponsors from 2004 to 2007.

Total number of Clinical Trial Applications notified to EMEA per type of trial

Data for 2004 were adjusted for covering 12 months.

Figure EudraCT 3: CTAs per type of trial



The total number of CTAs, for all types of trials, increased every year from 2004 to 2007. The increasing trend over time of the number of CTAs was not statistically different for the different categories.

Total number of Clinical Trial Applications notified to EMEA per country

The countries were defined in 5 categories depending on the level of activity considered as the number of CTAs submitted in 2007:

- Very important activity with more than 1000 CTAs in 2007 (category 1)
- Important activity with a number of CTAs between 249 and 609 in 2007 (category 2)
- Medium activity with a number of CTAs between 93 and 181 in 2007 (category 3)
- Low activity with a number of CTAs between 31 and 57 in 2007 (category 4)
- None or very low activity with a number of CTAs below 11 in 2007 (category 5)

Figure EudraCT 4: CTAs per country (category 1)

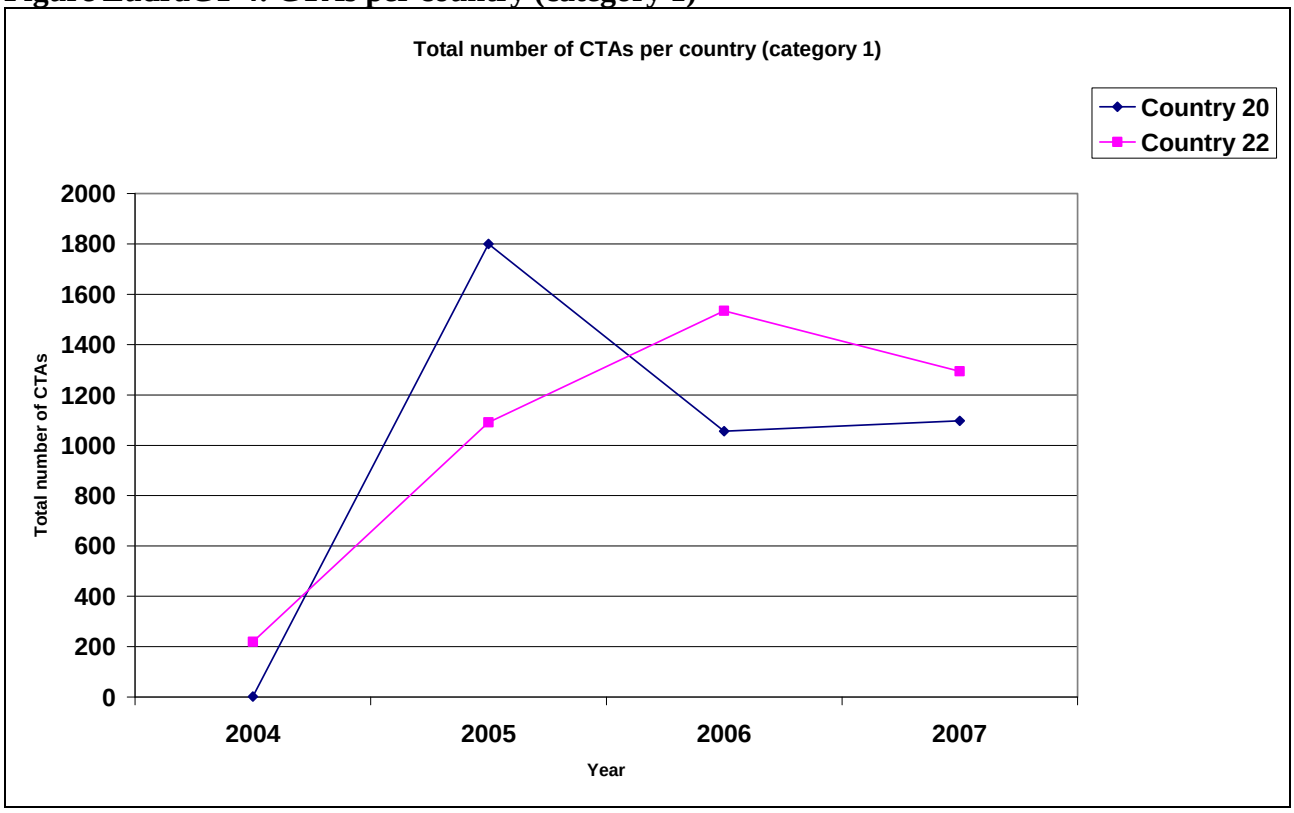


Figure EudraCT 5: CTAs per country (category 2)

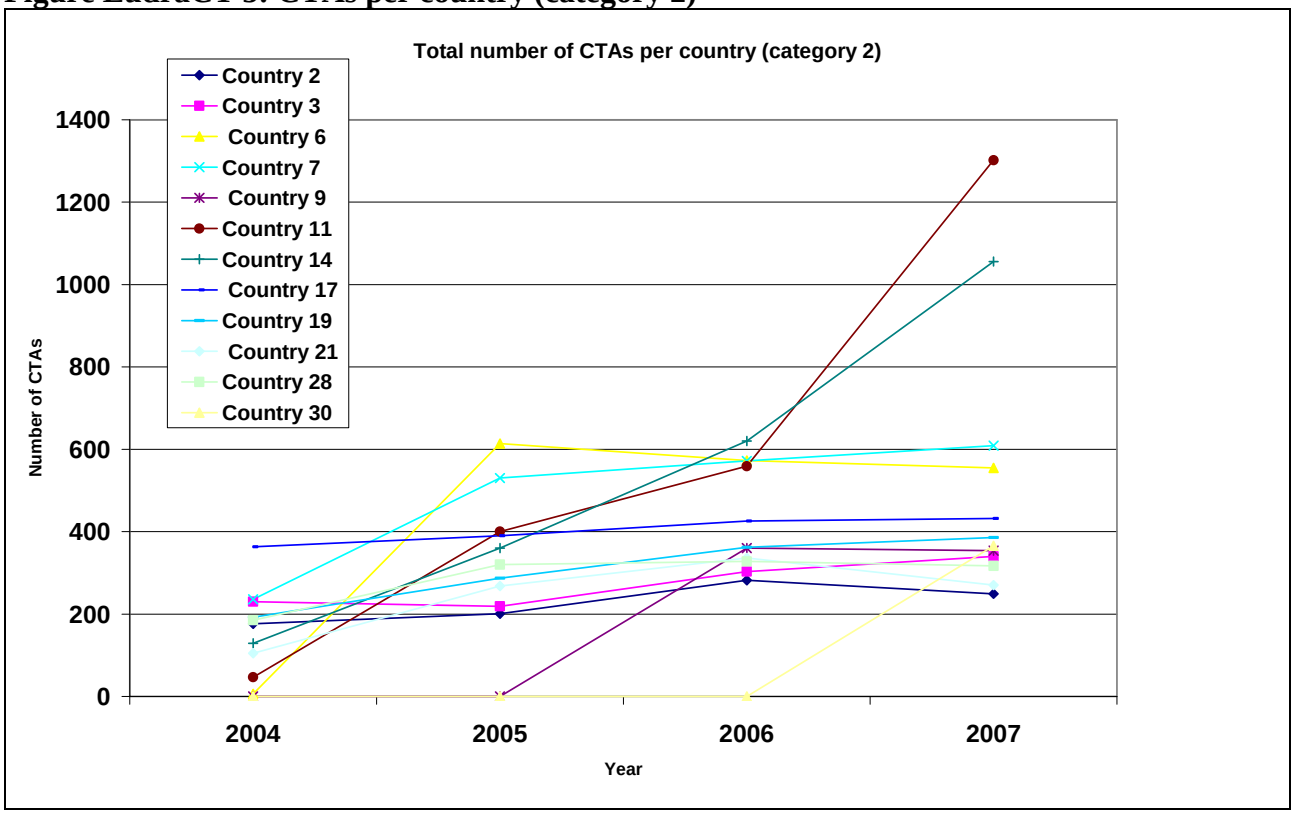


Figure EudraCT 6: CTAs per country (category 3)

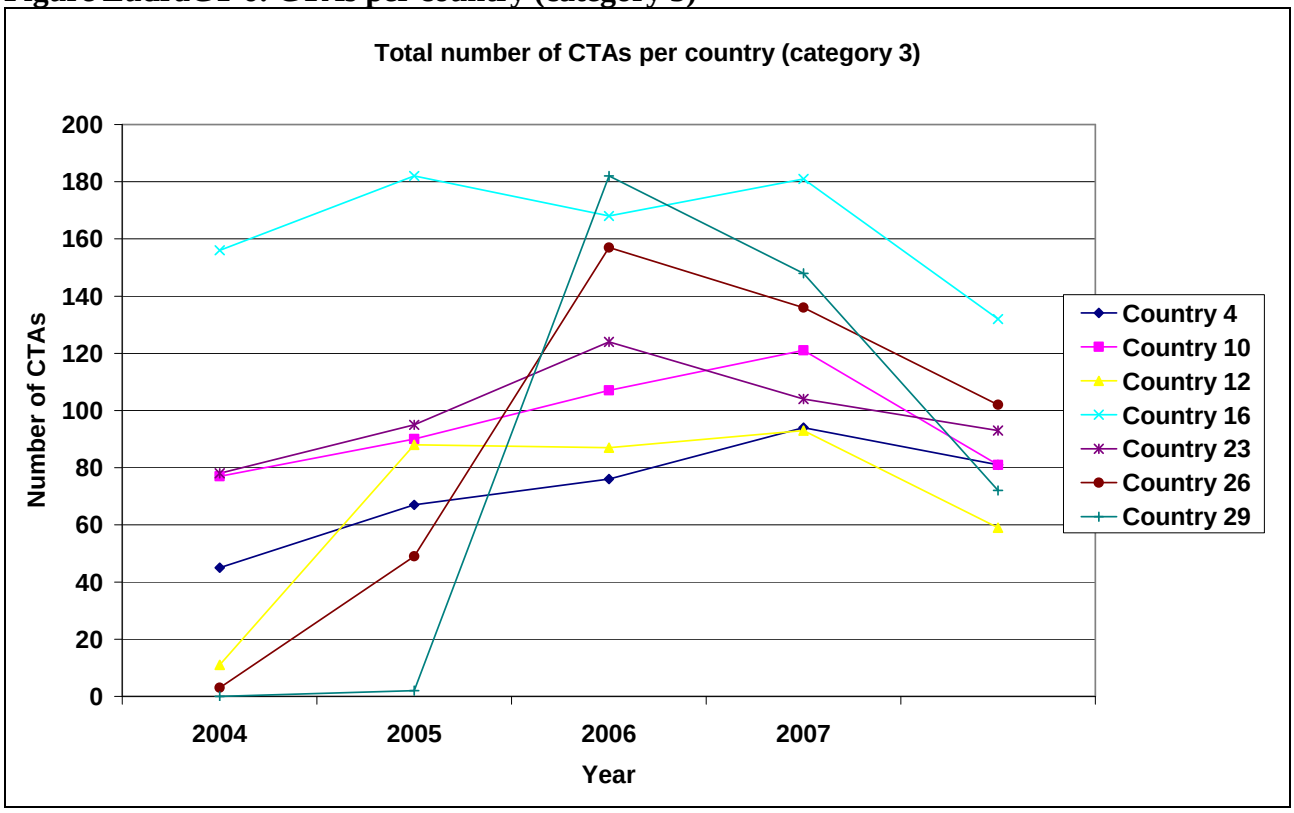


Figure EudraCT 7: CTAs per country (category 4)

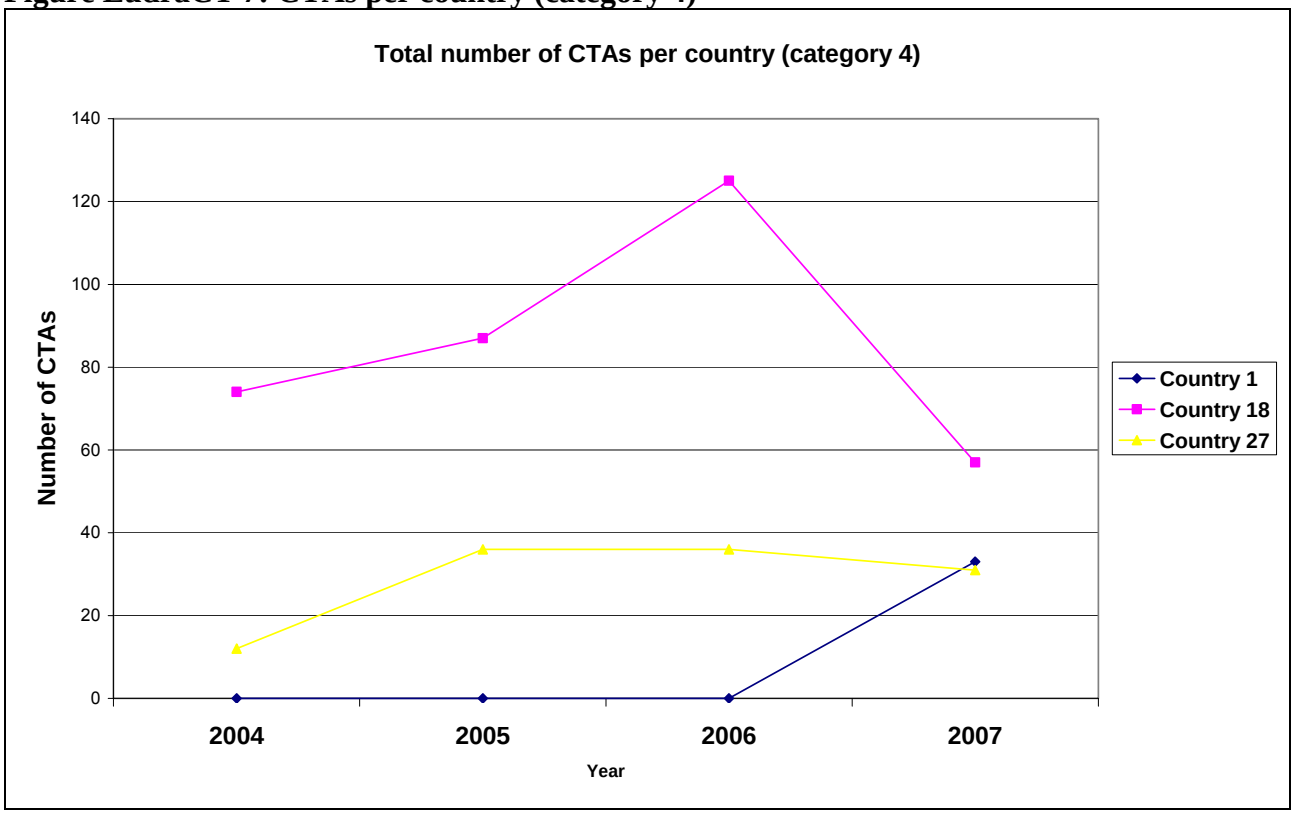
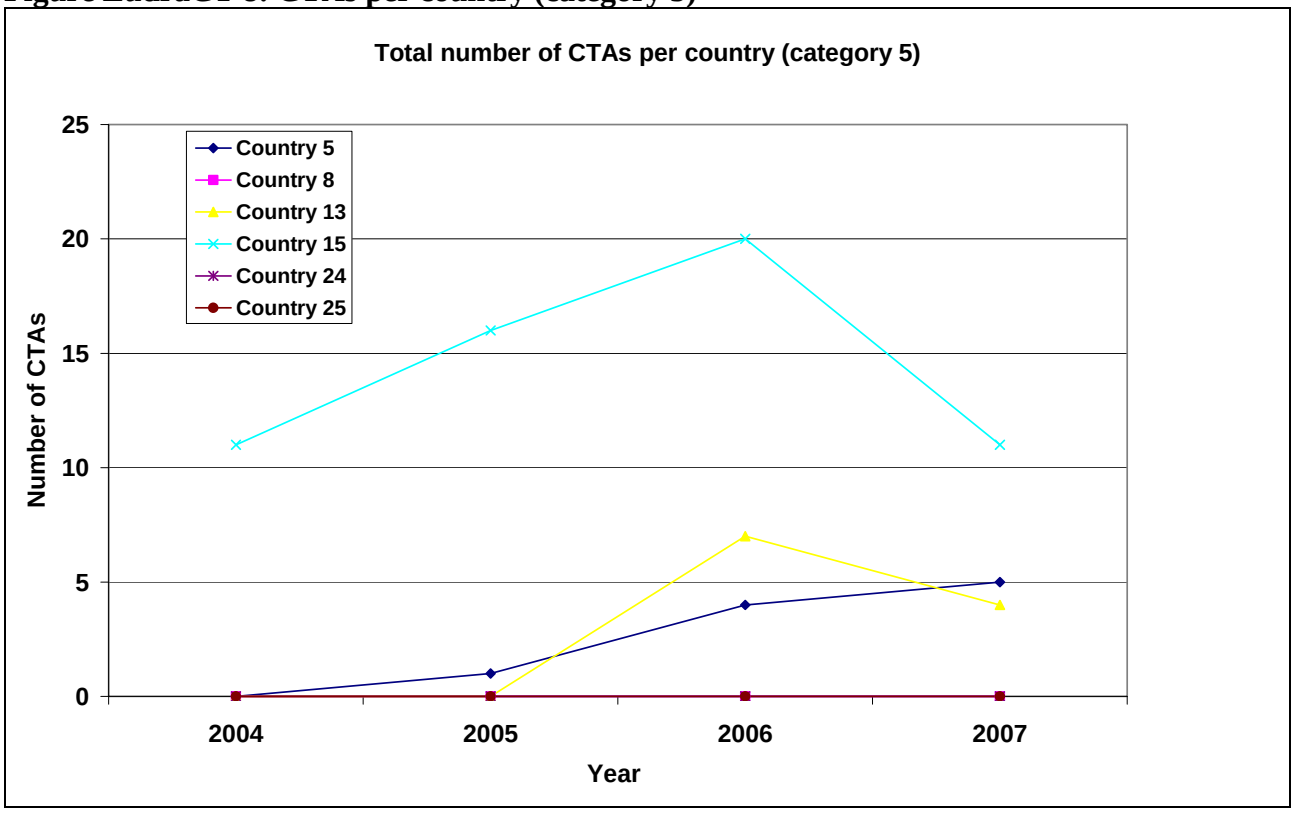


Figure EudraCT 8: CTAs per country (category 5)



- There was an increase of the number of CTAs from 2004 to 2007 which could not be explained by random fluctuations.
- Data showed drastic increases in the number of CTAs that occurred for several countries at various years. This probably reflected the time of enforcement of the CTD in the country.
- The consistent increase of the number of CTAs observed, whatever the breakdown of data, was probably due to the variation of the date of enforcement of the CTD in the different countries.
- Time trend in the number of CTAs when pooling all the countries did not reflect variation in the number of CTAs.

V. ECRIN experience[38]

Clinical research is the basis of a well functioning, evidence-based health care system. European Clinical Research Infrastructures Network (ECRIN) is designed to integrate clinical research in Europe through the interconnection of national networks of clinical research centres (CRC) and clinical trial units (CTU) and to develop services to provide support for multicentre clinical studies in Europe.

Entering into force in 2004, the European Directive 2001/20/EC aimed to harmonise European clinical research. The task of ECRIN Working Group 2 is to describe the regulatory framework for clinical research and how to interact with competent authorities in ten ECRIN countries (Austria, Denmark, France, Germany, Hungary, Ireland, Italy, Spain, Sweden, United Kingdom). These countries represent about 70% of the EU population (345 million out of 493 million inhabitants).
Knowledge of the regulatory requirements is a prerequisite for conducting multi-national clinical research. ECRIN seeks to elucidate legislative and regulatory discrepancies in order to obtain the knowledge and tools to better conduct European-wide multi-national clinical research. ECRIN's Working Group 2 performed a survey in order to collect relevant information on national regulations, rules, and requirements for all categories of clinical research, to delineate these different categories of clinical research, and to identify the national requirements for those categories of research. The information was expanded upon and verified through teleconferences, meetings, and correspondence.

Methodology

A draft version of the survey was designed and discussed during teleconferences until agreement on the final version. The survey contains general information on the objectives of the survey, instructions to complete the document, and three different sections (glossary, requirements for each category of research, and open questions).

Definition of categories of clinical research

Designing the survey required to reach an agreement on common definitions for categories of clinical research. Seven main categories were considered, each split into sub-categories.

1. Clinical trials on medicinal products.
2. Clinical trials on medical devices.
3. Other therapeutic trials (including radiotherapy, surgery, transplantation, transfusion, cell therapy, physical therapy, psychotherapy trials).
4. Diagnostic studies.
5. Clinical research on nutrition.
6. Other interventional clinical research (including complementary and alternative medicines, biobanks, physiology, physiopathology and psychology trials).
7. Epidemiology (observational studies).

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Survey on national requirements for each category of research

For each of the seven categories of research, the following questions were asked:

- is a submission to an ethics committee required (specify the name of the committee and who is responsible for the submission)?
- is a submission to competent authority required (specify the name of the competent authority and who is responsible for the submission)?
- is there a specific procedure for substantial amendments?
- is there a requirement for a sponsor and is co-sponsorship allowed?
- is insurance required (specify who is covered; sponsor, investigator, participant)?
- adverse event reporting (specify which adverse events have to be reported by the sponsor, when, and to whom)?
- is a safety report requested?

A list of further questions was included in order to detail some aspects of the regulation, of specific categories of research and expectations regarding clinical research in Europe. The survey also contained questions open to comments and suggestions from the WP2 members on how to improve EU clinical research, how to improve competent authority working practice, and what are the expectations for future EU regulation on clinical research.

The final version of the questionnaire was circulated to the ECRIN members of: Working Group 2 on 'regulation and interaction with competent authorities'; Working Group 1 on 'ethics and interaction with ethics committees', and Working Group 3 on 'adverse event reporting'. The preliminary results were discussed during several teleconferences and in a face-to-face meeting in Paris (19 and 20 May 2007) and Brussels (19 and 20 May, 2008). Moreover, specific teleconferences were organised between the chair and national representatives in order to discuss national aspects in-depth.

The graphic representation (Table ECRIN 1) is a summary of the regulatory requirements for various categories of clinical studies in the ten ECRIN countries (Austria-AT, Denmark-DK, France-FR, Germany-DE, Hungary-HU, Ireland-IE, Italy-IT, Spain-ES, Sweden-SE, United-Kingdom-UK) in terms of ethics committee approval, competent authority authorisation, need for a sponsor, need for insurance, and adverse event reporting.

Major findings

We identify the following main areas of homogeneity:

- Clinical trials on medicinal products require authorisation of the initial application and any substantial amendments from competent authorities, favourable opinion from ethics committees, a sponsor, insurance, suspected unexpected serious adverse reaction (SUSAR) reporting, and an annual safety report in all ECRIN countries.
- Research ethics committees must approve all interventional clinical trials in the ECRIN countries; all ECRIN countries have legislation, which protects personal data.
- Lack of an official national register for clinical trials in the majority of ECRIN countries, and none of the ECRIN countries are required to store depersonalised or pseudo-anonymised data from trial participants in data repositories.

We identify the following main areas of heterogeneity:

- National requirements regarding competent authority, sponsor, insurance, and adverse event reporting are highly variable for interventional clinical research other than clinical trials on medicinal products.

- The definition of interventional and observational studies varies. In some countries approval by a research ethics committee is not required for observational studies.
- Waiver of purchase cost of the investigational medicinal product for a non-commercial trial.
- Obligation to inform participants about the outcome of a clinical trial.
- Insurance requirements and insurance systems covering participants in investigator-initiated clinical research are highly variable, with additional differences between public or private insurance for clinical research.

Conclusions

The main conclusions of this survey are that:

- The extent of the legislation on clinical research varies from one country to another: some national legislation focus on clinical trials on medicinal products, whereas other legislation considers the protection of participants in all the categories of clinical research.
- There is partial harmonisation in the regulation for clinical research on medicinal products, as a consequence of divergent transposition of the Directive 2001/20/EC into national laws leading to substantial differences in the regulatory framework, making multinational clinical studies very difficult still. The main differences concern the number and role of competent authorities, the number and role of ethics committees, the process leading to the single ethical opinion, the interaction between competent authorities and ethics committees, the requirement for submission to a personal data protection board (or boards). Some countries allow multiple sponsorship, most do not. Insurance for academic research is covered by the public health system in some countries, and in others the union of pharmaceutical companies has contracted a national insurance package covering all the industry-sponsored trials. There are differences in the interpretation of the definition of investigational medicinal product (IMP), especially regarding the background treatment, with major consequences for SUSAR reporting, labelling, and provision by the sponsor. Under some circumstances and in some countries cell therapy products are considered as IMP and in other countries as non-IMP (and in this latter case the trials is not covered by the Directive 2001/20/EC). Finally some countries, and not others, have a definition for non-commercial sponsors or for non-commercial trials, with related adaptations and waivers.
- There are major discrepancies in the regulatory framework for other categories of clinical research, not covered by the Directive 2001/20/EC, especially regarding the requirements for a submission to competent authorities (often distinct from the medicines agencies, depending on the nature of the health product, and in some countries there is a need to submit to a competent authority even in the absence of a health product). There are also major differences in the requirements for a sponsor (required only in some countries, or for particular categories of research), and for adverse event reporting. Some countries have extended the concept of SUSAR to trials on medical devices, or even to all interventional research. There are major discrepancies regarding insurance, which may or may not be required depending on the country for the same protocol. In some countries the ethics committee decides on the need for insurance. There is a need to clarify the definition of categories of research and their interpretation (for instance the border between interventional and observational studies may differ between countries).
- In turn, protection of participants is achieved through submission of protocol applications to the ethics committee in every country, at least for all the categories of interventional research. These ethics committees may, or may not, be the same for every category of research. In some countries observational studies do not require submission to a research ethics committee.

Recommendations

The information gathered from the ten EU countries and the results of the analyses and assessments led to one overall conclusion: heterogeneity in clinical research and the different implementation of the European Directive 2001/20/EC hinders clinical development and is potentially putting EU citizens' health at risk. Furthermore, a number of weaknesses have been demonstrated regarding the function of the EU regulatory authorities. There is therefore a need for change. The outcome of the survey, the answers to the open questions, and the numerous discussions within the WG2 to prepare written suggestions for the EC/EMEA conference on the revision of the Directive 2001/20/EC held in October 2007 led to a series of recommendations to improve and further harmonise the regulatory framework of clinical research in the EU, particularly for investigator-initiated clinical studies.

These discussions highlight the need, at the EU level, for:

- reassessment of the 2001/20/EC Directive, which can currently lead to needless difficulties for academia and industry;
- consultation with both academic and industry sectors on future regulations and legislation followed by assessment of its impact;
- further definition and harmonisation of the roles of the ethics committees (protection of participant) and of the competent authorities (assessment of the health product);
- improved efficiency of the interaction between sponsors, and investigators with the regulatory authorities;
- improved methodology for clinical research;
- further definition and harmonisation of the categories of clinical research, in particular the definition of intervention;
- adaptation of the regulatory requirements considering the risk associated with the trial, with further definition of clinical research with low additional risk, allowing alleviation of needless regulatory requirements;
- promotion and prioritisation of pertinent, independent, investigator-initiated trials and the promotion of clinical research which examines both benefits and harms, or addresses important public health issues;
- open access to clinical trial data so that society can take full advantage of clinical research.

These discussions highlight the need, at the national level, for:

- - extension of the expertise of competent authorities to be able to function as a single authority for all categories of clinical research;
- - harmonisation of procedures between the national competent authorities and the national ethics committees, for all clinical research;
- - improvement of communication between the EU Member States on the implementation of the EU directives, as well as improved communication on how such requirements are implemented in day-to-day research.

Based on the requirements for change identified here, ECRIN Working Group 2 proposes the following solutions to protect the participants, to simplify the regulatory requirements for clinical research in the EU, to promote independent, academic, investigator-led clinical research, to promote clinical research in the EU, to remove bias in regulatory requirements, to create a transparent research community, and to improve the scientific quality and accuracy of clinical research.

1. **To protect the participant:**

- improvement of the scientific expertise within ethics committees with each ethics committee assessing a certain number of applications per year;

- obligatory publication of all depersonalised or pseudo-anonymised data and results of all trials in an open-access clinical data repository, regardless of findings, in order to ensure optimal use of data, to prevent needless duplication of trials and unethical randomisation of participants;
- creation of a consensual register of all trial participants, for all phases of trials in all categories of research. Information should include participant identification, fees received, and periods in which trial participants should be excluded from taking part in other clinical research in order to protect the trial participant. These data should be stored for a limited time only, be accessible by competent authorities, ethics committees, and investigators;
- regulation of the participation of healthy individuals in trials by setting an exclusion criteria period between trials, and by limiting an individual's annual indemnity;
- unification of the definition and the protection of vulnerable participants;
- development of insurance packages for clinical research rather than insuring individual trials. Such packages can be based on existing models available for public institutions (public health system insurance) or for industry sponsors (the union of manufacturers insurance package);
- promotion of independent and stricter governmental audit and inspection.

2. **To simplify the regulatory requirements for clinical research in the EU:**

- adoption of a single, harmonised and comprehensive EU legislation covering all categories of clinical research and all interventions, particularly to define intervention in a similar manner in all the EU countries (as for instance the same trial may be regarded as a clinical trial on medicinal product in one country, and as a non-interventional study in another);
- one-stop shop procedure for submission to a single competent authority in the EU for multinational studies, either through a centralised procedure, mutual recognition, or networking of national competent authorities;
- adoption of a single electronic protocol application for submission to both the ethics committee and competent authority throughout the EU. Such an e-form should be designed through collaboration with users, pilot tested and revised;
- delineation of the roles of ethics committees and competent authorities, whereby ethics committees deal with all of the issues related to protection of participants (from methodological assessment to personal data protection) and competent authorities deal with the assessment of the health product;
- abolition of additional national competent authority requirements, in order to prevent the overlap of responsibilities and reduce of the number of submissions for a given trial;
- modification of the regulatory requirements by applying proportionate risk-adapted regulations to all categories of clinical research;
- unification of the interpretation of the definition and labelling requirements for an investigational medicinal product;
- development of EU directive and guidance documents on collection and handling of human biological material. Establish links between national biobanks.

3. **To promote independent, academic, investigator-led clinical research:**

- prioritisation of relevant, independent, investigator-initiated trials and the promotion of clinical research which examines both benefits and harms, or, important public health issues;
- waiver of fees from national competent authorities and ethics committees for investigator-initiated trials;
- waiver of cost of the investigational medicinal product or device for investigator-initiated trials;
- provision of free practical support and scientific advice to independent investigator-initiated trials from competent authorities.

4. **To promote clinical research in the EU:**

- European collaborative research to be regarded as equally or more desirable as single nation-led clinical research (due to its increased external validity);
- improve access to the collective European population and emphasise the need for clinical research with large sample sizes in order to reduce the risk of random errors ('play of chance');
- facilitation of multiple sponsorship of clinical trials (with a single protocol, a single data base, and a single EudraCT number) where the responsibilities of each party are clearly defined, to enable more academia-led clinical research;
- promotion of clinical research in vulnerable populations (e.g., children, elderly, pregnant women) and rare diseases;
- single-centre and multi-centre trials should be supported by similar infrastructure throughout the European Union;
- funding opportunities for multinational clinical research projects in the EU.

5. **To remove bias in regulatory requirements:**

- direct government funding of national competent authorities and ethics committees, proportionate to the number of clinical trial applications handled;
- continuous review and subsequent update of EU directives, guidance documents, and good clinical practice guidelines according to transparent peer review and the best evidence, in order to improve the clarity and applicability of the requirements;
- full and transparent consultation with research communities in all EU Member States in advance of draft EU directive, regulation, or guidelines;
- removal of the distinction between commercial and non-commercial trials, which would suggest that the credibility of data from academic research is lower than for data obtained through industry-sponsored trials;
- incorporation of the same sensible regulatory requirements, protecting the participants without unnecessary burden, for investigational medicinal products to medical devices, surgery, psychiatry, psychology, physiotherapy, food/nutritional supplements, etc.

6. **To create a transparent research community:**

- - obligation to deposit the electronic protocol application forms for clinical research in an open-access international trials register, in order to avoid unnecessary duplication of ongoing trials and live up to the informed consent;
- - obligation to deposit the resulting adverse event reports, end of trial reports, complete and depersonalised or pseudo-anonymised data and results from the clinical research in an open-access data repository. Depositing data and results to be part of archiving requirement 24 months after the termination of the trial to allow time for peer reviewed journal publication.

7. **To improve the scientific quality and accuracy of clinical research:**

- raise the standard of clinical research by emphasising, and offering scientific advice on how to: achieve large sample sizes; minimise systematic errors ('bias'); minimise random errors ('play of chance'); achieve proper trial design; and pose research questions led by clinical relevance, not by profit;
- involvement of scientific professionals (other than physicians) as consultants or advisors during protocol preparation and all phases of the clinical trial;
- development of professional and accredited data centres and data management, tools, databases, and data handling for all clinical research;
- training in clinical research within a spectrum of scientific disciplines at the pre- and post-graduate level, especially in fostering interaction between academic researchers and industry;
- promotion of clinical trials, which compare two or more authorised interventions.

VI. The Experience of the European Organisation for Research and Treatment of Cancer[39]

1. Clinical research activity

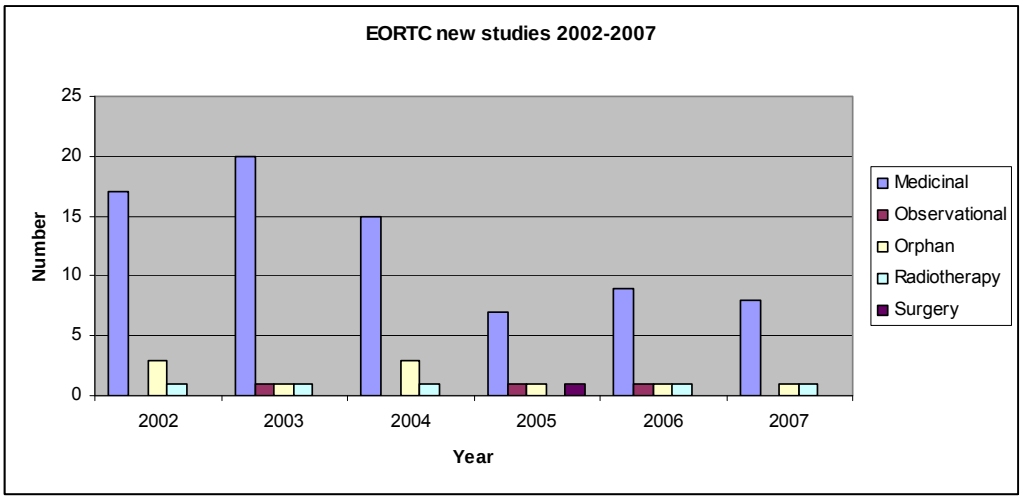

Figure EORCT 1 – EORTC new clinical studies 2002-2007

The EORTC initiated[40] 20, 21 and 18 clinical trials on medicinal products (including clinical trials on orphan diseases or medicinal products with orphan designation) in 2002, 2003 and 2004, respectively, followed by a significant decrease to 8, 9 and 9 clinical trials, respectively, for the years 2005, 2006, 2007. Its clinical research activity in other types of clinical studies (observational, radiotherapy and surgery studies) remained stable over these years. In total, the EORTC initiated 21 clinical studies in 2002, 23 in 2003, 19 in 2004, 10 in 2005, 12 in 2006 and 10 in 2007 [Figure EORCT 1].

All clinical studies (except for one mono-centre) were multi-national. There were 124 EU national submissions[41] opened countries in 2003 versus 34 in 2007. A decrease of almost one third in the number of participating sites was observed from 2003 to 2007, a drop from 330 to 120 sites. In summary, the ratio of sites per study and countries per study in 2002, 18 sites/ study; 7 countries/ study, increased in 2005 to 30 sites/ study and 9 countries/ study; these ratios then dropped from 2005 to 2007 (12 sites/ study; 3 countries/ study) [Figure EORCT 2].

[39] van Vyve D, Meunier F, Facing the Challenges of the European Clinical Trials Directive – The European Organisation for Research and Treatment of Cancer Perspective, European Oncology 2008, Volume 4, Issue 1
[40] Newly authorised studies are the ones for which Competent Authority and Single favourable opinion has been obtained in a given year.
[41] Each time a country has been authorised for a study, it is counted once.

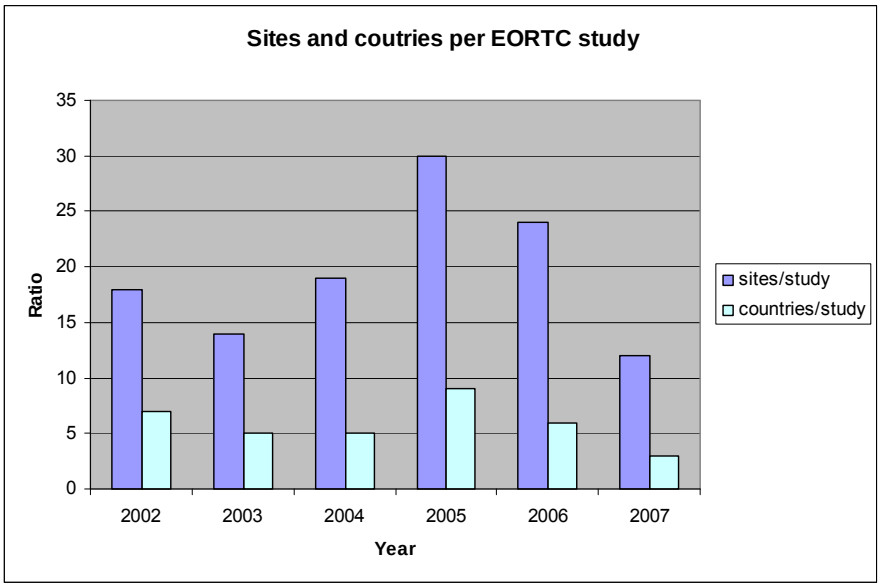

Figure EORCT 2 – Sites and countries per EORTC study

In addition, the number of patients treated in clinical studies, has decreased from 6500 to 5000 over the years [Figure 5], while the EORTC staff has increased. In 2003 6.3 FTEs were needed for all regulatory and administrative tasks (i.e. clinical trials applications) whereas this number has increased to 6.8 FTEs in 2007. Pertaining to clinical trial coordination and monitoring, the EORTC observed an increase from 54.4 FTEs in 2003 to 59 FTEs in 2007. Quality assurance resources rose from 2 FTEs to 2.83 for the same years. All pharmacovigilance tasks are now handled by 6.9 FTEs while 6 FTEs were working on those aspects in 2003 [Figure EORCT 3].

	Workload / full-time equivalents (as internal or outsourced staff)			
	Clinical Trials **applications** to Competent Authorities and Ethics Committees, incl. Investigational Medicinal Product Dossier preparation	Clinical trial **coordination** and **monitoring**	**Pharmacovigilance** tasks: SAE (Serious adverse event) / SUSAR (Suspected unexpected serious adverse reaction) reports, Annual Safety Reports	**Quality** Assurance
2003	6.3	54.4	6	2
2007	6.8	59	6.9	2.83

Figure EORCT 3 – EORTC workload (full-time equivalents)

This increased workload is associated with the medical assessment, preparation and distribution of SUSARs to national Competent Authorities, central Ethics Committees and to participating investigators. Before the implementation of the EU CTD, sponsors were required to report SADRs (Serious Adverse Drug Reactions), except for some countries which only required submitting Suspected Unexpected Adverse Drug Reactions (SUADRs) to the national Competent Authority in which the event occurred, if applicable (e.g. Belgium did not request to be notified at all). Since its transposition into EU Member States legislations, multiple reporting of SUSARs is now the rule: SUSARs must be reported to national Competent Authorities, central Ethics Committees and Investigators from all participating countries, and this reporting must be done according to rules and

formats that vary depending upon the particular member state. SUSARs must also be uploaded to the EVCTM (Eudravigilance Clinical Trial Module) in xml format. Hence, cross-reporting to Ethics Committees and Investigators is also required for SUSARs linked to an IMP under investigation in all other clinical trials involving the same IMP and conducted by the same sponsor.

The EORTC Headquarters staff has tripled despite a drop in the number of newly activated clinical trials and number of treated patients [Figure EORCT 4]. The time elapsed between protocol finalisation and first patient included in the clinical trial has increased from 311 days in 2003 to 348 days* in 2007.

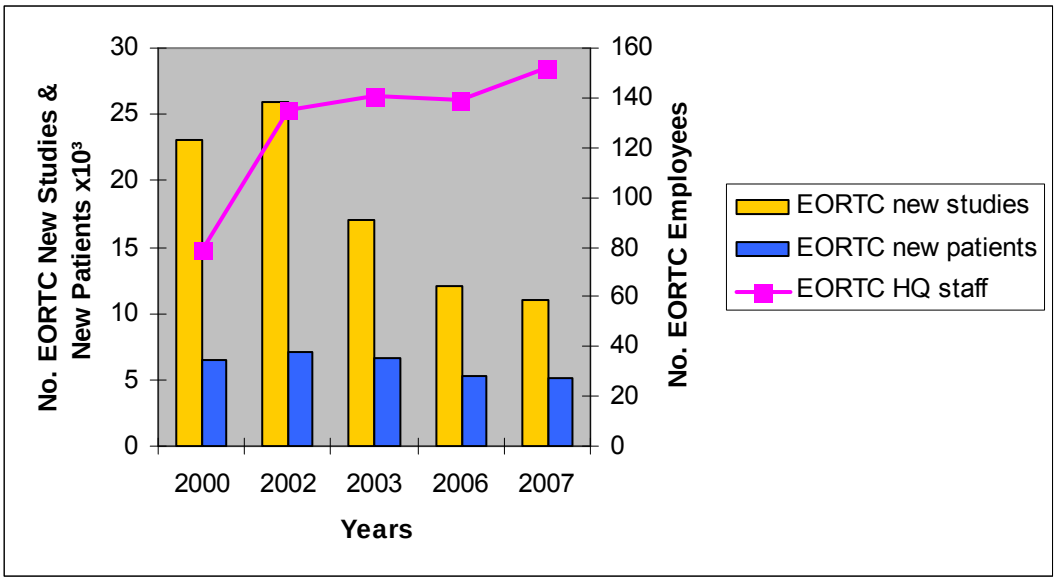

Figure EORCT 4 – EORTC recruited patients, HQ staff and new studies 2000-2007

The EORTC global costs of insurance coverage have multiplied almost five-fold since 1996 with successive increases of 32%, 22%, 63% and 128%, respectively, for the periods 1996-2000, 2000-2002, 2002-2005 and 2005-2006 [Figure EORCT 5]. Prior to the EU CTD, the EORTC insured its clinical trials globally with an annual policy covering all participating countries. Today, national variability in the type of policy required (fault or no-fault policy) and the ceiling of costs and/or coverage force the EORTC to hold two types of insurance policies in order to comply with the national regulations. One is the annual insurance policy that covers a given territory under which a given number of patients are insured per year regardless of the number of activated clinical trials. Up to today, the EORTC has only contracted 6 annual policies corresponding to the equivalent number of countries. The second is the individual insurance policy which is trial-based for a given country. Thirteen countries that participate in EORTC research were insured under this type of policy in 2006.

* average 2006-7

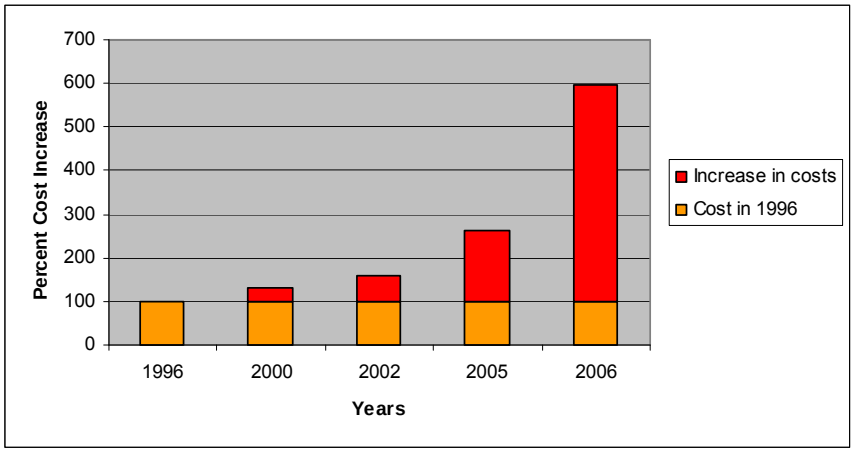

Figure EORCT 5 - EORTC Insurance Global Costs 1996-2006

2. Study cases

1. TEACH

The EORTC initiated the TEACH Survey (Thrombo-Embolism And Chemotherapy), a prospective survey on the incidence of venous thrombo-embolic events during chemotherapy for solid tumours. Finally, after several months of work, the EORTC decided to prematurely close this study (5 EU countries, 1 non-EU country, 13 sites and 64 recruited patients) because of unexpected regulatory and legal complications, i.e., qualification of the survey as interventional clinical trial and the resulting safety reporting requirements.

Initially, researchers thought this survey would not fall within the scope of the Clinical Trials Directive as it would not involve investigational medicinal products (IMPs) and would only consist of two additional ultrasound examinations to be performed prior to treatment. However, the involved National Competent Authorities have surprisingly arrived at very different qualifications for the TEACH Survey. Some have considered it to be a clinical trial, as defined in the EU CTD: Denmark, Germany and the United Kingdom. Other countries such as Belgium, France[42], Poland and The Netherlands have arrived at the opposite conclusion by conceiving this study as a non-interventional trial. Austrian and Greek national Competent Authorities have approved the study as such; without any comments even though safety reporting and on-site monitoring were requested by BfArM and the Danish Medical Authority. The study was finally authorized in Austria, Belgium, Poland, Serbia and The Netherlands and in a non-EU Member State: Turkey.

The TEACH study has been considered, depending upon the countries, as being either in or out of scope of the EU CTD based upon two aspects: 1) the interventional nature of the study (the two additional ultrasounds) and 2) the involvement of IMPs vs non-IMPs (standard chemotherapy: antineoplastic agents). Some countries[43] indeed consider standard treatment as IMP.

The main problem of this case consisted of the interpretation of some dispositions (mainly articles 1 and 2) of the Clinical Trials Directive and the resulting lack of harmonization of the solutions given

[42] A new juridical system, called “soins courants”, has been regulated by a French arrêté of 9 March 2007 which applies to acts and products used in the usual manner but specific monitoring modalities are established in a protocol in advance.

[43] i.e. Austria, Denmark, Germany, Hungary, Poland

by National Competent Authorities. To different qualifications, different juridical systems applied with different rules and protections. This kind of practical case underlines the problematic limitation of the Clinical Trials Directive's scope and the resulting legal vacuum for clinical studies other than clinical trials on medicinal products.

2. A collaborative EORTC/RTOG transatlantic clinical trial, "Phase III trial comparing conventional adjuvant temozolomide with dose-intensive temozolomide in patients with newly diagnosed Glioblastoma"

In 2006, the EORTC launched a Phase III clinical trial in collaboration with the RTOG (Radiation Oncology Therapy Group). This clinical trial is a randomized, multicentre study with the primary objective of determination whether dose-intensifying (increasing the "dose-density") of the adjuvant temozolomide component of the chemoradiation treatment enhances treatment efficacy as measured by overall survival of patients with newly diagnosed glioblastoma or gliosarcoma.

Patients are stratified according to recursive partitioning analysis class (III vs IV vs V), MGMT gene methylation status (methylated vs non-methylated vs indeterminate), and radiotherapy criteria used (standard vs revised European). Patients undergo radiotherapy daily, 5 days per week for 6 weeks. Patients also receive oral temozolomide daily during radiotherapy. Patients are then randomized to 1 of 2 treatment arms. Randomized treatment begins approximately 4 weeks after completion of radiotherapy.

- Arm I: Patients receive oral temozolomide on days 1-5.
- Arm II: Patients receive oral temozolomide on days 1-21.

In both arms, treatment repeats every 28 days for up to 6 courses in the absence of disease progression or unacceptable toxicity. Patients with responding disease may receive up to 6 more courses of temozolomide. After completion of study treatment, patients are followed every 3 months for 1 year, every 4 months for 2 years, and then every 6 months thereafter.

The EORTC actually started its first transatlantic (US – EU) clinical trial after the implementation of the EU CTD and experienced the limitation of the European legislation: the EU CTD has definitely neither encouraged nor facilitated collaborations with the U.S. The main challenges were to first have the study set up in parallel (central approval process in the U.S. vs. multiple national approvals in E.U.) and, second, to solve the pharmacovigilance issues: definitions of events, reporting timelines and requirements. Pharmacovigilance software systems and collected data elements were different from one continent to the other. Additional and unnecessary workload was observed. For example, events recorded in the US but not relevant according to US definition have had to be reported to EU national Competent Authorities and Central Ethics Committees corresponding to the EU SUSAR definition. Hence, the EORTC Pharmacovigilance Unit had to have access and be trained for the US system AdEERS.

This intercontinental trial has been successfully launched, but it started with a one year-delay in the E.U. after a lot of effort have been spent in the comprehension and setting up of this study according to different regulatory and legal frameworks. Working groups have even been established to better understand and solve all these issues.

VII. Forward Looks on Investigator-driven Clinical Trials

Schölmerich J, Billig H, Bouillon R, Makarow M, Højgaard L, Moquin-Pattey C, European Science Foundation-EMRC. March 2009 ISBN: 2-912049-95-4

Research Topic and Methodology

The European Medical Research Councils (EMRC) of the European Science Foundation (ESF) examined the situation of Investigator-Driven Clinical Trials (IDCT) in Europe. In five workshops with different themes and attended by different experts in their field, specific issues which needed to be addresses were identified and recommendations were elaborated. The themes of the 5 workshops were:

- Categories and design of IDCTs;
- Regulatory and legal issues, intellectual property rights and data sharing;
- Management of IDCTs;
- Education, training and careers, and authorship;
- Funding and models of partnership.

A total of 88 recommendations emerged, were subsequently processed following the advice of the Forward Look Management Committee, resulting lastly in a list of 26 recommendations. In a consensus conference the recommendations were discussed and ultimately ranked according to their priority for the participating experts.

A panel of experts subsequently convened to develop a strategy for the sustainable implementation of the recommendations. The advices for developing an implementation plan were presented in this Forward Looking Report. In addition, a separate meeting was held to consider particular problems faced by IDCTs in CEE countries. It was concluded that these countries face broadly similar problems to those in Western Europe, but that the problems tend to be more acute and extreme.

Results

The following recommendations were elaborated in this project:

Theme: Categories and Design of Investigator-Driven Clinical Trials

- *Recommendation 1:*

Categories of patient-oriented research

Regulators to define categories of clinical trial in a way that is based on the type of study, as follows:

1. Clinical trials on medicinal products
2. Clinical trials on medical devices
3. Other therapeutic trials (e.g. radiotherapy, surgery, transplantation, transfusion, physical therapy, psychotherapy)
4. Diagnostic studies (imaging, other)
5. Nutrition studies
6. Other interventional patient-oriented research (e.g. physiology, physiopathology, biobanks, complementary and alternative methods, psychology)
7. Epidemiological studies (i.e. observational)

- *Recommendation 2:*

Interventional *versus* observational studies

Regulators to devise a better classification of clinical studies to facilitate the coordination of studies and to prevent problems generated by different national interpretations. This revision needs to better

define the border between interventional and observational studies, especially for diagnostic interventions.

- *Recommendation 3:*

Phase I-II-III-IV categories

Regulators to consider the diversity of academic studies and dismantle the 'phase IV' category, which is very heterogeneous with randomised trials on marketed treatments, as well as pharmaco-epidemiology studies in which the treatment is not assigned by the protocol.

- *Recommendation 4:*

Commercial *versus* non-commercial trials

Regulators not to distinguish between commercial and non-commercial studies but between commercial and non-commercial (i.e. academic) sponsors, and support should be given to academic institutions acting as sponsors. In turn, regulatory requirements should be adapted to reflect the risk associated with the study, not its commercial or non-commercial objective.

- *Recommendation 5:*

Paradigm shift by biomedical breakthroughs

Funding agencies, universities and hospitals to:

- Rethink the model of patient-oriented research further to the -omics paradigm shift (e.g. develop new methodologies, etc.);
- Fully exploit in a more pre-emptive and well planned manner the knowledge produced by new biomedical breakthroughs. This will require the creation of sufficient infrastructure for translational studies (including tissue and sample banks) and harmonisation of regulations for sample storage, sample shipment and use of biobanks;
- Help clinical investigators with good infrastructure and well organised clinical research centres that provide adequate manpower to plan and execute clinical research and IDCT.

- *Recommendation 6:*

Adequate scale for IDCT

Funding agencies to allow universities, hospitals and learned societies to conduct solid, multinational, large-scale investigator-driven clinical studies based on the correctly powered scale. This should be facilitated by providing the necessary funding, and also by creating an appropriate environment (such as networks, infrastructure, less bureaucracy) to perform such studies. For smaller scale proof-of-concept studies the funding and structure of organisation of the trials should be adapted appropriately.

Theme: Regulatory and Legal Issues, IPR and Data Sharing

- *Recommendation 7:*

Risk-based approach to regulating clinical trials

Regulators to minimise requirements (submission to ethics committee) for studies whose risk is similar to usual care, and to use a broad risk-based categorisation.

For example:

Level A – low risk (such as non-interventional pathophysiology, imaging)

Level B – similar to usual care (equivalent to most phase IV clinical trials)

Level C – moderate risk (most phase III clinical trials)

Level D – high risk (most phase I-II drug trials, gene or cell therapy)

and to bear in mind to reduce the administrative burden.

- *Recommendation 8:*

Management by a risk-based approach

  - All procedures and requirements be adapted to the appropriate level of risk, include the risk-based approach in the CTD requirements and consider exempting low-risk IMP studies from the CTD requirements;
  - Specific populations (e.g. children) or the use of IMPs outside their licensed indication(s) should not be considered to be automatically 'Level D – high risk'.

- *Recommendation 9:*

Ethics committees

DG Sanco and national regulators to:

  - Define a common mission for the ethics committees;
  - Encourage networking and accreditation of ethics committees;
  - Harmonise national procedures for assessment by Ethics committees that might lead to a real single opinion per country;
  - Increase ethical standards of clinical trials.

- *Recommendation 10:*

Adverse event reporting

We recommend health authorities to:

  - Consider how best to facilitate adverse event detection and reporting;
  - Consider taking advantage of the EU-wide reporting to Clinical Trials of Investigational Medicinal Products (CTIMPs).

- *Recommendation 11:*

Insurance requirements

National funders, ministries of health, insurance companies and relevant government and academic institutions set up a multinational experts taskforce with a clear mandate to:

  - Harmonise insurance requirements;
  - Set up a not-for-profit insurance organisation for clinical trials;
  - Explore the possibility to insure studies through the national public health system;
  - Set-up insurance packages.

- *Recommendation 12:*

Intellectual property rights (IPR)

That universities:

  - Include a training and specific education in the clinical investigator curriculum on IPR issues;
  - Develop support for technology transfer professional training;
  - Endorse the continued development of standard template agreements, such as the ones developed for trials by the UK Clinical Research Collaboration (note: this need to be used with caution by those who have not received any training);
  - Encourage specifying in agreements the use of alternatives to litigation in the event of dispute, e.g. alternative dispute resolution, mediation;
  - Encourage development of technology transfer professional training and support, and also general education in IP for investigators;
  - Explore the potential for a more liberal regime in terms of providing exemption to patent infringement where research is being carried out for marketing approval by competent authorities;
  - Promote the creation of an affordable pan-European single language patent system.

- *Recommendation 13:*

Data storage capacity

That the following steps are taken in relation to data sharing, with due respect to the right of investigators to use their data for IP protection and publication within reasonable time:

  - Make explicit the policy on data-sharing in each trial protocol and consider data-sharing as part of the audit of the trial;
  - Continue work to improve access to datasets and to build a clinical trial clearing house (providing information about IDCTs);
  - Make available sufficient funding to support data sharing, to allow, for example, appropriate storage capacity and the installation of relevant architectures;
  - Harmonise data management systems by creating a European standard, e.g. by using ESFRI's European Life Science Infrastructure for Biological Information (ELIXIR) for creating an additional repository for clinical trials data.

- *Recommendation 14:*

Publication of clinical trials results

  - Negative results as well as positive results are published;
  - Sponsors, funders and all responsible organizations be obliged to register and publish all clinical trial data regardless of the type of trial or the phase;
  - The WHO recommendations and clinical trial platform should be implemented through national governments quickly, and registration should be free of charge and done rapidly;
  - The quality of data deposited in clinical trials registries be improved;
  - The transfer of results into clinical practice be facilitated.

Theme: Management of IDCT

- *Recommendation 15:*

Clinical trial authorisations (CTA) process

  - Procedures for submission of CTA to the competent authorities are streamlined in a more coherent and efficient way across Europe, ideally requiring only one centralised application or exploring alternative models such as a lead member state with mutual recognition, or specialisation and networking of national competent authorities;
  - A system allowing electronic submission and a shared database be implemented.

- *Recommendation 16:*

Sponsorship

  - Mechanisms are developed to address pan-European sponsorship of IMP trials (e.g. delegating responsibility; shared sponsorship in each EU country, with one leading sponsor collecting the EudraCT number and one single database);
  - The issue of sponsorship of non-IMP trials should be addressed.

- *Recommendation 17:*

Investigational medicinal products (IMP) requirements

  - The possibility be explored for a waiver for drug supply in public- or charity-funded studies and that the EMEA is asked for help to facilitate collaboration between pharma and academic investigators to ensure that adequate post marketing studies are undertaken;
  - The resources currently available in Europe and the level of the demand be explored, building on ECRIN's current initiative on biotherapy;
  - Marketed drugs provided from routine hospital or clinic supplies should be exempted from the same requirements for labelling and accountability in the pharmacy as non-marketed IMP (even if not in the licensed indications).

- *Recommendation 18:*

Pharmacovigilance reporting

  - National interpretations of pharmacovigilance requirements are harmonised within Europe and internationally, especially with the US;
  - Effective pharmacovigilance procedures be developed for pan-European non-commercial studies by facilitating electronic reporting via EudraVigilance through the competent authorities with onward transmission to other countries.

- *Recommendation 19:*

Pharmacovigilance notification

  - Immediate SUSAR reporting to ethics committees and investigators be limited to those reactions which affect the safety of current and future participants;
  - The key role of the Independent Data Monitoring Committee (IDMC) be recognised in monitoring the safety of the trial.

- *Recommendation 20:*

Project management

  - — Possible licensing application mechanisms are identified before starting the trial;
  - Existing commercial and open source software systems be reviewed with the goal of European level procurement and/or development.
  - Systems are developed that incorporate quality assurance and enable compliance with regulations and protocol.

Theme: Education, Training, Careers and Authorship

- *Recommendation 21:*

Education and training

  - Universities to establish new clinical investigator programmes, strengthen existing ones and include a training and specific education on IPR issues;
  - Universities, healthcare providers, regulators and the pharmaceutical industry to increase international cooperation in education relating to patient-oriented
  - research by building a European Medical Research Academy; there should be harmonisation of European training programmes for clinical investigators and other patient-oriented research professionals by agreeing on a common training syllabus for clinical investigators at all levels (as suggested in the ESF publication A European Syllabus for Training Clinical Investigators);
  - Universities, healthcare providers and regulators to establish quality control mechanism for clinical investigator training and training facilities by giving accreditation (a "driver's licence") to clinical investigators, and promote life-long training of clinical investigators by establishing mandatory training courses in appropriate subject areas;
  - Funding agencies to establish programmes supporting visits of clinical investigators to centres of excellence in different countries.

- *Recommendation 22:*

Careers

  - Universities, hospitals and/or funding agencies create full and attractive career opportunities for clinical scientists at all stages throughout their professional development: as young scientists during their clinical research training and finally as independent clinical researchers;
  - Universities, hospitals and learned societies present patient-oriented research as an attractive career option by providing predictable career paths (with transparent promotion criteria) for

clinical investigators and by offering them sufficient time to carry out clinical research and to maintain and update their clinical skills. Innovative models of employment should be tested to attract clinicians into research, to create individual career paths to attract young clinicians and to promote mobility of clinical investigators between academia and industry;
- Universities and hospitals build clinical research infrastructure such as hospital clinical trial units and provide better administrative support for clinical investigators;
- Funding agencies and learned societies should sponsor high-level European prizes for patient-oriented research to promote the visibility of such a career path for clinicians as well to highlight the importance of clinical research to the wider public.

- *Recommendation 23:*

Authorship

- Clinical researchers and medical journal editors to closely follow current recommendations relating to authorship and contributorship. Contribution should be based on the International Committee of the Medical Journals Editors' requirements; see www.icmje.org/sponsor.htm;
- Universities, hospitals and funding Agencies to develop strategies to improve listing of academic merits in the CVs of clinical investigators (e.g. by including registration numbers of clinical trials) and recognize the contribution of all who take part in clinical trials, including those who recruit participants.

Theme: Funding and Models of Partnerships

- *Recommendation 24:*

Level of funding for clinical research in Europe

- Innovative clinical trials should be strongly encouraged. This implies that the European Commission (for example through its Framework Programme) should specifically include adequate calls for innovative and scientifically sound IDCT which require international collaboration to generate adequate answers. The funding should be flexible and provide for the full cost of such trials which may be very expensive if large number of subjects recruited to long-term studies are needed to generate the necessary answers. Specific financial support for GMP production of the necessary products should also be part of the financial support, independent of industry;
- Patient-oriented research funding should be started or increased by governments and philanthropic organizations to allow adequate IDCT that can be organised at a more regional level;
- Where appropriate, joint funding should be sought with a stronger input from the patient representatives and other sources of funding;
- A funding mechanism be established for pan-European clinical studies, including pilots and demonstration projects to show the benefit of the clinical research infrastructure;
- Funding be increased for the training and life time careers of the best clinical investigators.

- *Recommendation 25:*

Prioritisation and mechanism of funding IDCT

- A forum at the European level is created to advocate for medical research;
- Specific public funding mechanisms should be established for IDCT and clinical research;
- The different review processes for prioritising funding of trials should be harmonised, for example by using an appropriate peer review system; mechanisms for a dialogue between applicants and peer reviewers have to be part of a peer review process of clinical trials. This peer review process involves considerable expert resources and needs to be remunerated accordingly. In some cases evaluators of grant applications should be given incentives.

- *Recommendation 26:*

Models of partnership

- Specific funding opportunities for IDCT should be established or, where already existing, be expanded to allow appropriate funding for all aspects of clinical research and IDCT. This should include:
- Funding for full career development from training through to support for the best clinical scientists;
- Funding for infrastructure for clinical research and IDCT (physical infrastructure, manpower and access to the necessary laboratory and function tests and clinical imaging);
- Competitive funding for bottom-up or top-down initiatives for clinical research projects. In addition:
- An implementation plan is drawn up to formulate and drive specific actions (based on the given recommendations) and the people who will take care of this be identified;
- A common European-wide funding mechanism is established for supporting EU-wide IDCT;
- European topics of interest be clearly co-ordinated;
- The funding of all stakeholders involved in patient-oriented research (academia, but also regulatory affairs agencies, ethics committees, charities, etc.) be pooled;
- Networks of disease-specific, patient-oriented research excellence be built;
- Funds are made available not only for clinical trials but also for novel add-on biological studies. Funding streams for clinical trials should cover all types, not just medicines (for example in the past charity money has typically been used for pilot projects, because of the willingness of charities to take risk and the speed with which they make funding decisions);
- Scientists be supported in making their bids to the various funding sources – foundations, banks, venture capitalists, etc – according to the different expectations of these bodies;
- Research synergies in biomarker research between BBMRI, IMI and competent authorities be identified and harnessed.

Comments

These recommendations are not only very relevant for non-commercial sponsors but many of them could be helpful for all types of sponsors and should accordingly be pursued in the up-coming discussions on improving the landscape for clinical trials in Europe.