ESF–EMRC Position Paper • December 2011

Proposal for a revision of the "Clinical Trials Directive" (2001/20/EC) and other recommendations to facilitate clinical trials

Contents

Foreword

Improvements in medical treatment can only be achieved through clinical research. Therefore strengthening European clinical research is an important goal of the European Medical Research Councils (EMRC) of the European Science Foundation (ESF). One major objective is to facilitate investigator-driven clinical trials, which is a key part of patient-oriented clinical research and the basis for continual improvements in patient care.

Patient safety and the quality of clinical trials have improved in the EU Member States through the implementation of the Clinical Trials Directive 2001/20/10 EC. However, there are still a number of challenges in the conduct of clinical trials, especially a high bureaucratic burden.

In consequence there have been many discussions at national, European and international levels in recent years on how to improve this situation. EMRC in 2009 published a Forward Look on investigator-driven clinical trials (IDCT)[1]. It is based on a thorough analysis of the issues faced by academic investigators conducting IDCTs, and five top recommendations were identified.

Two of these are:
"To streamline procedures for obtaining authorisation for IDCTs",
and
"To adopt a "risk-based" approach to the regulation of IDCTs".

Different actions at various levels were taken by EMRC to implement these important recommendations, in collaboration with other institutions.

At global level, EMRC triggered the formation of a working group from the Global Science Forum (GSF) of the OECD. This group set up recommendations to facilitate international clinical trials. The resulting report will be published in January 2012.

At the European level, EMRC set up expert groups with European representatives and with representatives from the National Institutes of Health (US) to elaborate concrete suggestions on how to revise the Clinical Trials Directive.

In 2010 EMRC organised several workshops with these expert groups together with representatives from the Directorate General for Health and Consumers (DG Sanco) from the European Commission. The workshops aimed to identify the important issues that hamper clinical trials and work out proposals on how to facilitate transnational clinical trials.

The main results of these discussions are summarised in this position paper. The principal recommendations were:

- To revise the Clinical Trials Directive relating to some issues such as definitions, application procedures, emergency trials.
- In other areas to find national or European solutions without revising the Clinical Trials Directive such as more detailed guidance documents and general recommendations.

We would like to thank our high-level expert groups for their excellent work.

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Abbreviations

CAP: Coordinated Assessment Procedure
CTD: Clinical Trials Directive
DG Enterprise: Directorate General for Enterprise and Industry
DG Sanco: Directorate General for Health and Consumers
ECs: Ethical Committees
EMRC: European Medical Research Councils
ESF: European Science Foundation
IMP: Investigational Medicinal Product
NCAs: National Competent Authorities
Non-IMP: Non–Investigational Medicinal Product
SAs: Substantial Amendments
SAEs: Serious Adverse Events
SUSARs: Suspected Unexpected Serious Adverse Reactions

1. ESF Forward Look "Investigator-Driven Clinical Trials", 2009, ISBN: 2-912049-95-4; www.esf.org/fileadmin/links/EMRC/FL_IDCT.pdf

Introduction

The European Union Directive 2001/20/EC (CTD) was adopted in 2001 to regulate clinical trials in Europe. Its aims were to improve patient safety and the quality of clinical research, and facilitate transnational clinical trials. However, challenges in conducting clinical trials have remained at national and international levels. On the one hand the bureaucratic burden for clinical trials has increased dramatically. On the other hand there are still many differences at the national level between the various agencies or interested parties involved. Authorisation procedures of national competent authorities (NCAs), ethical committees (ECs), insurance requirements, the definition of "sponsor" responsibilities, compliance, interpretation of "good clinical practice" and reporting of adverse events related to the medicinal product have all slightly different focuses or priorities. In addition, the current regulatory framework is applicable to all interventional trials regardless of the amount of risk involved (whether the trial is conducted for regulatory approval of new drugs, for optimisation of treatment or treatment procedures, or to compare the effectiveness of existing therapies). This makes some international trials difficult to conduct in academic settings because of financial constraints.

There have been many discussions and activities at national, European and international levels in recent years on how to improve this situation.

As a result of activities involving various stakeholders – including EMRC – the European Commission began a consultation process in 2007 on the consequences and principal issues of the CTD. In 2010 responsibility for the CTD shifted from the Directorate General for Enterprise and Industry (DG Enterprise) to the Directorate General for Health and Consumers (DG Sanco). Public consultations and multiple workshops with all stakeholders were organised between 2007 and 2010. As a consequence the European Commission has now decided to revise the CTD.

In February 2011 the European Commission consultation paper "Revision of the CTD"[1] was published and interested stakeholders were invited to submit their comments[2]. The main suggestions will be discussed below together with the recommendations from our expert groups. Many of these recommendations were taken into account in DG Sanco's consultation paper.

1. http://ec.europa.eu/health/files/clinicaltrials/concept_paper_02-2011.pdf
2. http://ec.europa.eu/health/human-use/clinical-trials/developments/ct_public-consultation_2011_en.htm

Focus areas

Multiple and divergent assessments of clinical trials (Articles 6, 7, 8 and 9)

Context and issue:
The initiation of an international clinical trial is complicated. In many countries a separate assessment procedure for ECs and NCAs is necessary. In addition, assessment procedures differ from country to country and there is a lack of harmonisation.

EMRC recommendation:
Establish one single entry point with one electronic application package for NCAs and ECs for all Member States which could then be distributed to the different countries. Define responsibilities for ECs and NCAs in the directive.

European Commission consultation paper:
Suggests a single submission with a coordinated assessment procedure (CAP).

EMRC conclusion:
The suggestion of a single CAP applicable in all countries is highly welcome. However this CAP should be clearly described and the role of NCAs and ECs should be well-defined.

Definitions (Article 2)

Context and issue:
The content of the CTD has to be implemented in national law by the different European countries. In the past, many problems occurred because of different interpretations of the CTD at national level. Therefore there is a need for clearer definitions in the directive especially on the two following points.

1) "Clinical trials" vs. "non-interventional trials"

Context and issue:
Each country interprets interventional clinical trials and non-interventional clinical trials differently. The definition is very narrow so that a trial can easily fall "outside definition". As a consequence, there is an "all-or-nothing" approach in terms of requirements. Once a clinical trial is defined as interventional the CTD has to be applied, with all the associated administrative and financial consequences.

EMRC recommendation:
The requirements defined in the directive for such trials should be assessed on a risk-based approach[3].

European Commission consultation paper:
Suggests introducing harmonised and risk-proportionate requirements for clinical trials.

EMRC conclusion:
The criteria for these risk-proportionate requirements have to be clearly defined.

2) Investigational Medicinal Product (IMP) vs. non-IMP vs. auxiliary medicinal product

Context and issue:
There is a lack of a precise definition for an IMP. For multi-centre trials a NCA in one Member State may classify a medicinal product applied within the trial (e.g. rescue medication, challenge agents) as an IMP whereas a NCA in another Member State may consider it a non-IMP.

EMRC recommendation:
A harmonised and clear definition of what constitutes an IMP across the EU would help to minimise the inconsistencies for multi-site studies.

European Commission consultation paper:
Suggests to clarify the definition of "investigational medicinal product" and to establish rules for "auxiliary medicinal products".

EMRC conclusion:
The definitions and rules should be as simple as possible and clear.

Insurance (Article 3(2)f)

Context and issue:
Insurance for patients participating in a clinical trial is obligatory – regardless of the risk involved – whether the trial is conducted for regulatory approval or for optimisation of treatment/treatment procedures, or to compare the effectiveness of existing therapies. This makes clinical trials very costly even if the risk of the trial is similar to daily care. In addition there is a lack of harmonisation for insurance within Europe resulting in drastically differing costs.

3. For more information please see below.

EMRC recommendation:
Two options:
- Clinical trials, even those with low risk, should be insured. In turn, the coverage and duration, and therefore the cost of the premium should be adapted to the trial-associated risks for patient safety.
- Exempt trials with registered IMPs conducted in the registered indication which involve only minimal risks from the necessity of an additional insurance cover.

European Commission consultation paper:
Two options:
- Remove insurance and compensation for low-risk trials.
- Introduce a compensation scheme by Member States.

EMRC conclusion:
Both options could help simplify the insurance requirements but a risk-adapted insurance scheme would be the preferred solution.

Safety reporting (Articles 16 and 17)

Context and issue:
Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring during a clinical trial have to be reported. The current reporting system is highly complex. Different interpretations between Member States lead to various reporting requirements and procedures. Information needs to be provided to multiple parties including ECs, NCAs and investigators in multiple formats. Electronic submission is not always possible.

EMRC recommendations:
- Define clear and simple electronic forms for reporting of SAEs and SUSARs for all Member States with clear definitions of what to report (one sheet to report on) within the scope of the CTD.
- The system has to be structured. It should be clear at what point a trial and/or safety reporting has to be terminated.
- A Data Safety Monitoring Board for SUSARs should be implemented in large trials with patients suffering from a life-threatening disease.
- The directive should be clear on what has to be reported; over-reporting of SUSARs should be avoided, instead a continued risk/benefit analysis and an evaluation of the SUSARs in light of the consequences for subjects' safety are warranted.
- Establish a web-based system which includes a sim-

ple reporting form for SUSARs. Upon submission of the form, the data are submitted electronically to the NCAs and the ECs. The system provides the reviewing-accredited research EC with an overview of all reported SUSARs. SUSARs submitted by investigators are imported into the EudraVigilance database by an office of the NCA to make sure that the data are correct.

European Commission consultation paper:
In general: define more precise and risk-adapted rules for the content of the application dossier and for safety reporting.

EMRC conclusion:
This suggestion is welcome but the criteria have to be clearly defined.

Substantial Amendments (Article 10a)

Context and issue:
Amendments are alterations made to a study after a favourable ethical opinion has been given. Substantial Amendments (SAs) require a favourable opinion from the ECs and/or NCAs before they can be implemented. It is often not clear which SAs need reporting and to whom; there is no harmonisation across Europe.

EMRC recommendations (no European Commission comment):
- Define SAs that need reporting, consult and disseminate the existing EC guidance document[4].
- Clarify mutual roles of ECs and NCAs and put in place coordinated review for those instances where SAs need review of both bodies.
- Make it more simple to submit and review SAs, for instance via electronic systems.
- Mutual recognition and harmonised assessment would be useful.

Labelling (Article 14)

Context and issue:
IMPs are required to be labelled for use in clinical trials. These rules are very strict for low-risk trials with marketed IMPs.

EMRC recommendations (no European Commission comment):
- Additional labelling of authorised products for clinical trials should not be necessary when these are already used in daily medical practice.
- Current restrictions in the CTD on packaging and labelling by university-based pharmacies should cease when the drugs involved are used only within the study. It should be possible that all IMPs, for example, are made up in one hospital pharmacy and delivered to the other participating study sites, since many sites do not have their own pharmacy.

Sponsor (Article 2e)

Context and issue:
The single sponsor is "responsible" towards the NCAs and the ECs. The CTD regulates the *responsibility*[5] but not the *liability*[6] of a sponsor.
- Fund-raising possibilities for non-commercial clinical trials are frequently national and possibly restricted to national sponsors. Therefore, multi-sponsor non-commercial trials have a better chance to find sufficient support.
- Different interpretation and rules over single sponsorship exist in different countries. Definition of the sponsor is not clear (e.g. "funder" versus "sponsor"), resulting in lack of harmonisation.
- In the US the responsibility and liability are not separated. This makes clinical trials in Europe difficult: studies from the US National Institutes of Health in the EU can be funded but not sponsored.

EMRC recommendation:
Change and clarify the definition of the sponsor in the CTD, define the terms "delegation"/"legal representative" of the sponsor, "co-sponsorship", roles, responsibilities, "liability". Definition should allow for two or more persons to take on the responsibilities between them.

European Commission consultation paper:
Maintain the concept of a single sponsor and clarify that the "responsibility" of the sponsor is without prejudice to the (national) rules for liability.

EMRC conclusion:
- If true harmonisation can be achieved and the liability issues are defined separately from the responsibility

4. The Guidance Document has been revised in March 2010 and contains several pages with examples for substantial / non-substantial amendments: http://ec.europa.eu/health/documents/eudralex/vol-10/

5. One person who is responsible to run the trial.
6. "wrongdoer" against a damaged person (in case of harm, patient will take action against everyone involved in the trial).

issues, then the single sponsor solution might be viable. Until then, other models (co-sponsorship) should be possible, otherwise IDCTs in the academic setting might not be feasible.
- It should be clarified that in case of collaboration with organisations from non-EU countries, single sponsor requirement is only applicable for EU territories.

Clinical trials in emergency situations (Article 2j)

Context and issue:
It is difficult to initiate or run clinical trials in emergency situations. There is no regulation for informed consent and there are different regulations and procedures in the different Member States.

EMRC recommendation:
The concept of consecutive consent should be considered for clinical trials for patients in emergency situations where patients are not able to give informed consent and do not have a legal representative. Currently, consent is required from a legal representative. National solutions have been developed and could serve as a model [7,8].

European Commission consultation paper:
Informed consent and obtaining the information from the investigator may take place during or after the clinical trial under clearly defined conditions.

EMRC conclusion:
Both suggestions could be an option to simplify clinical trials in emergency situations.

Risk assessment and risk-based approach

Context and issue:
The current regulatory framework is applicable to all interventional trials regardless of the amount of risk involved.

EMRC recommendation:
A risk-based approach for clinical trials should be introduced.

European Commission consultation paper:
Suggests more precise and risk-adapted rules, which could help simplify, clarify and streamline the rules for conducting clinical trials in the EU.

EMRC conclusion:
It should be clearly worked out what a risk-based approach should look like.

General recommendations

- Make it simple to set up a clinical trial regardless of the definition issues. Provide tools and templates and use friendly electronic systems in English so that physicians/researchers are able to follow the regulations "automatically".
- Make it simple for clinicians to use medicinal products with marketing authorisations in clinical trials.
- If authorised drugs are used they should be reimbursed by the healthcare system.
- Improve education and training for clinical trials.

Conclusion

The CTD was implemented into national law in 2004 and has improved patient safety as well as the quality of clinical trials. However, as described above, different issues still remain that have to be resolved and discussed in detail within many stakeholder groups.

This position paper is the result of a long discussion process with various experts from different stakeholder groups (see below). It contains concrete recommendations on how to facilitate European clinical trials. For some issues, a revision of the CTD will be necessary while for others, local, national or European solutions outside the directive are sufficient. Our recommendations have been discussed with representatives from DG Sanco during workshops organised by EMRC and/or DG Sanco. We are very pleased to see that some of our recommendations have been taken into consideration by its consultation paper.

However it is important to follow up the CTD revision process and see how the content of this paper will be implemented in the revised CTD proposal. We therefore strongly recommend that stakeholders are given the opportunity to comment on the CTD proposal.

7. *The Netherlands:* therapeutic trials can be performed in emergency situations if "beneficial", non-therapeutic trials cannot be performed.
8. *Germany:* There are different special procedures for informed consent (e.g. Heidelberger Model) which, for example, involve a judge. If the patient dies the use of data is yet unclear.

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