

WRITTEN SUBMISSION ON THE OPERATION OF THE CLINICAL TRIALS DIRECTIVE (DIRECTIVE 2001/20/EC) AND PERSPECTIVES FOR THE FUTURE

Only one written submission by organisation to be submitted to the EMEA by 14 September 2007!

Please note that the written submissions and the presentation slides from the meeting will be included in appendix to the report of the meeting and will be published at the same time as the report.

Name of Organisation	Country
European Forum for Good Clinical Practice (EFGCP)	Belgium

The comments and recommendations provided here result from 2 meetings with experts from academia, industry, industry associations, ethics committees and patients organisations from many different European countries, organised by EFGCP in order to identify and discuss areas for improvement in the Clinical Trials Directive (CTD). The proposals presented below are aspects that were agreed among all participants.

In addition, several recommendations were made which received strong support but not approval from all participants; however, these proposals should be further considered:

- A recommendation to include a revision of the GCP Directive 2005/28/EC into this upcoming CTD review process
- A recommendation to define specific facilitating conditions for academic treatment optimisation trials
- A recommendation to consider adding clinical trials with medical devices to the CTD
- A recommendation to include a request for publication of the results of all clinical trials performed in a peer-reviewed journal.

Please submit by 14th September 2007 at the latest to **Kati Almasi** on CTCONF@emea.europa.eu.

Please use the format provided – add as many additional boxes as needed.

Aspects of the Directive 2001/20/EC that work well

Comments	Suggestions
1) Achievement of a single ethics opinion per country is a real improvement	1) However, there is a need to agree on the exact content of Module 2 of the application form.
2) An agreed IMPD format is very helpful	2) However, the content of the CTA dossier should be made identical in all EU member states.
3) 1 CTA and 1 ethics opinion per Member State submitted in parallel or sequentially is a good opportunity to reduce the overall timelines for approval of clinical trials.	3) However, the interaction between Competent Authorities and Ethics Committees is not well enough established and varies, country by country. This frequently leads to delays in study start due to the need for approval of substantial amendments, or requests for protocol changes, by one of the two parties.

Aspect of the Directive 2001/20/EC that do not work well	
Comments	Suggestions
<p>1) Article 2 – Definitions</p> <p>Change in the definition of ‘sponsor’</p> <p>Especially in multinational academic clinical trials, there is a need for the organisation of co-sponsorship</p>	<p>1) EFGCP Proposal:</p> <p>‘sponsor’: an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial; <u>co-sponsorship should be permitted where appropriate and must be covered by a contractual agreement which specifies the roles, responsibilities and liabilities of each sponsor.</u></p>
<p>2) Article 2 – Definitions</p> <p>Change in the definition of ‘subject’</p> <p>The two different types of subjects should be mentioned for clarification purposes.</p>	<p>2) EFGCP Proposal:</p> <p>‘subject’: an individual – <u>a patient or a healthy volunteer</u> – who participates in a clinical trial as either a recipient of the investigational medicinal product or a control;</p>
<p>3) Article 2 – Definitions</p> <p>Additional definition of ‘SUSAR’</p>	<p>3) EFGCP Proposal:</p> <p>(q) suspected unexpected serious adverse reaction (SUSAR): an adverse event assessed as serious and unexpected and for which there is a reasonable suspected causal relationship with an investigational medical product</p>
<p>4) Article 6 – Ethics Committee</p> <p>EFGCP considers a need for formal accreditation of Ethics Committees to ensure their proper establishment, function and supervision.</p>	<p>4) EFGCP Proposal:</p> <p>1. For the purposes of implementation of the clinical trials, Member States shall take the measures necessary for establishment, <u>accreditation</u> and operation of Ethics Committees.</p>

<p>5) Article 8 – Detailed Guidance</p> <p>EFGCP considers that there should be a requirement for adequate education and training to be provided for all personnel involved in the clinical trials process.</p> <p>Experience of EFGCP members revealed that there is no established dialogue between Ethics Committees and responsible Health Authorities about clinical trials approval during the CTA process. This should be formally established to avoid prolongation of the approval process due to substantial amendments required by one of these two parties in the clinical trial approval process.</p>	<p>5) EFGCP Proposal:</p> <p>The Commission, in consultation with Member States and interested parties, shall draw up and publish detailed guidance on the application format and documentation to be submitted in an application for an ethics committee opinion, in particular regarding the information that is given to subjects, and on the appropriate safeguards for the protection of personal data.</p> <p><u>All personnel involved in clinical trials including Competent Authorities, Research Ethics Committees, sponsors and investigators should be qualified by means of education and training.</u></p> <p><u>Guidance should be produced to clarify and encourage appropriate dialogue between all Ethics Committees and Competent Authorities involved in the approval of a clinical trial.</u></p>
<p>6) Article 9 - Commencement of a clinical trial</p> <p>1. For consistency reasons, 'Competent Authority' should be spelled with 'C' and 'A'</p> <p>2. EFGCP is of the opinion that the efforts for the preparation of a multinational clinical trial could be substantially reduced if there were only the need for <u>1</u> CTA from the EMEA to avoid duplication of efforts for submitting the same documentation to all Competent Authorities of the countries involved in the trial and to reduce the workload of the national Competent Authorities who all review the same documentation at the same time. Such an approach would also help to truly reduce the approval period to 60 days as substantial amendments approval due to different opinions of the national Competent Authorities could be avoided. Another possibility could be the sole approval</p>	<p>6) EFGCP Proposal</p> <p>1. Member States and the Agency shall take the measures necessary to ensure that the procedure described in this Article is followed for commencement of a clinical trial.</p> <p>The sponsor may not start a clinical trial until the Ethics Committee has issued a favourable opinion and inasmuch as the Competent Authority of the Member State concerned or the Agency has not informed the sponsor of any grounds for non-acceptance. The procedures to reach these decisions can be run in parallel or not, depending on the sponsor.</p> <p>2. EFGCP Proposal:</p> <p>(2) Before commencing any national clinical trial, the sponsor shall be required to submit a valid request for authorisation to the <u>Competent Authority</u> of the Member State in which the sponsor plans to conduct the clinical trial or to a dedicated CTA Committee for multi-national trials at the Agency.</p>

<p>from one national authority e.g. the national authority of the coordinating investigator. The national authorities would have to be informed about the single specific CTA to enable them to fulfil their obligations of clinical trial supervision and reporting of SUSARs. Whichever system would be adopted would have to allow for one Member State to refuse the CTA without blocking the clinical trial from being performed in the other Member States.</p>	<p>(3) If the <u>C</u>ompetent <u>A</u>uthority of the Member State concerned, or the Agency, notifies the sponsor of grounds of non-acceptance, the sponsor may, on one occasion only, amend the content of the request referred to in paragraph 2 in order to take due account of the grounds given. If the sponsor fails to amend the request accordingly, the request shall be considered rejected and the clinical trial may not commence.</p> <p>(4) Consideration of a valid request for authorisation by the <u>C</u>ompetent <u>A</u>uthority concerned as stated in paragraph 2 shall be carried out as rapidly as possible and may not exceed 60 days. The Member States may lay down a shorter period than 60 days within their area of responsibility if that is in compliance with current practice. The Competent Authority can nevertheless notify the sponsor before the end of this period that it has no grounds for non-acceptance.</p>
<p>7) Article 10- Conduct of a clinical trial</p> <p>The definition of 'substantial' is not clear and permits considerably different interpretations by sponsors, Competent Authorities and Ethics Committees. Also the term 'otherwise significant' does not help with the understanding of the type of amendments that are expected to be submitted for approval. EFGCP therefore proposes to delete the terms 'substantial' and 'otherwise significant' in this article.</p> <p>Again for consistency purposes, Competent Authorities and Ethics Committees should be spelled with capital letters.</p>	<p>7) EFGCP Proposal:</p> <p>(a) after the commencement of the clinical trial, the sponsor may make amendments to the protocol. If those amendments are substantial and are likely to have an impact on the safety of the trial subjects or to change the interpretation of the scientific documents in support of the conduct of the trial, or if they are otherwise significant, the sponsor will consider them substantial and shall notify the <u>C</u>ompetent <u>A</u>uthorities of the Member State or Member States concerned or the Agency of the reasons for, and content of, these amendments and shall inform the <u>E</u>thics <u>C</u>ommittee or <u>C</u>ommittees concerned in accordance with Articles 6 and 9.</p>

8) Article 17 - Notification of serious adverse reactions

EFGCP proposes to restrict expedited SUSAR reporting to the competent Health Authorities. During the EFGCP Annual Conference 2007 on *Ethics Committees in Europe – How to Work with Diversity?*, Ethics Committees members from 32 countries as well as the members of the EFGCP Ethics Working Party and the participants of the 2 EFGCP meetings on the Revision of the Clinical Trials Directive unanimously agreed to this suggestion. The reasons:

Ethics Committees are ‘flooded’ with SUSAR reports from all over the world that require administrative handling. Ethics Committees have neither the capacities nor the competence nor digital means to do ‘signal detection’ or otherwise systemically identify a change in benefit and risk of the clinical trial. On the contrary, their capacities for protecting the patients are blocked by this administrative burden. Other ways need to be identified to enable Ethics Committees to make the required judgements, recognising that Competent Authorities already take appropriate action on receipt of such SUSARs..

A more efficient approach would therefore be a separation of responsibilities for Competent Authorities and Ethics Committees. EFGCP proposes that the sponsor submits safety reports at to be agreed minimum intervals of at least once a year throughout the lifetime of a clinical trial to the Competent Authorities involved including a listing of all SUSARs which occurred over the previous reporting period and a cumulative report of the subjects safety since the start of the clinical trial. The Ethics Committees concerned should receive a summary of these reports evaluating the benefits and risks for healthy volunteers or patients who have participated, are participating or will be participating in the respective clinical trial.

EFGCP also considers it vital that other important safety information is reported expeditiously e.g. non-compliance of an investigational site (whereby “non-compliance” should be defined).

A special process needs to be introduced for the situation of temporary hold or premature termination of a clinical trial due to safety concerns:

Established procedures for rapid information exchange, escalation and appropriate communication to all involved Health Authorities, Ethics Committees, investigators and study participants need to be in place to avoid potential harm to individual study subjects.

8) EFGCP Proposal:

Article 17

Notification of **suspected unexpected** serious adverse reactions **and other important safety information**

1. (a) The sponsor shall ensure that all relevant information about suspected unexpected serious adverse reactions (SUSARs) that are fatal or life-threatening is recorded and reported as soon as possible to the **Competent Authorities** in all Member States concerned, in any case no later than seven days after the sponsor is made aware of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days. **Any change in the benefit-risk evaluation of the ongoing trial resulting in either a temporary hold or premature termination of this study should be reported immediately to the Competent Authorities and Ethics Committees in all concerned Members States, in any case no later than seven days after the sponsor has become aware of the change in the benefit- risk balance.**
 - (b) All other suspected **unexpected serious** adverse reactions shall be reported to the Competent Authorities concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor.
 - (c) Each Member State shall ensure that all suspected unexpected serious adverse reactions to an investigational medicinal product which are brought to its attention are recorded.
 - (d) The sponsor shall also inform all investigators.
2. At a minimum (to be agreed) interval or at least once a year throughout the lifetime of the clinical trial, the sponsor shall provide to the Member States in whose territory the clinical trial is being conducted a listing of all suspected serious adverse reactions which have occurred over the previous reporting period and a cumulative report of the subjects’ safety since the start of the clinical trial. The Ethics Committees concerned should receive a summary of this report, evaluating the **benefits and risks** for healthy volunteers or patients who have participated, are participating or will be participating in the respective

	<p>clinical trial.</p> <p>(...)</p> <p>4. <u>In the event of Competent Authorities of Member States or Ethics Committees becoming aware of any non-compliance having occurred at an investigational site during a clinical study, the Competent Authority or the Ethics Committee concerned shall notify the sponsor of that clinical study and all other sponsors conducting clinical studies at that site, of the specific concerns of non-compliance that have been identified.</u></p> <p>5. <u>In the event that the Competent Authorities in concerned Member States, Ethics Committees or the sponsor consider that a temporary hold or premature termination of a clinical trial due to safety concerns is necessary, established procedures for rapid exchange of information, escalation and appropriate communication to all stakeholders including investigators and study participants need to be followed to avoid potential harm to the individual study subject.</u></p>
<p>EFGCP is of the opinion that the Clinical Trials Directive should pay due regard to legislation that applies to the collection, preservation and transfer of human biological material within the context of clinical trials.</p>	

What can be remedied within the present legal framework (by modification of guidelines or clarifications)?

Comments	Suggestions
<p>1) EFGCP recommends that a change be made to the preamble of the Commission Directive 2005/28/EC concerning non-commercial clinical trials: the responsibility for special modalities should not be left to the Member States level as this will lead to considerable diversification of conditions for multinational non-commercial clinical trials. Instead the European Commission should provide concrete guidance on how far requirements for non-commercial clinical trials can be softened without compromising GCP and quality standards.</p>	<p>1) EFGCP Proposal</p> <p>(...)</p> <p>(11) Non-commercial clinical trials conducted by researchers without the participation of the pharmaceutical industry may be of great benefit to the patients concerned. Directive 2001/20/EC recognises the specificity of these non-commercial clinical trials. In particular, when trials are conducted with authorised medicinal products and on patients with the same characteristics as those covered by the authorised indications, requirements already fulfilled by these authorised medicinal products, as far as manufacturing or importation are concerned, should be taken into consideration. However, it could also be necessary, due to the specific conditions under which non-commercial trials are conducted, that Member States foresee specific modalities to be applied to these trials not only when conducted with authorised medicinal products and on patients with the same characteristics, in order to comply with the principles imposed by this Directive, in particular as far as the manufacturing or import requirements for authorisation and the documentation to be submitted and archived for the trial master file are concerned. The conditions under which the non-commercial research is conducted by public researchers and the places where this research takes place, make the application of certain of the details of good clinical practice unnecessary or guaranteed by other means. Member States will ensure in these cases, when providing for specific modalities, that the objectives of the protection of the rights of patients who participate in the trial, as well as, in general, the correct application of the good clinical practice principles, are achieved. <u>Although no distinction should be made between commercial and non-commercial / academic trials as far as GCP and quality requirements are concerned, some deviations from the general rules could be considered for non-</u></p>

	<u>commercial trials. The Commission will prepare a new draft with guidance in this respect.</u>
2) Creation of a global, easily accessible database, containing all national requirements in English should be added to the Guidance on CTA approval.	2)
3) The request to establish support for administrative and regulatory advice by providing a helpdesk for commercial and non commercial clinical research at the European level should be added to the Guidance on CTA approval.	3)

What should a new legal framework look like?

Comments	Suggestions
1) EFGCP strongly recommends that the Clinical Trials Directive should be converted into a Regulation and that a single central Clinical Trial Authorisation for multinational clinical trials should be introduced by the EMEA.	1)

Participants to the discussion process of the EFGCP written submission

Dr. Antonio José Barros Veloso, President, Comissão de Ética para a Investigação Clínica (CEIC), Portugal

Dr. Tatiana Besse-Hammer, Medical Clinical Studies Coordinator, Institut Jules Bordet, Medical Oncology, Belgium

Dr. Michael Bone, Chairman, Association of Research Ethics Committees, Respiratory Medicine - South Tyneside NHS Foundation Trust, United Kingdom

Dr. Xavier Carné Cladellas, Chief of the Pharmacology Unit, Hospital Clinic I Provincial de Barcelona, Clinical Pharmacology Unit, Spain

Ms. Emmanuelle Ceysens, Legal Advisor, Institut Jules Bordet, Oncology, Belgium

Dr. Maria Conceição, Jurist, Comissão de Ética para a Investigação Clínica (CEIC), Portugal

Dr. Marek Czarkowski, Chairman of Bioethics Committee, Warsaw Chamber of Physicians and Dentists, Department of Internal Medicine and Endocrinology - Medical University, Warsaw, Poland

Ms. Siska De Moor, EU Regulatory Manager, Schering-Plough, EU Regulatory Affairs, Belgium

Ms. Geneviève Decoster, IT & GCP Consulting, Belgium

Prof. Jacques Demotes, ECRIN Coordinator, Institut National de la Santé et de la Recherche Médicale (INSERM), DRCT, France

Mr. Mats Ericson, Director, Regulatory Intelligence, Wyeth Research, Global Regulatory Affairs, France

Prof. Nicola Fabris, General Director, Consorzio Italiano per la Ricerca in Medicina (CIRM), Italy

Dr. Antonio Faria Vaz, Vice-President, Comissão de Ética para a Investigação Clínica (CEIC), Portugal

Dr. Jean-Pierre Girre, Medical and Regulatory Affairs Senior Advisor, Innate Pharma; Board Member, European Forum for Good Clinical Practice (EFGCP), France

Dr. Karin Heidenreich, Senior Public Affairs Manager, Novartis Pharma, Public Affairs, Belgium

Prof. Jean-Marc Husson, Director, Eudipharm; Board Member, European Forum for Good Clinical Practice (EFGCP), France

Prof. Dr. JanHasker G. Jonkman, Professor, University of Groningen, Pharmaceutical Science; Board Member, European Forum for Good Clinical Practice (EFGCP), The Netherlands

Dr. Ingrid Klingmann, CEO, Pharmaplex, Co-Chairperson, European Forum for Good Clinical Practice (EFGCP), Ethics Working Party, Belgium

Ms. Christine Kubiak, Project Manager ECRIN Coordination, Institut National de la Santé et de la Recherche Médicale (INSERM), DRCT, France

Ms. Diana Kyriakaki, Clinical Regulatory Manager, Zeincro Hellas, Clinical Operations, Greece

Mr. Michael Leader, Healthcare Director, EuropaBio, Belgium

Prof. François Lemaire, President, AP-HP, DRC, France

Mr. Pedro Marques, European Aids Treatment Group (EATG), Portugal

Prof. Françoise Meunier, Director General, European Organisation for Research and Treatment of Cancer (EORTC), Central Office, Belgium

Dr. Brian Moulton, CEO, Irish Clinical Oncology Research Group, Ireland

Dr. Detlef Niese, Head, External Relations, Novartis Pharma, Clinical Development & Medical Affairs, Switzerland

Dr. Monika Pietrek, Executive Vice President, PRA International, Global Scientific and Medical Affairs Department, Germany

Ms. Stefanie Pintgitzer, Manager, EuropaBio, Healthcare Council, Belgium

Dr. Monique Podoor, Director, European Organisation for Research and Treatment of Cancer (EORTC), Data Center, Belgium

Mr. Ysbrand Poortman, Advisor, European Genetic Alliances' Network (EGAN); Board Member, European Forum for Good Clinical Practice (EFGCP), The Netherlands

Ms. Isabelle Rooseleer, Regulatory Affairs Manager, Merck Sharp and Dohme, Belgium

Dr. Thorsten Ruppert, R & D, German Association of Research-Based Pharmaceutical Companies (VFA e.V.), Germany

Prof. Jean-Paul Sculier, President, Institut Jules Bordet, European Lung Cancer Working Party, Belgium

Prof. Barbara Sickmüller, Deputy Director General, German Pharmaceutical Industry Association (BPI), Germany

Dr. Jiri Simek, Chairman, Czech Forum of Ethics Committees, Czech Republic

Prof. Ernst Singer, Chairman, Medical University of Vienna, Ethics Committee, Austria

Dr. Jean-Pierre Tassignon, President, Crossover CRI; Chairman, European Forum for Good Clinical Practice (EFGCP), Switzerland

Ms. Dominique Van Ophem, Regulatory Affairs and Quality Assurance Manager for Clinical Research, Cliniques Universitaires Saint Luc, Coordination Générale, Belgium

Ms. Malou Vicente, Clinical Researcher, Institut Jules Bordet, Chemotherapy, Belgium

Mr. Tomislav Vurusic, European Aids Treatment Group (EATG), Croatia

Dr. Frank Wells, Co-Chairperson, European Forum for Good Clinical Practice (EFGCP), Ethics Working Party, United Kingdom

Prof. Sighild Westman Naeser, Committee Member, Central Ethical Review Board, Sweden