

**"CLINICAL TRIALS DIRECTIVE"  
IMPACT ASSESSMENT**

**Response to the European Commission's  
"ASSESSMENT OF THE FUNCTIONING OF THE "CLINICAL TRIALS DIRECTIVE"  
2001/20/EC:  
PUBLIC CONSULTATION PAPER" (9 Oct 2009)**

**European Hematology Association**

January, 2010



## 1. Introduction

The European Hematology Association (EHA) represents 3.600 hematologists. On behalf of its members EHA participates in the assessment of the Clinical Trials Directive (CTD) which was initiated by the European Commission on October 9, 2009.

## 2. Data collection

For the data collection, 22 leaders of large European research groups in hematology were approached. In total, 19 responded (see annex 1). This report was prepared on the basis of their input.

## 3. Comments and suggestion

The comments from the EHA to the specific consultations made are hereby detailed:

**Consultation 1:** Examples for improved protection. Studies showing benefits of the Clinical Trials Directive.

In general, responders indicated that the CTD has contributed to the protection of participants in clinical trials. The CTD requires a better organization and a high standard of information procedures. However, since the criteria for patients' safety in clinical trials varied amongst European countries, some responders mentioned that the implementation of the CTD did not change their standards regarding patient safety before and after the introduction of the CTD.

### **Example 1:**

The consensus forms in the studies AIEOP-BFM ALL 2009 for Acute Lymphoblastic Leukemia (approval still pending) and ICC APL 01 for Acute Promyelocytic Leukemia are clearly more informative than the criteria that were used in studies of the Italian Association of Pediatric Hematology/Oncology (AIEOP) before the implementation of the CTD.

These two studies also improved markedly their organization for notifying SAE and SUSAR.

### **Example 2:**

Academic studies of the German CLL Study Group (GCLLSG) were previously not monitored. CTD now ensures higher data quality and reliability.



Ref:

- 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. 2007 Jan;43(1):8-13.
- Hoey R. The EU clinical trials directive: 3 years on. Lancet. 2007 May 26;369(9575):1777-8.
- Hedgecoe A, Carvalho F, Lobmayer P, Raka F. Research ethics committees in Europe: implementing the directive, respecting diversity. J Med Ethics. 2006 Aug;32(8):483-6.

**Consultation 2:** Is this an accurate description of the situation?

Responders mentioned that there is a wide divergence in the approval process depending on the country, the degree of decentralization of Ethical Committees (EC) and the need of specific requirements by each National Competent Authority (NCA).

Example:

The European Leukemia Net, a project that was financially supported by the European Commission, originally planned to perform some European Studies. Because of the above mentioned reasons this was only partly possible and the study design had to be changed.

**Recommendation:**

Although ethical differences between EU countries have to be respected, the negative effect of the involvement of too many ethical committees (EC's) in clinical trials is a major drawback. This reduced power of studies, delays recruitments, restricts possibility for patients to enter studies and markedly impacts on the realization timing of studies. A harmonization by involving international reviewers in the different European countries could help. More specifically, these reviewers could advice European countries on the effect of their advice and the advice of other European countries concerning the same clinical trial. Besides advice on the contents, reviewers can also advice on the harmonization of the planning.

Furthermore it is recommended to develop strategies to reinforce this part of the CTD. One of the reasons for involving several EC's within the same country may simply be that EC's at various Universities/Institutions may be competitive and feel obliged to add their own comments. One could circumvent this problem by involving reviewers from the sites of more than one EC (University/Institution).



**Consultation 3:** Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?

Responders stated that the description in the EC public consultation paper is accurate. Time to approval varies notably from country to country and within a given country, from center to center, with a broad time range. In competitive trials, this makes patients' enrollment difficult in countries/centers where the process is slow.

**Example 3:**

The start of the AIEOP-BFM ALL 2009 study was delayed because of the above mentioned reason. As a result of that, costs increased and there was a major delay in the implementation of new treatments.

**Recommendation:**

See under 2

**Consultation 4:** Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail?

For trials involving several countries it would be preferable to have a centralized authorization for the entire EU. In trials performed in a single country, approval by the NCA would be adequate (as previously indicated by the CTD), provided that the EU regulation is met.

Alternatively it could be established that each NCA authorization should be valid for all member states. Regarding the approval of Ethical Committees of each member state this should be considered valid for all centers in that member state. This would reduce the waiting time and the bureaucracy and therefore costs, increasing patients' opportunities. To this purpose it would be necessary to solve discrepancies of legal aspects specific for each member state.

**Consultation 5:** Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail?



As in the previous item, in trials involving several EU countries it would be better to have a centralized authorization for the entire Community. In trials performed in a single country, approval by a centralized or a single reference national EC would be adequate. The present system of that consists of an EC approval for each participating institution should be discouraged/avoided for the reasons ad described above.

**Consultation 6:** Is this an accurate description of the situation? Examples?

Discrepancies in the definition of aspects such as substantial amendments, adverse reactions and interventional/non-interventional trials favor conflicts. Definitions should be harmonized for all the EU countries. Regarding substantial amendments and adverse reactions, it is true that different criteria lead in practice to over-reporting.

Another aspect of uncertainty was mentioned. This regards trials where drugs authorized for marketing are used with different modalities (doses, duration, administration route, etc) and evaluated for efficacy in non profit studies. These studies are not observational, but sometimes it seems not very appropriate to consider them interventional. In other words, when authorized drugs are used and the endpoints of the study are non-drug related the procedures could be simplified.

**Examples 4**

If a study wants to asses the effect of an NRM monitoring –or of any marker at the time of enrolment or later- in an other wised standard therapeutic procedure, on response to treatment, rate of remission or outcome, procedures should be less cumbersome.

**Consultation 7:** Is this an accurate description? Can you quantify the impacts? Are there other examples for consequences?

Regarding insufficient patients' protection, responders mentioned that discrepancies in adverse effect reports do not lead in practice to decreased patients' safety. A practical consequence of discrepancies is over-reporting, not the contrary. Again, if the endpoint is a given biomarker there is no patient protection issue (if not ivasive).

Regarding the increase of costs, responders stated that without contributions for example from charity funds of commercial companies, it would be practically impossible for public institutions to conduct studies that comply to the CTD. In this respect it has become difficult for academic institutions to promote/perform non-commercial trials.



### Example 5

SUSAR reporting is costly and involves logistics sometimes too complicated for single centers or small non-profit study groups. One solution could be to grant cheap or free access to existing reporting systems of various pharma companies or large academic study groups. Preferably, on the long run a pan-European SUSAR reporting system could be established.

**Consultation 8:** Can you give indications/quantifications/examples for the impact of each option? Which option is preferable? What practical/legal aspects would need to be considered in further detail? In particular, are the divergent applications really a consequence of transposing national laws, or rather their concrete application on a case by-case basis?

Responders regard both options valid. Moving towards a common regulation that would avoid national transpositions would make the process more straight forward.

Another aspect can also be considered for non profit studies. There are still drugs licensed in one State and not in the other. This is the case for example for L-Asparaginase products. Studies on these drugs in different countries may thus be extremely difficult on a cooperative basis.

**Consultation 9:** Can you give examples for an insufficient risk-differentiation? How should this be addressed?

Responders reported that randomized comparisons of well established therapies should not require the same level of insurance and rules of adverse events reporting as phase I or II trials with new agents/combinations.

**Consultation 10:** Do you agree with this description? Can you give other examples?

In non-commercial trials, each academic institution or national cooperative group should be accepted as a sponsor. In studies promoted by industry, a single sponsor seems adequate.

### Example 6

In the AIEOP-BFM ALL 2009 study, there is one single sponsor (University of Kiel) for 6 different EU States. The process of legal contracts between the University of Kiel and contractors of other states is complicated and time consuming.

**Example 7**

The same situation occurred for GCLLSG in which the University of Cologne is the single sponsor. In the CLL7 and CLL10 studies this has led to a delay of approval by the Austrian authorities of more than 6 months, during which Austrian patients could not participate in these successful trials while already being aware of the studies.

Many examples can be given on the same lines.

**Consultation 11:** Can a revision of guidelines address this problem in a satisfactory way? Which guidelines would need revision, and in what sense, in order to address this problem?

Responders mentioned that a revision is necessary, including the mentioned aspects but also regarding issues of insurance and multiple sponsors, in trials promoted by academic institutions. The major drawback regards the need of a single sponsor, insurance and approval procedures.

**Consultation 12:** In what areas would an amendment of the Clinical Trials Directive be required in order to address the issue? If this was addressed, can the impacts be described and quantified?

The following suggestions were mentioned. A review or amendment of the Directive would be adequate. This should focus on allowing centralized approval in trials involving several countries. Also, several measures should be implemented for less costly and easier promotion of academic trials.

**Consultation 13:** Would you agree to this option and if so what would be the impact?

Academic trials should be regulated by a common European Directive that would recognize their particularities. Leaving academic trials under NCA regulations would not facilitate international collaborations.

**Consultation 14:** In terms of clinical trials regulation, what options could be considered in order to promote clinical research for pediatric medicines, while safe guarding the safety of the clinical trial participants?

There are several reports in the literature addressing the problems of implementing clinical directive in pediatric patients. Research of new therapeutic options in this population should not be heavily limited by regulatory restrictions. Role of parents/tutors should be emphasized,



approaching the level of decision of an adult individual giving his/her informed consent.

A suggested model could be to promote a network of excellence among selected pediatric institutions throughout Europe in order to share the same approach when designing clinical trials in this field.

**Consultation 15:** Should this issue be addressed? What ways have been found in order to reconcile patient's rights and the peculiarities of emergency clinical trials? Which approach is favorable in view of past experiences?

A possible participation in clinical trials in the ICU setting, in case of necessity of this resource, could be included in the consent forms of patients admitted to the hospital. The role of designated representatives in case of patients' impossibility to give consent could also be emphasized.

**Consultation 16:** Please comment? Do you have additional information, including quantitative information and data?

Responders regarded this as a very important issue. Non-EU members should implement the same safety and monitoring rules as EU institutions. Random on-site audits should be frequently performed in non-EU participating centers.

**Consultation 17:** What other options could be considered, taking into account the legal and practical limitations?

All the proposed options are adequate, although some of them may be difficult to apply. Measures 7.3.1. to 7.3.5. seem to be the most feasible.

**Consultation 18:** What other aspect would you like to highlight in view of ensuring the better regulation principles? Do you have additional comments? Are SME aspects already fully taken into account?

The aspects to be highlighted should be:

- a) Centralized approval by a single EU agency and a single EC in trials involving several countries.
- b) Ways to facilitate clinical trials promoted by academic institutions by decreasing bureaucracy and costly procedures.





- c) Less strict regulations regarding insurance, adverse event reporting and monitoring in randomized trials using well established therapies.
- d) Ensuring safety of patients treated outside the EU, in trials promoted by or with participation of European centers.
- e) National or European funding programs should be established which facilitate academic trials aiming at the use of lower doses of certain drugs in various indications (e.g. the monoclonal antibody alemtuzumab in doses of  $1/3^{\text{rd}}$  of the recommended dose was efficient in the maintenance treatment of patients with chronic lymphocytic leukemia (CLL). These trials could lower health care costs considerably, but will usually not be funded by pharma.
- f) Common platform for insurance of academic clinical trials (at the European level) e.g. Austrian insurance companies do not cover costs of patient treated in Romania (in trial settings). Therefore, patients will have to be entered into multinational trials run by European networks. There is thus a need to harmonize protocols and to facilitate the execution of these protocols in member states.  
E.g: pediatric and adult ALL. Acute promyelocytic leukemia.



**ANNEX 1 Overview respondents Assessment Clinical Trial Directive**

<b>Nr</b>	<b>Respondents</b>
1.	Prof. Dr. Michael Pfreundschuh; German High-Grade Lymphoma Study Group University of Homburg / Saar
2.	Prof. Dr. Wolfgang Hiddemann, German Low-Grade Lymphoma Study Group; Klinikum Großhadern, München;
3.	Prof. Dr. Rüdiger Hehlmann; German CML Study Group, University of Heidelberg, Mannheim
4.	Prof. Dr. Hermann Einsele; German Multiple myeloma Group University of Würzburg, Würzburg;
5.	Prof. Dr. Andreas Engert; German Hodgkin's Lymphoma Study Group; University of Köln, Köln
6.	Prof. Dr. Gerhard Ehninger Study Alliance Leukemia University of Dresden;
7.	Prof. Dr. Hartmut Döhner; German-Austrian AML Study Group; University Ulm
8.	Prof. Dr. Bob Löwenberg; HOVON Erasmus University Rotterdam, The Netherlands
9.	Prof. Hervé Dombret; ALFA Group; Institut Universitaire d'Hematologie Hopital St. Louis, Paris



10.	Prof. Jorge Sierra CETLAM Barcelona
11.	Prof. Dr. Miguel Sanz; PETHEMA University of Valencia
12.	Prof. Dr. Emili Montserrat Barcelona
13.	Prof. Dr. Alan Burnett; MRC (AML); University of Cardiff
14.	Prof. Dr. Peter Hillmen MRC (CLL); University of Leeds
15.	Prof. Dr. Pierre Fenaux Hopital Avicenne Bobigny
16.	Dr. Andrea Moicean Romanian Acute Leukemia Study Group
17.	Prof. Dr. Richard Greil; Head of the Austrian Lymphoma Group (AGMT)
18.	Prof. Marco Vignetti MD; Coordinator, Trial Office / Data Center; GIMEMA Foundation
19.	Prof. Jose Maria Ribera Santasusana ICO Hospital Germans Trias I Pujol Barcelona