

Impact Assessment on Directive 2001/20/EC – public consultation

Stakeholder: Academic research organization for independent research

Background

The authors represent a working group of the **DGHO German Society for Hematology/Oncology** on the impact of drug law on clinical trials, with focus on scientifically driven clinical trials, especially on optimizing and standardisation of the diagnostics and treatment of cancer and leukemia patients. The authors also represent the **German Competence Network for Acute and Chronic Leukemias and the Competence Network for Malignant Lymphoma**. These networks have been funded by the German government for more than ten years with the specific aim to strengthen the field of academic clinical research and investigator initiated trials (IITs). The networks represent leaders of clinical trials and large clinical trial groups with long-standing expertise in trials for more than 30 years with several hundred participating hospitals, overseeing data from thousands of patients.

The need for subgroup oriented treatments in rare disease entities highly requires a closer transnational cooperation in international networks, a necessity applying to therapy optimization trials as well as particular innovative drug trials. Many of the study groups have therefore established international networks with the aim to initiate and conduct multinational trials on a European level. Therefore authors also speak on behalf of the **European Leukemia Net (ELN)** as well as the **European MCL Network** which are funded by the European Commission. The authors are also supported by representatives of other European bodies (European Haematology Association, European Society for Medical Oncology).

Based on this background we have to state, that the Directive 2001/20/EC may have had some positive effects for trials sponsored by the pharmaceutical industry, but unfortunately disregarded independent clinical trials, which especially in haematology-oncology are setting the standards of clinical care, in an unacceptable way. The achievements described in the background section of the consultation paper mainly reflect the overall situation for Europe and for commercial sponsors. By handling academic clinical trials in the same way as pharmaceutical industry-sponsored trials, the directive poses a dramatic threat to the successful performance of such trials, for which an urgent medical and public need exists all over Europe.

Good Clinical Practice of the ICH focussed on trials and data for drug authorities only. Thus for trials which aim to optimize treatment with approved drugs, which represent the common rationale of clinical care in oncology, the directive is inadequate. Therefore the following comments focus on academic, interest independent therapy optimization trials (for definition see page 2).

Introduction

The directive clearly had a huge negative impact on academic clinical research and patient care, as it failed to differentiate between academic/therapy optimization trials with a non-commercial-sponsor and market-oriented trials in an appropriate way. Therapy optimization trials focus on mainly registered drugs, to further improve treatment options in the setting of standard care - and the outcome of life-threatening diseases. These trials are mainly coordinated and conducted by academic investigators - medical professionals - who are active in the daily clinical patient care. These investigators are often organised in national or international study groups with long-standing experience and high international reputation.

The objective of research in therapy optimization trials and most of the other academic trials is mainly improvement of survival and also quality of life, but not the comparison of single

drugs. In addition many of these trials cover treatment principles such as drug combinations and also non-drug therapies. This is not at all reflected by the Directive.

In the field of cancer, leukemias and lymphomas a large proportion of patients were treated within such trials, which had a significant impact on quality of care, survival and cure rates and are therefore essential for the patients. Most of the progress in leukemia and lymphoma has been achieved by academic trials.

Negative effects of the directive 2001/20/EC on academic trials include:

- remarkably slower trial implementation
- **dramatically increased costs for bureaucratic issues** lead to a reduction of the number of trials and funds available for scientific questions
- as a consequence there is a shift from completely independent academic trials to trials dominated by pharmaceutical companies; **thus the independence of academic research has significantly decreased since the introduction of the EU directive; clinical trials are monopolized by industry**
- international trials which would be urgently needed particularly in rare diseases have been severely hampered
- less patients are treated in therapy optimization trials
- a loss of benefit as less data can be evaluated
- to take this in numbers: **thousands of patients suffering from a life-threatening disease hope for improved standard treatments within therapy optimization trials which are now significantly delayed or is impossible.**

Thus, the decreased number of conducted trials represents an increased risk for our oncology patients!

- Problems are not a matter of training of clinical investigators.
- Investigators need a more intelligent and cost-effective way to use the available resources – particularly by reducing bureaucracy.
- Investigators do not need additional large centralised (expensive) institutions or networks such as ECRIN to help investigators through the procedures but
- do need regulations which can be easily understood and applied by academic investigators

The following definition is suggested for academic trials:

- Therapy optimization trials= improvement of standard therapy and not evaluation of a single drug
- medicinal products with marketing authorization are used
- generally no aim to obtain or extend marketing authorization beside exceptional cases
- use of combination therapies including non-drug therapies and evaluation of diagnostic procedures
- trial results are of scientific interest
- non-commercial sponsors
- funding by non-profit organisations

Consultation item n°1:

Can you give examples for an improved protection? Are you aware of studies/data showing the benefits of Clinical Trials Directive?

In fact, we cannot give a “real life” example for an improved protection. In contrast the patient safety is reduced since less patients with life-threatening diseases such as leukemias, lymphomas and solid tumors are treated within well planned and well conducted prospective

clinical trials and therefore defined treatment protocols and collection and evaluation of safety and outcome data are lacking.

Furthermore, the question does not reflect the main problems regarding therapy optimization trials. These trials had considered safety aspects also before the directive such as

- acknowledgement of the competent authority
- approval by independent institutional review board
- working principles as given by the Declaration of Helsinki
- continuing education and introduction in the clinical trial concept
- offer the regular use of expert consultations during conduction of the trial

The directive has mainly increased the administrative and bureaucratic burden for clinical trials. Many study groups, scientists and hospitals are no longer able to initiate, coordinate or participate in these trials. In fact, the paper-work requested by IRBs and authorities has not led to any improvement of patient safety.

We have conducted a survey (questionnaire on conditions for investigator-initiated trials) in the Competence Network for Acute and Chronic Leukemias in cooperation with DGHO German Society of Hematology and Oncology and the Competence Network for Malignant Lymphoma; publication in preparation) asking directors of hematology-oncology hospitals in Germany. About one third of the directors stated that they are no longer able to include patients in the appropriate non-commercial trials – not surprisingly because of the huge administrative and additional costs to initiate and conduct a clinical trial as a participating center.

Various reports have already described and measured a similar negative effects on the performance of therapy optimization trials (Bosch 2005; Druml et al. 2006, Elwyn et al. 2005, Hearn et al. 2007, Hemminki and Kellokumpu-Lehtinen 2006; Hackshaw et al. 2008, ICREL Report 2009, Keim 2007, Prichard-Jones et al. 2008, Singer et al. 2005, van Vyve 2008).

**Key Issue n° 1: Consultation item n°2:
Is this an accurate description of the situation? What is your appraisal of the situation?**

Yes, the description is accurate.

The interpretation of regulations varies between different European countries. There are examples for trials which could not even be activated in single countries due to prolonged administrative procedures.

Establishing a single CA for trial application in Europe could be helpful although this is not the major problem. Even with one single CTA the problems with various IRBs remain. Also the problem of sponsor responsibility, which is a major problem of academic trials, would represent a major obstacle.

The splitting of the sponsor function may be especially helpful for academic and therapy optimization trials. A national sponsor for each of the member states may be useful since currently it is impossible for an academic sponsor to fulfil the different interpretations of the EU directive in various European countries.

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

The description is absolutely correct. **Moreover all problems mentioned have to be multiplied for for academic trials!**

The delay in the initiation of national as well as multinational therapy optimization trials has to be highlighted. Academic study groups have expertise regarding the optimisation of

treatment but they do not represent large bureaucratic bodies to deal with the requests of numerous authorities and institutions. Accordingly, some trials could not be initiated and are still in preparation process for more than 5 years in the framework of the European Leukemia Net.

Overall the implementation of the EU directive led to a huge loss of human and financial resources, a backdraw in clinical research and negative effects for Europe in the international competition.

Consultation item n°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?

A voluntary cooperation of competent authorities is no solution since it does not provide the required mandatory guidelines for clinical trial procedures.

Streamlining the procedures (reference chapter 3.3.2.1a) is a reasonable option. It relies on improved collaboration of existing institutions. Thus the set-up of an additional central administrative institution is not required. The following aspects should be highlighted:

- The major problem is the (national) interpretation of the regulations including the trial application as well as inspections. Transparent procedures on interpretation have to be set-up; **a public “clearing-house” for complaints is needed.**
- The procedure should be adapted according to the estimated risk of clinical trials and accordingly **significantly limited for academic therapy optimization trials.**
- Procedures should also consider the fact that **there are many trials without a specific investigational product**
- Paperwork and forms have to be reduced dramatically
- No technical hurdles e.g. specific software requirement should be set-up.
- The central procedure could be restricted to trials intended to be multinational
- The time-lines for acceptance should not be prolonged
- Language-problems should be considered; should all European study protocols, applications and attachments be written in English? This may be a hurdle for practical application by physicians in some European countries.

Consultation item n°5:

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

It is probably correct that IRB fall into the ambit of the member states. However national procedures refer directly to the directive 2001/20/EC, changing the “may” to “must” aspects.

At least in Germany, **the administrative work regarding the IRB applications is one of the major problems for academic therapy optimization trials.** This applies for the application procedure e.g. approval of qualification of centers, qualification of participating physicians (e.g. CVs, financial disclosure, certificates for GCP training) etc. to approximately 50 different IRBs in Germany, translation of all documents (e.g. in Spanish if initiated in Spain), fees (160-3000€ per IRB in Germany, safety reporting, amendments etc. **In Germany for two trials with planned 13 centers and 15 patients and another trial with 280 centers between 12.000 and more than 100.000 copied pages of documents had to be submitted to the IRB!**

The interpretation of the legislation by the IRBs differs dramatically in the member states.

Since this is a result of the directive the EU should take measures to reduce the IRB related paper-work particularly for academic trials and to provide guidelines for the interpretation and practical application of the legislation in the different countries.

In principle, we would be in favor of one IRB in the country of the principal investigator (3.4.1). This procedure may also allow to exchange the SOPs of IRB in different countries. Again the disease-specific expertise of existing IRBs should be expanded. The set-up of a new central bureaucratic structure should be avoided. We also do not rely on a voluntary network of IRBs. Mandatory rules are needed.

Consultation item n°6: Is this an accurate description of the situation? Can you give other examples?

The description is accurate.

Example 1: Substantial amendments lead to huge paperwork, additional costs including fees and currently the interpretation of “major” amendments is very variable. No clear and obligatory information in interpretation is available e.g. by the national authorities. Therefore not surprisingly an overinterpretation occurs. Thus, more detailed information should be provided to the authorities and investigators, e.g. e.g. a new product information should not considered a substantial amendment.

Example 2: The number of persons which have to be informed by SUSAR reports differs by country. In Germany they have to be directed to CA, IRB and all investigators. All institutions are overwhelmed by reports and practically, this led to a reduced alertness. In particular for combination therapies the interpretation of a single adverse event is extremely difficult. Instead, more focus should be placed on the annual safety summary reports and SUSAR reports should only be addressed to the CA.

Example 3: In addition we **seriously suggest to modify the definition of a non-interventional study** (trial is a misleading term for a non-interventional design) in Article 2 © 3rd sentence: “No risky or burdensome additional diagnostic or monitoring procedures shall be applied to the patients and.....”. **According to this revised definition, most therapy optimization studies with approved drugs may be classified as non-interventional studies or trials.**

Inspections:

An additional example for different interpretation of the regulation is the frequency and strictness of inspections by the authorities. In Germany inspections of clinical trial centers and hospitals are performed by the CA but also by local authorities. The inspections of academic and therapy optimization trials are carried out strictly according to ICH-GCP. Centers have additional costs for fees and pre-requisites similar to those for pharmaceutical-industry-sponsored trials. This results in a tremendous additional work load for clinical trial centers and deep frustration of participating hospitals.

Monitoring:

Although the ICH-GCP guideline leaves room for the definition of monitoring in each specific trial, the authorities generally consider an on-site monitoring as necessary – also for therapy optimization trials. On-site monitoring leads to a dramatic increase of costs and is nearly impossible in therapy optimization trials with a large number of centers and in rare diseases with a low number of patients per center. **The regulation should very clearly mention that central monitoring like regular telephone-interviews and data management is sufficient in low-risk therapy optimization trials** and that also for other academic trials reduced monitoring can be considered.

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

Regarding drug-safety: Not the number of reports increases safety but the meaningful interpretation which is often only possible if a certain number of events is analysed. Therefore, the focus should be shifted from single-reports to meaningful summary safety reports. Furthermore safety can be improved by better information of the physicians e.g. in study meetings, which is one major task of the academic clinical trial groups, e.g. in the field of leukemias, lymphomas and solid cancers. Academic trials and treatment-optimization trials are extremely important for post-marketing authorisation surveillance of drugs.

Administrative costs have increased considerably. It is questionable whether the tremendous paperwork has in any way contributed to patient safety. As a consequence, the number of real independent academic trials has dramatically decreased. However the aim should be not to fund a limited number of very expensive trials. We need more, cost-effective “real life” trials in order to improve patient care, outcome and clinical research particularly in rare, life-threatening diseases. Therefore the administrative burden should be reduced significantly.

Funding should also cover costs hospitals participating in clinical trials which have additional work-load such as contract issues, investigator tasks, study nurse work for documentation etc. which is not covered by the health care system.

Consultation item n°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?

Given our experiences with the EU Directive so far, we cannot suggest to adopt the directive as a regulation!

There are various important issues:

1. Rapid changes are urgently warranted in order to stop the waste of money and human resources as well as the loss of scientific merits. Whatever option leads to a rapid reduction of administrative burden for academic trials would be preferable.
2. Definite and transparent interpretation of regulations is needed.
3. Therefore probably both options are needed:
 - a. A rapid amendment to the clinical trials directive (4.3.1) in order to reduce the most negative effects on academic trials or to completely exclude academic trials
 - b. Adopting the directive in a regulation which is the only way to avoid different national interpretations
 - c. Set-up a public forum/clearing house for issues of interpretation, discussion of interpretation, criticism and suggestions from the academic communities

We are extremely concerned about the permanent damage induced by additional delays in adopting a modified directive and the subsequent transfer in national legislations

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

Basically, the principle of proportionality is not considered at all in the Directive.

- It represents a major difference whether an imminent death has to be prevented and survival prolonged in a fatal disease like leukemia or solid cancer, or whether the long term outcome after various lipid lowering strategies is compared.
- Another considerable difference is the registration status of a drug. In oncology many trials aim to optimize the applications of approved drugs with regard to dosage, duration and sequence of treatment. Such trials typically involve only risks which are close or equal to those of usual medical care (as the drugs used have been approved already and are used in routine health care anyhow).

The regulations have to be adapted to the individual risk profile of a trial. A number of factors for risk stratification of trials could be applied as previously reported for risk-adapted monitoring (e.g. OPTIMON, ADAMON (Brosteanu et al. 2009):

- Comparison of the study design to clinical standards outside a trial e.g. in low-risk trials only minor additional safety concerns can be detected in study patients compared to off-study patients.
- Phase of approval of a medicinal product (if any specific)
- Trial-specific factors e.g. study population or trial-specific-aspects like protocol compliance, assessment of endpoints

The risk factors should be used to stratify the trials and reduce the regulatory requirements dramatically for low-risk trials. This applies for

- **IMP** documentation (no single IMP in many of the academic/therapy optimization trials)
- If registered drugs are used: No labelling of IMP, no specific documentation of drug preparation in pharmacies
- Competent authority acknowledgement not confirmation
- Single IRB application
- Central monitoring only e.g. regular telephone-interviews
- Reduced CRF documentation, particularly documentation of AEs
- More flexibility regarding data management
- Reduced safety reporting (e.g. annual summary reports of SAEs/SUSARs) to be sent to only one organization - preferably CA
- National sponsors in international trials
- Divided national sponsors in international trials
- No insurance since in therapy optimization trials particularly in cancer patients nearly all risks are excluded by insurance policies
- No fees for authorities and IRBs
- Reduced inspections, no costs for inspections
- Reduced application documents (e.g. no financial disclosure)

Consultation item n°10: Do you agree with this description? Can you give other examples?

We absolutely agree with this description. For practical realization of international academic trials we need the opportunity to have responsible national sponsors in each participating country. The clinical trial protocol may remain identical with the same Eudra-CT number. Alternatively, a complicated system of delegation contracts would have to be set-up or the identical clinical trial has to be initiated separately in various countries I.

Consultation item n°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?

Particularly in rare diseases, e.g. leukemias, mantle cell lymphoma, marketing authorization holders are not interested to apply for registration. Therefore, non-commercial trials are essential to evaluate these treatments independently. This offers the unique opportunity to provide patients access to new treatments, to re-evaluate and further optimize their application including long-term observation. Furthermore, many non-commercial trials at least in hematological malignancies test multi-drug combinations including other treatments, e.g. irradiation, haematopoietic stem cell transplantation. In selected cases only, these data may later be used for extension of marketing authorization.

The best solution is to provide directives for academic trials across Europe in a separate directive or in a new chapter of the current directive (see below). It is a pre-requisite to find appropriate definitions not only based on the type of sponsor (academic/industry) but also on the risk of the study (see above). However this would be only complimentary. The real problem can only be addressed by a EU directive defining non-commercial / low risk trials with reduced regulatory requirements. Member states should be asked not to over-regulate these trials.

Consultation item n°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?

An amendment of the existing directive would be preferable. However there will be a significant time delay to transfer these changes into national law with the risk of a loss of major fields of academic research in Europe.

The effect will be a strong stimulation of subsequent academic clinical trials which would be activated more quickly, with less funding and more in number. Thus the position of Europe in international scientific competition would be strengthened.

Until then only a shift toward more and more rapid funding could help to foster EU clinical trials for patients with a life-threatening diagnoses. These funds need to be given in advance before the start of a trial as prefinancing is not possible for participating centers and costs up to 100.000€ arise even before the start of a trial.

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

Academic trials (IITs and therapy optimization trials) should be excluded from this Directive and described in separate directives for IITs across Europe. According to the principle of subsidiarity academic trialists could agree to follow GCP/ICH rules but without specific regulations as applicable for commercial trials as it already took place over the past 30 years.

ELN could mediate such an agreement.

Alternatively, in a revision a special chapter for IITs could be introduced with distinct definitions of IITs and regulations for such studies. This should be done in close cooperation with independent academic trial groups and networks of excellence.

If academic trials are excluded from the directive the member states should be requested to adopt their national legislations accordingly or to go back to the standard before 2004.

Consultation item n°14: In terms of clinical trials regulation, what options could be considered in order to promote clinical research for paediatric medicines, while safeguarding the safety of the clinical trial participants?

What is stated for research in children applies to all rare diseases, subentities and also to older patients. In these entities the interest of pharmaceutical companies is limited, the patient numbers are low and therefore even international academic trials are urgently required. For such studies in **orphan diseases** adapted regulatory procedures as for pediatric patients are warranted.

Networks as suggested for pediatric populations are already existing, partly supported by EU funds e.g. in the field of leukemias (European Leukemia Net, www.leukemia-net.org). However these academic networks can impossibly deal with the current legislation for international trials.

Consultation item n°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 favourable in view of past experiences?

No comment

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

One reason to move trials in non EU countries are the lower expected costs. It is correctly stated that major costs in EU trials result from human labor. One reason for the high costs of clinical trials in the EU is the excessive bureaucracy and the regulatory overload induced by EU and national regulations. In addition to high costs, this leads to major delays in activation of clinical trials. Both problems lead to disadvantages for European countries in competition for clinical trials – both studies initiated by pharmaceutical companies or academic trials.

Some issues such as inadequate standard treatment in third world countries have to be considered. In these countries standard oncological treatment is often not available. Therefore, it may happen that patients without adequate upfront treatment will be entered into clinical trials with experimental drugs. This does not only results into ethical issues but also leads to biased results.

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

No comments

Consultation item n°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 control of bureaucracy on different levels in the European countries is limited. Many aspects of the drug regulations are matter of interpretation and there is a variety of examples that regulatory authorities often select the most strictly way of interpretation. Also interpretation may differ among countries and even among various representatives of authorities. This leads to uncertainties for investigators and generally to increased

bureaucratic requirements. A European clearing house for these issues and complaints brought up by investigators, study groups etc. should be inserted. This would not only support the performance of clinical trials but also allow a “real life” evaluation of the practical implementation of the Eu directive in different European countries.

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