Unit SANCO/C/8

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Stakeholder Group:

Independent academic study groups organised in the

- German Society for Haematology and Oncology
- Competence Network for Acute and Chronic Leukaemias
- Competence Network for Malignant Lymphoma
- European Leukemia Net

The authors represent a working group of the **DGHO German Society for Haematology/Oncology** on the impact of drug law on clinical trials, with focus on academic investigator initiated 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 Leukaemias and the Competence Network for Malignant Lymphoma**. The Competence 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.

All involved groups are severely concerned about the serious constraints against academic clinical trials after the Clinical Trials Directive. If independent clinical research is hampered as in the current regulation scientific progress, independent gain of knowledge and state of the art patient care is endangered in Europe.

It is a specific aim of these groups to conduct **treatment optimisation trials**. In these trials drugs are used in combination and together with other treatment approaches such as risk stratification, specific diagnostics, irradiation or stem cell transplantation. Them aim is not to test drugs but strategies. The trials are extremely important to define independent from industry treatment pathways in 'real-life'. They became nearly impossible after the EU directive whereas before the directive in some diseases more than 70-80% of newly diagnosed patients were treated in these treatment optimisation or quality control trials.

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.

General remarks

The concept paper includes a number of well-balanced conclusions regarding the negative impact of the Clinical Trials Directive on clinical research in general and on academic research in particular.

Some of the suggestions for revision rely on the optimistic assumption that further harmonisation of regulation in Europe will be possible. This assumption has to be challenged, based on the previous experience.

Some suggestions promote a risk-adapted approach to clinical trials regulation, which is very reasonable. **Concerning risk assessment especially in cancer trials it is often neglected that not the trial per se is the major risk for the patient. Rather the risk to die from the disease and to be treated outside a standardized treatment approach based on individual physicians desicion may put the patient at risk.**

Particulary for treatment optimisation trials in hematology/oncology there is a high risk for the patients by the disease itself. In line several publications show, that patients treated within clinical trials have a better survival than those not treated in a clinical trial.

Details of risk definition and the corresponding adaptations of the regulatory issues are extremely important to know and will show whether this approach is helpful for the conduct of independent academic clinical research and in particular for treatment optimisation trials. The latter trials became nearly impossible under the current regulation and are on the other hand extremely important for the improvement of cure rates in rare malignant diseases such as leukaemias.

The mentioned details of trial risk stratification should be discussed with the academic stakeholder groups because the majority of low-risk trials come from these groups. The commission should be aware that their interest is different from pharmaceutical companies and completely different from organisations such as clinical trial centre networks or contract research organisations making their business from complicated regulations.

IRB approval as a major issue is not part of the revision of the Clinical Trials Directive

The most important critical point for the impact of the revision on clinical research is however the fact that IRB approval shall be kept completely under the responsibility of member states (1.3.1).

Currently in many European countries, particularly in Germany, IRB approval is the most complicated, time consuming, bureaucratic and costly part of the clinical trial application. There is no harmonisation, even not within single member states. IRBs act indepently and ask for numerous different submissions including complete translation of protocols into national language.

In Germany, in a national trial, applications (up to 9 dossiers per IRB) have to be sent to 50 different IRBs. Only investigators approved by the IRB are allowed to conduct the majority of tasks, associated with a clinical trial. For approval a recent CV with original signature has to be obtained. The CV has to include a complete list of trials, in which the investigator is involved including title, phase, begin and end. Furthermore the investigator has to submit certificates for education in GCP. The duration of education is regulated e.g. 1 day course for inexperienced investigators although each IRB may have a different opinion on that. Some IRBs even ask for regular updates of the GCP training. Some IRBs reject investigators because the CV does not have the correct format or because they do not rely that the investigator has sufficient medical training. In large national trials several hundred investigators have to be approved. From each participating centre qualification forms are requested including a complete number of on-going trials at the site. Also this document has to be signed by investigator and director of the department. Since during medical education responsible physicians often change on the wards, regularly additional investigators have to be confirmed by the IRB. Some IRBs even ask for CVs and certificates from study nurses. For each step of the application variable fees are requested. There are examples of first submission of a large clinical trial to IRB where more than 100.000 paper copies have to be submitted to the IRBs.

If the commission intends to improve the situation of clinical trials in Europe, particularly of academic trials, there is an urgent need to reduce the requirement issued by the different IRBs and give clear guidelines for limited paper-work and regulatory requests particularly for low-risk clinical trials.

The only way to strengthen clinical research in rare diseases (see below) is to establish one national IRB.

Consultation Item 1

A single European submission for international European trials would be the best way to overcome administrative overload. For this purpose one set of forms would have to be provided. The deadlines for the review of submissions should not be extended. It remains a problem that there will be multiple responses from the different member states. The current voluntary harmonisation process appears to be a reasonable approach at first. However, unfortunately, after central assessment, again dossiers have to be submitted to the different national authorities, without any clarity how these dossiers have to look like. At the same time deadlines are very tight. This process is not manageable for academic study groups.

Consultation Item 2

We agree. The recommendations coming from different national authorities need to be evaluated and harmonised before they are submitted to the sponsor. Otherwise the different views with partly conflicting recommendations would remain a problem.

Consultation Item 3

Although we agree that a harmonised central approach has several logistical problems and it may not possible to finance such an approach, it would be the best way to address the problem. We cannot see any ethical or other national differences, which cannot be addressed in a central committee, which includes members from different states. Ethics are of over-riding importance and should not be subject to national interpretations.

Consultation Item 4 and 5

The procedure described here appears to be a suitable compromise. The tasks described under a) are correct.

However if tasks summarised in b) and c) remain completely under the decision of the local ethical review board, major problems of clinical trial application remain unchanged (see general remarks).

Consultation Item 6

We would suggest referring the topic to the commission or the agency. The option to ‚opt out' cannot be accepted because the issue that one member state thinks that a study is a risk for public health whereas others do not, is not acceptable. A simple majority decision is also not appropriate

for this situation. The European authority has the duty to provide sponsors with a reasonable decision and therefore has to seek for a compromise.

Consultation Item 7

Things should be kept simple. If the CAP is a reasonable procedure, which can be finalised without prolonging the timelines, it should be mandatory for all multinational trials. To reduce workload of central authorities CAP should not be extended to national studies.

Consultation Item 8

The approach to define low-risk trials type A is excellent. It would extremely help for the conduct of investigator initiated or treatment optimisation trials.

We would support the definition of type A trials. However we would not support the statement that a drug has to be used 'within the authorised indication'. Nowadays authorisation if often very narrow and pharmaceutical companies do not seek for extension of authorisation e.g. for rare diseases. In order not to discriminate studies for rare diseases we would state **'within the authorised or a similar indication'**.

Type A trials should also include **all trials with other non-drug treatment approaches such as stem cell therapy or irradiation** if carried as defined by current standard of care. **Type A trials should also included all treatment optimisation trials** which represent general strategies and not aim for approval of particular drugs.

In this type of trials also the pre-requisites for reliability of data should be defined differently compared to higher risk trials. In particular approaches for a risk-adapted monitoring procedure should be encouraged. Several authorities have the position that on-site monitoring should be performed in all types of trials and act accordingly during their inspections. However on-site monitoring is neither necessary nor manageable in large treatment optimisation trials with large patient and/or site numbers. The Directive should refer to ICH/GCP were it is stated that monitoring must be adapted in individual studies.

The major question is, who should make the pre-assessment and which timelines would be defined. In principle it should work and would help to focus the workload of authorities on trials with higher risks.

Consultation 9

We absolutely agree with the statements about the current situation in different European countries.

There are in principle two options:

<u>Define low risk trials within the EU directive:</u>

The regulatory requirements for this type of trials need then to be reduced considerably including submission dossier, monitoring, safety, authority fees and particularly IRB approval. If the reduction of requirements for all theses issues is not achieved, the situation of academic and independent trials will not change and the limitations for independent academic research will not be alleviated.

Extend the definition of non-interventional trials:

The definition should be extended anyway because the current definition limits any type of epidemiologic research. It is not clear why an epidemiologic study is not allowed to have a protocol describing the research and standard diagnostics and treatments. Such protocols, if written by expert groups, are extremely helpful to ensure the standard of care particularly in rare diseases.

The member states should at the same time be requested to limit the requirements for non-interventional trials to an absolute minimum e.g. data protection rules and one single IRB approval.

To maintain and extend the term of non-interventional trials would help epidemiologic research, registries and standard of care research. Also treatment optimisation trials testing treatment strategies including combinations of registered drugs, non-drug approaches, risk stratification etc. could be summarized as non-interventional. It should be made clear that these are not designed to test drugs but disease management pathways and therefore not within the field of central drug authorities. In this type of trials neither extensive GCP requirements, nor rules to demonstrate qualification of centres and investigators, nor on-site monitoring or patient insurance should be requested. It is extremely important to conduct these trials because they set standard of care in unselected patient populations and unselected hospitals reflecting real-life treatment results.

Consultation 10

We agree with the appraisal that specific rules for non-commercial trials are difficult to define. Non-commercial or academic trials may range from phase I to phase IV trials and may also be conducted with non-authorised drugs.

Therefore we are in favour of a risk-adapted approach as mentioned in Consultation item 8.

The position of a non-commercial sponsor is important however with respect to fees for authorities, fees for IRB and submission and safety procedures. Non-commercial sponsors should be free to opt out regarding certain expensive technical procedures e.g. electronic submission of SUSARs etc. They should also be offered reduced fees.

Consultation 11 and 12

We absolutely agree with the risk-adapted approach to define clinical trials and the respective regulatory requirements. The relevant issues are covered with the exception of the following topics:

- Need to have a patient insurance in low risk trials
- Definition of an investigational medicinal product

In order appraise the approach details regarding the respective regulations have to be presented.

Consultation 13

In principle we support the suggestion to narrow the definition of ‚investigational medicinal products'. There are two points to consider:

- A new definition should not lead to additional regulations for auxiliary medicinal products
- The commission should consider that some clinical trials use non-medicinal product approaches or combinations.

In oncology studies often authorised products are used within the authorised indication or in a very similar indication but in various combinations. The aim of these trials is treatment optimisation. **Often it is impossible to even define one ‚investigational medicinal product'** because the combination of different drugs including non-drug approaches is studied.

Therefore it should be possible **not to have an ‚investigational medicinal product'** in a clinical trial and to have auxiliary medicinal products only. The regulation of these auxiliary medicinal products should be limited to an absolute minimum e.g. mentioning the name of the products in the protocol.

It should be made clear that auxiliary medicinal products, although used in clinical trials, have to be paid by health care systems including the preparation of the drug in hospital pharmacies and the application to patients.

Consultation 14

We would favour option A to remove insurance requirements for low-risk trials. Option B would lead to lack of international harmonisation and delays. Furthermore if, by definition a clinical trial participation has a comparable risk as standard therapy, there is no need to have an additional insurance.

To avoid insurance in all low-risk trials would considerably reduce costs and administrative work of sponsors and investigators. Overall – as outlined in annex – the insurance practically never pays for damage.

Consultation 15

We would not support option 1. Although it is clarified that responsibility and liability are different things, there will most probably no total harmonisation of the regulatory framework e.g. including national IRB approval, insurance, health care system, contractual issues with participating centres etc.

Therefore the regulation should have the option to have in international trials co-sponsors for each participating country. These co-sponsors should take the responsibility for the respective country including the responsibility to report to the main sponsor who can still be approached by the authorities. The main sponsor has however in this case not the duty to check the conduct of the trial in the different participating countries e.g. by audits.

Consultation 16

Overall we agree. However the concept paper does not address one type of clinical trials, which became extremely difficult under the Clinical Trials Directive.

<u>Studies in rare diseases</u>

In rare diseases such as subtypes of leukaemias or other cancers often a large number of centres have to participate in a clinical trial. In some entities sufficient number of patients can only be recruited in multinational settings. Many centres have to be activated with all bureaucratic and regulatory procedures although never a patient is recruited. On the other hand these cancers always represent an emergency situation and in the best interest of the patient treatment has to be started quickly.

Urgently variable procedures for rapid activation of centres – as soon as a patient is identified - need to come into place. It should be possible to initiate a centre within 2-3 days including regulatory approval and IRB approval.

Consultation 17

We agree

Consultation 18

No additional comments

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