

Comments of the European Leukemia Net on the Draft Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

and the Draft Reports from:

**Committee on the Environment, Public Health and Food Safety
Committee on Industry, Research and Energy
Committee on the Internal Market and Consumer Protection**

The Clinical Trials Directive 2001/20/EC had a severe negative impact on the independent academic research in Europe. This is mainly due to the fact that henceforth treatment optimisation studies and academic trials had to follow the same regulatory processes as registration trials of the pharmaceutical industry. The regulation did not even acknowledge the importance of independent academic research. In doing so, the regulators disregarded the fact that therapeutic optimisation studies do not pose an additional risk for the patients. On the contrary, the obstruction of these trials became a sizable risk towards optimal therapy of many diseases.

The European Leukemia Net represents national European study groups which are focussed since decades on the treatment optimisation for rare hematologic malignancies, such as acute and chronic leukemias. Many of these diseases became curable and this is a success of the study groups. Furthermore these trials represented the high quality standard of care for leukemias in many European countries. They do not aim to register or even test single drugs but evaluate treatment strategies with combined treatment approaches. Some of them cannot even define an investigational medicinal product. Furthermore they are of utmost importance after marketing authorisation of drugs to define their optimal use on a population-based, non-selected patient collective and provide additional efficacy and safety data. These studies are needed for optimal patient care and should therefore be manageable with respect to costs and efforts for the participating hospitals and physicians.

The European directive severely hampered these trials and as a result made international and even national trials in rare diseases such as leukemias nearly impossible. As a matter of fact the European regulation is on the way to destroy very successful academic research infrastructure, which had been admired in many parts of the world. It endangers independent academic research, by forcing researchers to seek for support from the pharmaceutical industry to somehow finance the extremely complicated bureaucratic procedures and increases the risk for patients since treatment optimisation trials cannot be realised any more.

Now the European commission had taken some of the concerns of academic researchers into account for their draft regulation. However the different reporters made additional suggestions, which will provide additional, unmanageable burden for academic researchers. Some tried to discard nearly all of the suggested improvements for low interventional clinical trials.

These suggestions culminate in the fact that even the intellectual property on clinical research data shall be taken from academic investigators by forcing them to upload their complete data bases for public access.

If these suggestions will be accepted – and at present there is no evidence that reporters and the directive acknowledge academic clinical research as a specific field of interest, which needs to be protected – we cannot see the future motivation and opportunity to do any independent research in clinical trials.

We are in charge of our patients, have no lobby and no time to bring our interests and the interest of our patient to public.

We can only hope that our representatives in the parliament will not only accept the suggested facilities for independent clinical trials, withdraw their suggestions endangering independent scientific opinion and intellectual property but even make additional suggestions to create a future basis for optimised patient care within prospective academic treatment optimisation trials.

Please find a more detailed report on the draft regulation and the rapports in the following.

Dr.Nicola Gökbuget

Head of Information Center of the European Leukemia Net

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Draft regulation

The European Commission has apparently identified many of shortcomings of the current directive and suggested a number of reasonable approaches for international trials:

1. Central submission of all documents for fast authorization procedure
2. Risk-adapted assessment of clinical trial applications with shortened procedures for low risk trials
3. Definition of low risk (minimal interventional) trials with registered drugs and risks comparable to current standard of care
4. Clearer definition of investigator responsibilities (one responsible investigator per center)
5. Electronic reporting of suspected unexpected severe adverse events (SUSARs)

The new regulation may help to harmonize pre-requisites for clinical research throughout Europe. However, there is still a number of ambiguities.

Overall the new draft regulation represents a positive attempt to improve harmonization of clinical trial organization in Europe. A number of suggestions from coordinators of academic trials have been considered (see above). Still a few details could turn out to be problematic for academic trials as summarized below.

- Although the draft regulation contains a definition of low intervention trials, there is still no option to perform a non-interventional trial as soon as a pre-defined treatment is given. This means that there will be no way to conduct academic treatment optimization trials with IRB approval but without competent authority approval as it was successfully done in the past.
- The regulators again do not acknowledge trial types – treatment optimization trials - where no investigational drug can be specified but treatment principles are tested.
- The regulation mentions EU portals for submission of applications and SUSARs. It is not clear whether these software solutions will be easily usable and free of costs for academic sponsors.
- The deadline for sponsors to respond to questions from regulators is only 6 days which will be extremely difficult to meet for academic sponsors.
- The draft regulation states that all studies cited in an application have to be conducted

according to the current or previous EU regulation or comparable regulations. It will be impossible to assure this e.g. for historically published trials which still may contain important valid data. Regulators should restrict this requirement to pivotal trials.

- The regulation states that only trials registered in a public registry (primary registry of the WHO) can be cited in a clinical trial application. This kind of censorship of scientific knowledge and scientific freedom cannot be accepted. Sponsors should be free to cite whatever published trial they consider necessary for the purpose of the trial. It is ethically unacceptable not to consider important published information due to regulatory arguments only. **The clinical trial registration needs should be separated from the scientific rationale of a trial.** It cannot be the duty of scientists applying for clinical trial approval to take care for registration of other historic clinical trials. In addition, the most frequently used trials registry – clinicaltrials.gov – is not a WHO primary registry!
- The draft regulation does not clearly define who is responsible to assess the qualification of investigators and sites. If this remains the duty of ethical committees (IRB), the bureaucratic workload will not be reduced significantly. The task should be clearly allocated to a regulatory authority because this is not an ethical issue.
- The regulation states that changes in the trial master file must be trackable. How can this be done in a file which consists of 20 or more folders?
- A number of regulations mention details for the use of ‘auxiliary’ products which are drugs used in a clinical trial in addition to an investigational medicinal product. In academic trials virtually all medication may be defined as auxiliary. Off-label use should be certainly allowed. The documentation should be as limited as possible, if drugs are used in the context of clinical standard.
- The most time consuming part of clinical trial authorization is nowadays approval by an ethical review board. It is not clear how and whether this problem will be solved just by the definition of narrow timelines. One important step would be the limitation of IRB approval to ethical issues. Regulatory authorities, not IRB, should perform the assessment of qualification of centers and investigators.
- The regulation does not consider the problem of rare diseases. If this type of diseases is studied, many centers have to be activated although the majority will never include a patient. The academic research needs mechanisms for rapid activation of centers in case that a patient comes up.

Rapports

All rapports mention the need of ethical review board approval of a clinical trial. This is of interest since IRB approval has already been part of the draft regulation. Without explicit mentioning, the draft regulation contained all needs of ethical approval and this was defined as a duty of each involved country. There are other very alarming suggestions in the different rapports which are summarized in the following.

ENVI (Environment, Public Health and Food Safety) Rapport

- The rapporteur suggests a clinical trial report, which contains beside other information the complete protocol, statistics analysis plan, and individual anonymized patient data in the

form of tabulations or listings. Academic researchers will not be willing and able to publicly offer their complete study data. **Beside the public interest there is also their right for intellectual and scientific property.** They might plan to publish additional analyses and create a basis for their future trials. The rapporteur does not acknowledge the fact that clinical science is performed in a competitive environment. Those who do the efforts and spend funds for conducting a trial cannot be forced to provide all their results to others for undefined purposes. Furthermore, clinical trial data are extremely complex with thousands of different variables. Academic researchers will be unable to format and upload all their databases in a self explanatory and searchable format. In the end, after enormous efforts, nobody will be able to perform any reasonable analyses with this bulk of data. **There is a high risk of conflicting results, which will lead to confusion instead of clarification.** The suggestion as a whole will create incredible bureaucratic workload, lead to disadvantages for European research in contrast to other parts of the world and in the end will lead to no or very little new scientific information. **We cannot believe that such far-reaching suggestions shall be part of European regulation with ideas about practical realisation, the practical needs, without prior interaction with different interest groups and without any rationale for the potential benefit for patient safety. How can the commission justify an enormous burden for hundreds and thousands of clinical trials just to offer the opportunity for some interest groups to re-analyse the data of a few trials even although the potential benefit of such analyses has never been demonstrated.**

- The rapporteur strengthens the need that clinical trials cited in an application need to have been performed according to EU or comparable regulations. It will be impossible to assure this requirement e.g. for published historic trials which still may contain important valid data. Regulators should restrict this requirement to pivotal trials.
- The rapporteur strengthens the regulatory statement that only trials listed in a public registry (WHO primary or partnered register) can be cited in a trial application. **This kind of censorship of scientific knowledge and scientific freedom cannot be accepted.** Sponsors should be free to cite whatever published trial they consider necessary for the purpose of the trial. It is ethically unacceptable not to consider important published information based on regulatory arguments only. The clinical trial registration needs should be separated from the scientific rationale of a trial.
- The rapporteur adds the suggestion that clinical trial participants shall be provided with information on the results. **This would lead to enormous workload for the centres.** They would have to keep contact information of patients – probably even longer than the hospital needs to – in order to contact patients later on, when the final report is ready. The information need and information wish of the patient is not considered. The paragraph should be reworded in the way that patients can receive information upon request.
- In addition to the already problematic suggestion to provide complete study reports and tabulated original data, the rapporteur even suggests to upload incomplete data in case of trials with more than 12 months of temporary halt. This will not lead to any benefit for the safety of the patients since incomplete data can by definition not be used for a reasonable analysis.
- The rapporteur suggests that for the clinical trial application all existing evidence including systematic reviews and meta-analysis has to be discussed. **It is unacceptable that one type of scientific publication is by definition considered superior to others and needs to be cited**

independent of quality. It has never been shown that systematic reviews have a higher benefit for patients and safety compared to other publications. This kind of censorship of scientific freedom by regulations cannot be accepted.

- The rapporteur also suggests that each application should include a complete statistical analysis plan. Again, particularly in academic trials, additional analyses which were not originally intended should be allowed as long as analysis of the primary and secondary endpoints are predefined. This scientific freedom is needed to consider new ideas and developments coming up during the conduct of a trial.
- The rapporteur demands that sponsors and investigators shall archive the content of the clinical trial master file for an indefinite period of time after concluding the clinical trial. **This is unprecedented!** Neither academic sponsors nor participating centres have the capacities to store 20 or more paper folders per clinical trial for indefinite periods. There is currently no practicable way to generate electronic formats of trial master files and also no technology to electronically store documents for an indefinite period. Furthermore, it is impossible to define a budget for storage costs for an indefinite time-period. It is furthermore impossible to store the content of the trial master file – even if it would be possible to generate an electronic format – in a public database because the file contains personal information on patients and physicians. This requirement is absolutely impossible to fulfil and can only lead to the result that hospitals will no longer participate in trials.

ITRE (Industry, Research and Energy) Rapport

- The rapporteur apparently does not acknowledge at all the specific needs of independent academic trials. It is very unfortunate that several problematic industry trials are cited in order to stress the need for more strict regulations whereas all the achievements from academic research seem to be not considered at all.
- A chapter on the risk of clinical trials in relation to standard care and the risks of the disease and the suggestion that regulations on these low-intervention trials should be less stringent was totally deleted. **This is extremely disappointing and neglects all the efforts of academic study groups conducting industry independent publicly funded trials for treatment optimization. These trials even reduce the risk for patients but cannot be conducted any longer, if the administrative burden is not reduced.**
- Similar to the ENVI rapporteur the rapporteur stresses the need to upload complete clinical trial data into a public database and the requirement that all trials cited in a clinical trial application have to be conducted according to the current EU regulations.
- In addition, the rapporteur suggests high penalties for sponsors not delivering the trial report in due time.
- In contrast to the draft regulation, which allowed exceptions from immediate SAE-reporting if predefined in the protocol, the rapporteur suggests that investigators have to report all SAEs. In contrast to the draft regulation, SAEs shall be reported by the investigator to EU data base and IRB. **This is even more than requested in the common practice where sponsors have to report only SUSARs.** Already now – due to the overload with meaningless SUSAR reports – the alertness of investigators, sponsors, and IRBs decreases. The paper load is virtually not manageable. Any effort should be made to limit immediate reporting to

reasonable extent. More detailed information can then be given in a structured safety report.

- Similar to the ENVI the rapporteur suggests that a trial master file has to be stored indefinitely.