Statement of the „Deutsche Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie e.V. GMDS" (German Association for Medical Informatics, Biometry and Epidemiology) concerning the Public Consultation Paper: Assessment of the Functioning of the "Clinical Trials Directive" 2001/20/EC of the European Commission.

The German Association for Medical Informatics, Biometry and Epidemiology (GMDS e.V.) appreciates the initiative of the European Commission (EC) to consider 'various options for further improving the functioning of the Clinical Trials Directive (CTD) with a view to remedy shortcomings and unintended negative consequences while taking the global dimension of clinical trials into account.'

The GMDS is a professional association for medical information scientists, biometricians and epidemiologists with about 1700 members.
Our statement mainly focuses on issues that are highly relevant for the issue of drug safety and the members of the GMDS. We use the notation of the PCP to ease understanding.

Major comments

It would be very helpful if the terminology used would follow the accepted standards of science.
Currently the usual word choice of the EC often causes confusion, e.g. the word trial should only be used for experimental research and designs like the randomized trial. Non-experimental research should be called a study. Non-intervention in the EC terminology refers to specifications in the study protocol concerning the therapy/treatment, the diagnostic work-up, and the monitoring/follow-up of the study participants, whereas in the scientific literature the term non-interventional study covers all observational studies, e.g. cohort study, case-control study, cross-sectional studies, although all these study designs standardise diagnostic work-up and if appropriate, the follow-up. A study should be called interventional only if the directions for treatment ~~and medical care~~ are specified in the study protocol.

The short title 'Clinical Trials Directive' is often misunderstood in the sense that the CTD covers clinical trials of all kinds. To avoid such a misunderstanding it should be changed to Clinical Drug (or Medicinal Product) Trials Directive.

The Note for Guidance: Good Clinical Practice(GCP), both of the EU (1991) and of the EMEA/ICH (1997), asked that it should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities. One has to keep in mind that there are many studies and trials that do not intend to do so. The legislation of many MS has however adopted the GCP–standard for basically all drug research (with the exception of non-interventional studies) thus there is a conflict with the constitutional right of freedom of research. The public consultation should thus result in a rational limitation of the ambit of the CTD to those areas where the rights of the research subjects have to be protected by the EU and the data are intended to be submitted to NCAs or to the EMA.

Item 6

We doubt that it is a wise decision to get non-interventional trials (better: studies, NIS) covered in the future by the Community legislation on pharmacovigilance. Pharmacovigilance is typically focussed on safety issues, whereas many NIS are not.
As 'current medical practice' varies, and will vary in the future too among the MS, it is only consequent that the borderline between a clinical trial and a NIS is drawn differently in individual MS. To reduce the size of this problem we strongly recommend to modify the current definition of a NIS in the CTD Article 2 (c) 3rd sentence: No *risky or burdensome* additional diagnostic or monitoring procedures shall be applied to the patients and…….

Item 8

We do not recommend to adopt the CTD as a Regulation. As has been seen many of the problems with SUSARs and substantial amendments are due to conditions which will not be modified by a Regulation. We are also afraid that a Regulation will result in a lower level of patient safety than the current level achieved in Germany.

Item 9

We agree with the assessment of the PCP that the requirements are not always risk-commensurate. More precisely, the CTD does not at all adjust its requirements with regard to the potential risks of a trial. In our opinion it makes a major difference whether a drug has been approved already or not. When a drug has been approved already one can assume that the benefits exceed the risks, whereas if the drug has not been approved one does not know. Therefore we recommend to differentiate between approved drug (use) and non approved drug (use).
A drug use is authorized~~approved~~ if the approved indication, dosage, and duration of use are adhered to. The objectives of such studies are often very important, e.g. clinical endpoint trials. As approved drugs are available for use anyhow (without any special requirements) it is hard to understand why the proper monitoring and documentation of the treatment and its outcomes should be penalized by lots of red tape, insurance, approval by drug authorities and the like. Such studies typically only involve risks which are close or equal to those of usual medical care. We recommend that the NCAs are notified about such studies and that Ethics Committees have to review them prior to their initiation, but that they are not covered by the CTD.
We are against a risk differentiation based on the status of the sponsor, e.g.. commercial vs academic. The degree of patient (or volunteer) protection must not depend on the status of the sponsor, i.e. a manufacturer or academic investigator, or on the status of a so called 'non-commercial study'. The only ethically and scientifically acceptable risk differentiation is based on the prior knowledge about and experience with a drug, and on the vulnerability of the patient sample.
At last, a final remark regarding this point. The current regulation is highly contra-intentional in the areas of drug safety studies. Many drug safety studies need to be done in the 'real medical world setting' to find the inherent risks of drug use under the conditions of routine health care.
When there is no intervention concerning the choice of an approved treatment in a study, there is usually no study specific risk, which is discernible from routine health care. If there are no standardised specifications ~~re~~ of diagnostic work-up and follow-up such a

(scientifically invalid) study is considered a non-interventional study, which is not covered by the CTD. Just by adding standards for observation which carry no extra study-related risk for the study participants (and may even improve patients' safety) this study is considered a clinical trial, which is covered by the CTD.
As the most absurd example for the non-sensical and unintended negative consequences of the CTD we report just one example: About 15 years after the approval of a drug (typically used for senior patients) there was a signal raising the suspicion that the drug may cause an excess mortality. The manufacturer planned a cohort study to check the validity of the signal. Eligible for the cohort study were only those patients who had been treated with this drug prior to approval in phase II and Phase III-studies about 15 years ago. These former trial participants respectively their relatives should be identified by the then investigators and their survival status should be notified, and compared with an appropriate control group. According to the CTD this study was considered by the legal representative in the Ethics Committee as a trial, as the assessment of the survival status is not part of 'current medical practice'. Thus an insurance was needed although there was no study-related drug administration and many of the former participants were already dead!
Similarly, investigating the pregnancy outcomes of women who had been vaccinated against the H1/N1 flu (in agreement with official recommendations) has be considered as a clinical trial as a careful and standardized assessment and documentation of pregnancy outcomes, e.g. of minor and major congenital malformations and developmental retardations at pre-specified time points is in many countries not 'current practice'.
Thus the CTD rewards methodologically weak research (by calling it non-interventional, which is not covered by the CTD) and penalizes methodologically sound observational research. This is contra-intentional to the aim to promote the safe use of drugs. . Thus we recommend to add to the definition of a non-interventional study of the CTD Article 2 c 3rd sentence …No *risky or burdensome* additional diagnostic or monitoring procedures shall be applied to the patients…

Item 13

One should not forget that the scope of the Note for Guidance: Good Clinical Practice for Trials on Medicinal Products in the European Community of the EC in 1991 focussed explicitly on trials and data that were meant for drug authorities. The same is true for the Note for Guidance on Good Clinical Practice ICH Topic E6 of 1997. As many investigator-initiated trials do not have this objective but try, e.g. to optimise the administration of approved drugs in the treatment of cancer , the red tape burden for this type of trials should be reduced. See comments for Items 6 and 9 too.

Item 15

There is no doubt that patients in medical emergency situations have a right to receive evidence-based medicine of the highest standards, too. We are aware that there are considerable problems in many countries to perform a randomized trial with emergency patients. We do not think that a regulation concerning emergency clinical trials in a uniform manner for all MS will be very helpful at present. We rather think that there is a need for public discussion about this issue in those countries which do not have an appropriate solution yet, so people can raise their concerns. Only then a solution can be found which is acceptable and does not harm the trust of the people in the scientific and ethical soundness of experimental therapeutic research.
The Additional Protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research contains in its Article 19 a specific provision. In force as an

international legally binding instrument of the Council of Europe, this protocol should be listed in an appropriate rank.

Additional comments

2.4 Sponsors involved in clinical trials

Individual researchers who act as sponsor and investigator at the same time have been forgotten. But for investigator-initiated trials this combination is typical.

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