Cover letter

Copenhagen, January 7 2010

Sirs,

Thanks for providing us with the opportunity to express our concerns and suggestions regarding the European legislation on clinical research on behalf of DCRIN. DCRIN in the Danish National Clinical Research Infrastructure of ECRIN (the European Clinical Research Infrastructures Network), which is the FP6- and FP7-funded pan-European, ESFRI-roadmap infrastructure project designed to support multinational clinical research in Europe. For this purpose, ECRIN has developed; through its working group on regulation, an in-depth awareness on regulatory requirements for clinical research, not only for clinical trials on medicinal products but for all categories of clinical research, interventional or observational (see ECRIN-TWG Deliverable 4, www.ecrin.org).

ECRIN is based on the connection between national networks of clinical research centres and clinical trials units, and currently covers 13 EU and associated countries (Austria, Belgium, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Spain, Sweden, Switzerland, United Kingdom), and plans extension to all the EU member states and to associated countries. It provides consulting and services to multinational clinical research initiated both by academic investigators and by industry sponsors. A particular focus is put on academic clinical research, that represents only 11% of phase 1, but 72% of phase 4 clinical trials on medicinal products (we therefore pay particular attention to the risk-based approach to regulation). Another major concern are the clinical studies other than clinical trials on medicinal products, in which industry sponsors are almost absent, but that are critical for the scientific competitiveness of the European Union.

DCRIN participated via ECRIN in the EC-EMA conference on the Directive in October 2007 and prepared written suggestions for EU. ECRIN was the initiator and a prominent partner in the ICREL project (all the ICREL participants were also ECRIN partners). ECRIN was also a major player in the preparation of the European Science Foundation Forward Looks on investigator-driven clinical trials. Currently ECRIN is a partner of the roadmap initiative preparing, through a series of workshops, suggestions for an improved legislation on clinical research.

Best regards, on behalf of the DCRIN

Christian Gluud
DCRIN National Coordinator
The Copenhagen Trial Unit, Centre for Clinical Intervention Research
Rigshospitalet, Copenhagen, Denmark

DCRIN

DCRIN's assessment of the functioning of the « Clinical Trials Directive » 2001/20/EC

Summary of the clinical trials in the EU and CTD and achievements and shortcoming

Consultation item 1:

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

- The Clinical Trials Directive resulted, at the EU level, in an improvement in the protection of participants - but primarily in clinical trials on medicinal products.
- It resulted only in a partial harmonisation; because of the divergence in interpretation and in transposition into national legislation.
- It clearly defined the responsibility of sponsors and of member states. The latter supervises the clinical trials through the competent authorities and the ethics committees.
- The EudraCT database should be regarded as a tool to improve transparency for all types of clinical trials. The data on the EudraCT database should not be regarded as proprietary data. The medicinal products used may be proprietary, but can then be protected through patents. The information in EudraCT needs to be in the public domain in order to live up to the Declaration of Helsinki. Likewise, the EudraVigilance reporting systems facilitate the detection of safety issues, taking advantage of the pan-European collection of information, and may also serve as a possible tool for transparency in safety reporting. These data are certainly not proprietary. They originate from the patients that willingly consented to participate in clinical research. Keeping such data hidden from public scrutiny is expropriation and should be considered immoral and unethical.

Key issue 1: Multiple and divergent assessment of clinical trials

Consultation item 2:

Is this an accurate description of the situation? What is your appraisal of the situation?

- Yes, this is an accurate description.
- There is a need to make a distinction between

- national trials where divergent opinions between ethics committees and competent authority may be a problem, and
- multinational trials, where divergent national opinions between competent authorities and between ethics committees may raise problems.

Consultation item 3:

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

- Yes, we agree with this description that is in line with the written suggestions proposed by ECRIN for the October 2007 consultation and the ECRIN-TWG deliverable 4.
- Quantification of the impact can be found in the ICREL report (in which ECRIN was a participant)
- This results in unnecessary complexity and increased costs.
- This also leads to duplication of assessment, and misuse of expertise. This is not a cost–effective use of scarce human resources.

Consultation item 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 details?

- The voluntary harmonisation process (VHP) developed by the *Clinical Trials Facilitation Group (*CTFG) represents a progress, but is not sufficient
- A distinction should be made between national and multinational trials. It may be responsible in a first step to introduce changes only for multinational trials.
- There is a need for a single submission to the CA for multinational trials, with a single dossier at a single web site, and with a single opinion achieved by a single authority at the EU level, as the competent authority assesses the product, which is the same across the EU. This could be set up progressively, with
  - In the short term, for a transition period, the designation of a reference member state after application to a single portal, and with a mutual recognition process. This raises the question of how to designate the 'lead' competent authority for a given protocol: based on specialisation of the competent authorities or based on the country of the sponsor and the principal investigator or through other criteria?
  - But in the long-term, a centralised process, as the competent authority giving the clinical trial authorisation in the EU should

become the EMA. This makes sense as EMA already gives the marketing authorisation. Some national competent authorities are understaffed and expertise is lacking in certain areas and in certain countries. These problems must be addressed as well.
    - There should maybe still be a possibility for a given country to withdraw from a trial, but this raises the problem: is it then fair to sell the product on that market later on if the product turns out to apparently offer more benefit than harm?
- The above description should only be on option at the beginning, the sponsor having the capacity to select either the submission to national CA (with a unique dossier, like in the VHP), or to this centralised, one-stop shop procedure. In the long run, there should be a centralised application to the EMA.
- It should not be restricted to selected categories of trials (like phase 1 trials, or 'advanced' therapy trials), but should cover all types of multinational clinical trials involving a product.

Consultation item 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 details?

- There is a need for a procedure based on a one-stop-shop electronic submission with a single dossier, common for all the ethics committees, data protection agencies, and the (single) Competent Authority.
- There should be a clear definition of the documents that must be translated in the local languages (4-5 pages executive summary, information to patients, and informed consent sheet).
- There is a need, in the perspective of the single clinical trial application to competent authorities, to clearly define at the European level the respective roles of the competent authorities (assessment of the product), and of the ethics committees (protocol methodology, site assessment, degree of monitoring, and informed consent).
- National ethics committees should work together in the assessment of a single multinational trial, exchanging information on their assessment of protocol, allowing to release a single opinion from ethics committees in multiple countries as the competent authorities will do in the VHP.
- A possible way to achieve this single opinion by multiple national ethics committee would be to assign the evaluation of the protocol and methodology to one 'lead' ethics committee, and to ask for opinion of the national ethics committees on the site assessment and informed consent.
- There is a need to promote the cooperation and networking among the ethics committees in the EU, with the objective to share common tools and

methodologies, to harmonise practice, to promote common training programmes, to develop quality assurance systems, ensuring the reproducibility of procedures.

- A pan-European accreditation or certification system (without duplication in countries where certification already exists) for ethics committees could be used to ensure their capacity and competence, assess their level of activity and their quality assurance system, therefore reducing their number in countries where such institutions are in excess.
- This networking and accreditation or certification system could be placed under the umbrella of DG Health and Consumers (DG SANCO) (as now the supervision of medicines is a mission of DG SANCO) rather than of pan-European networks of ethics committees (like EUREC), as this does not raise issue regarding their independence as they should primarily be independent from sponsors.

Key issue 2: inconsistent implementation of the clinical trials directive

Consultation item 6:

Is this an accurate description of the situation? Can you give other examples?

- Yes, this is an accurate description.
- There is a need for an unequivocal definition of amendments and a need for changes in the SUSAR reporting system.
- The ethics committees should have access to the EudraVigilance database, and there should be open access to safety data. Again, academic sponsors and industry sponsors cannot take these data as their proprietary data and hide tem from public scrutiny. The information in the EudraVigilance reporting systems must live up to the Declaration of Helsinki. Safety data are certainly not proprietary. They originate from the patients that willingly consented to participate in clinical research. Keeping such data hidden from public scrutiny is expropriation and should be considered immoral and unethical.
- Regarding the scope of the EU legislation, currently restricted to clinical trials on medicinal products, the fact that DG Health and Consumers is now in charge of the supervision of clinical research opens new positive perspectives. This is very important for academic institutions as a lot of investigator-driven clinical research is devoid of medicinal product or of any health product, whereas multinational cooperation is a major advantage (for example in genotype-phenotype studies in rare diseases, etc…).
- DCRIN is in favour of an extension of the new EU legislation to all categories of clinical research, as this will ensure the same level of protection to participants in every category of clinical research, and possibly improve and

harmonise national legislations. We propose to start with a legislation covering clinical trials on medicinal products, then to assess this legislation, and if it doesn't cause harm to clinical research and promotes multinational collaboration, to extend the EU legislation to all other clinical research areas, where the fragmentation of the national legislative system is considerable, making multinational cooperation very difficult (see ECRIN-TWG deliverable 4).

- The scope of the Directive also refers to the 'interventional' nature of the trial, however, there are divergent interpretations in the definition of intervention, some countries considering that a diagnostic intervention is not an intervention. As a result, a pharmacoepidemiology study with a diagnostic intervention is considered interventional in some countries, and non-interventional in other countries. There is a need for a clear definition of the boundaries between interventional and non-interventional studies.
- There is also a need to harmonise the national legislations on safety reporting in non-interventional studies, which is relevant to the post-marketing safety studies without intervention.
- This abrupt change in regulatory framework between a pharmaco-epidemiology study with or without diagnostic intervention highlights the need for a smooth transition in the regulatory requirements, with a risk-based approach to regulation.

Consultation item 7:

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

- Yes we agree with this description (which is in line with the ECRIN and ICREL data)

Consultation item 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 details? In particular, are the divergent applications really a consequence of transposing national laws, or rather their concrete application on a case-by-case basis?

- We would promote a regulation rather than a directive. The reason is that even where the Clinical Trials Directive could have been clearly and unequivocally transposed into national legislation several differences have occurred.

- The regulation should include new provisions for SUSARs, annual safety reporting, amendments, definition of intervention, roles of ethics committees and competent authorities, single application, etc..
- We would recommend a two step process for the achievement of the single opinion, as well as for the field of the legislation (first clinical trials on investigational medicinal products, then other categories of clinical research if the first legislation is efficient) (cf. above)

Key issue 3: regulatory framework not always adapted to the practical requirements

Consultation item 9:

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

- Regualtory requirements are currently not making any valid distinction between a phase 2 clinical trial, a diagnostic test accuracy study, or a head-to-head comparison of two marketed medicinal products.
- There is a need to agree on the definition of risk: hazards to trial participants, hazards to data protection, hazards to public health?
- There is a need to agree on risk categories: how many, which boundaries? This system should not be too complex as complexity may lead to divergent interpretations.
- There is a need to define a procedure for the assessment of risk by the sponsor and investigator, and for its validation. This should be the role of the ethics committees to check the risk assessment and secure that the trial protocol takes sufficient steps to take the risks into consideration (safety reporting; interim analyses; degree of monitoring, etc.).
- There is a need to define which processes should be affected by the level of risk? (expedited ethical review; notification to competent authority, requirement for the sponsor, for insurance, safety reporting, monitoring, inspections, etc).
- And for each process to define which should be the risk-based adaptations.
- There is a need for an immediate and substantial improvement in the adverse event reporting system. Transparency is the watchword – but here maybe overlooking the safety and benefit during a trial would be more secure in a quality-assured and educated independent data safety and monitoring committee than requesting to break the blind when SUSARs occur during a placebo-controlled trial and hereby violating the objectivity of the trial.

Consultation item 10:

Do you agree with this description? Can you give other examples?

- Multiple sponsors and flexible sponsorship arrangements should be allowed (either co-sponsors or joint sponsors), however, they should be bound by a consortium agreement, with a 'principal' sponsor and cosponsors, a single EudraCT number, a single protocol (including amendments), and a single database.
- There is a need to make a clear the difference between joint sponsors
    - sharing legal and penal responsibility (liability, indemnity, data ownership, inspection),
    - and task delegation (submission to CA and EC, vigilance, monitoring, etc…) that requires a task delegation contract.
- There is a need for a clear framework for this co-sponsorship. Sharing some responsibilities based on geography (one sponsor per area or country) would be more useful for multinational cooperation than sharing responsibilities based on processes (regulatory submissions, safety, GCP).
- There is a need for flexible sponsorship requirements (single compared to. co-sponsorship) depending on the nature of trial (national compared to. multinational, type of trial). Public institutions should be able to select the best adapted solution for each individual trial.

Consultation item 11:

- A revision of the guidelines cannot solve these issues, however, an immediate revision of guidelines on the definition of IMP, and the immediate release of guidelines on monitoring, on ethics committees etc… could, for a transient period, partly improve the situation.

Consultation item 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?

- There is an absolute need to improve the current EU legislation, and to replace the current EU Directive by a regulation.
- In the long term, this new legislation should cover all the categories of interventional clinical research, as the protection of participants should be the same as far as they take risks.
- We propose to start with a revised legislation for clinical trials on investigational medicinal products that, if the legislation convincingly improves multinational collaboration without causing harm to clinical research, should be extended to all categories of clinical research in a second step (see above).

Consultation item 13:

Would you agree on this option and if so what would be the impact?

- No, we disagree on this option. The same rules should apply to commercial and non-commercial trials as far as they have the same level of risk.
- Data from non-commercial trials should be useable for registration purposes.
- Regulatory requirements should be adapted to the risks that the trial participants may run, - not to the commercial or non-commercial objective of the trial.
- In turn, academic institutions acting as sponsors in clinical trials, especially multinational trials, should be supported by the appropriate infrastructures for conducting such trials.

Key issue 4: adaptation to peculiarities in trial participants and trial design

Consultation item 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 trials participants?

- Promoting and facilitating paediatric trials are excellent initiatives. However, clinical research in all patient populations should benefit from improvements like full transparency, support measures, infrastructure, networks, etc.

Consultation item 15:

Should this issue be addressed? What ways have been found in order to reconcile patient's rights with the peculiarities of emergency clinical trials? Which approach is favourable in view of past experiences?

- The waiver of consent in legally incapacitated participants should be mentioned in the new legislation with clear definition and procedures, and also with a clear procedure for the withdrawal of consent from continuing on the examined interventions when the temporarily incapacitated patient recovers his/her ability to consent, with data still being usable for intention-to-treat analyses.

Key issue 5: ensuring compliance with good clinical practice (GCP) in clinical trials performed in third countries

Consultation item 16:

Please comment? Do you have additional information, including quantitative information and data?

- DCRIN lacks data regarding trials with investigation centres in third countries (which represents a limited amount of academic trials, except in some areas like HIV, malaria, tuberculosis, but also cardiovascular diseases, cancer etc.).
- There is a need to assess the impact of genetic background on intervention effects – this should deal with both harms and benefits.
- There is a need to conduct inspections in third countries. USA FDA is already opening daughter institutions in third countries.
- There is a need for capacity building, and for enforcement and supervision of GCP compliance.

Consultation item 17:

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

- The options we consider are
    - Capacity building in third countries - here ECRIN has a capacity building programme to develop clinical research infrastructure in EU countries that can be adapted to other world regions.
    - Transparency rules: mandatory registration of the whole trial protocol plus with the 20 WHO trial items before inclusion of the first trial participant and obligatory reporting of all clinical trials data and results. This requires the development of a registry for clinical trials with information in local language to provide the patients with access to information.
    - And enforcement of compliance to improved GCP guidelines. We should remember that these guidelines are grossly insufficient and should be improved (Grimes et al., Lancet 2005;366(9480):172-4) as suggested in the CONSORT Statements (www.consort-statement.org).
- Enforcement can be achieved in different ways:
    - EMA inspections for the registration trials.
    - Ethics committee inspections for other trials.
- EU should consider abandoning sponsor-controlled trials and setting up mechanisms for conduct of trials by independent parties.

Consultation item 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?

- Insurance : there is a need to promote
  - harmonised legislation on insurance and indemnity;
  - insurance packages rather than individual insurance coverage for a single clinical trial, and for both public and private sponsors (as exists for instance in Sweden);
  - indemnity coverage by the public health system for clinical trials sponsored by academic institutions (even for foreign sponsors) (like in Denmark).
- Need for measures to prevent fraud and misconduct.
- Need for legislation requesting full transparent trial protocol registration and full disclosure of all trial data and results.
- Need for getting the requirement to full transparency regarding all interventional clinical research into the EU legislation.
- Need for making it fully clear that any clinical trial necessitates the conduct of one of more systematic reviews with meta-analyses in order to estimate the following: a – what is the best control intervention?; b- what is the best alternative experiments intervention?; c – what trial size is needed to detect or reject a certain intervention effect?
- Need for long-term follow up of trial participants through public registers to monitor for late benefits or harms.
- Need to plan an assessment of the impact of the new legislation to follow its main consequences, with the development of a system to continuously monitor the relevant metrics on the clinical research activity and quality
  - protection of participants;
  - quality of trials;
  - harmonisation and facilitation of multinational trials;
  - attractiveness for industry to have their trials conducted by independent academic research organisations;
  - competitiveness of European research.