Cover letter

Sir,
Many thanks for providing us with the opportunity to express our concerns and suggestions regarding the European Legislation on clinical research on behalf of ECRIN. ECRIN (European Clinical Research Infrastructures Network) is the FP6- and FP7-funded pan-European, ESFRI-roadmap infrastructure project designed to support academic 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[1].

ECRIN is based on the connection between national networks of clinical research centres / 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 primarily by academic 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 issue is the clinical studies other than clinical trials on medicinal products that are critical for the scientific competitiveness of the European Union.

ECRIN participated in the EC-EMEA conference on the Directive in October 2007 and prepared written suggestions. 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 ESF-EMRC 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.

The comprehensive awareness developed by ECRIN results in numerous concerns regarding the current legislative framework for clinical research in Europe and in the Member States, and makes it possible to participate in the consultation through a consistent set of suggestions. The following document represents the outcome of discussions within the ECRIN working group on regulation. Consensus was reached for most of the suggestions proposed in the documents, and if not we mention which ECRIN partner(s) expresses an opinion divergent from the majority.
Warmest regards

Jacques Demotes *jacques.demotes@inserm.fr*
ECRIN coordinator
On behalf of the ECRIN working group on regulation

[1] *ECRIN-TWG deliverable 4, www.ecrin.org*

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

Summary of the clinical trials in the EU and CTD and achieveents 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 only in clinical trials on medicinal products).*
- *It resulted in a partial harmonisation, because of the divergence in interpretation and in transposition into national legislation.*
- *It clearly defined the responsibility of sponsors, of member states (through the competent authorities and of ethics committees in the supervision of the trial).*
- *The EudraCT database can be regarded as a tool to improve transparency (EudraCT should be used as a transparency tool for all trials, not only paediatric trials) whereas 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.*

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 studies where divergent opinions between EC and CA may be a problem, and*
  - *multinational studies, where divergent national opinions between competent authorities, and between ethics committees also 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).*

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 CTFG is a substantial progress, but is not sufficient.*
- *It is possible to make a distinction between national and multinational studies, and propose in a first step to introduce changes only for multinational studies. Some participants however prefer the idea of keeping, in a longer term, a national evaluation for national studies.*
- *There is a need for a single submission to the CA for multinational studies, with a one-stop shop dossier, 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, either based on specialisation of competent authorities or on the country of the sponsor and the principal investigator or other.*
  - *But in the long-term, a centralised process, as the competent authority giving the clinical trial authorisation in the EU should become the European Medicines Agency (this makes sense as it already gives the marketing authorisation). Some national competent authorities are understaffed and expertise at the national level may be lacking in certain areas and in certain countries.*
  - *However, there should be a possibility for a given country to withdraw from a trial.*
- *This should 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.*
- *It should not be restricted to selected categories of trials (like phase 1, or advanced therapy), but should cover all types of multinational clinical trials.*

(The NIHR CRN CC (UK ECRIN partner) supports further development of the VHP but does not support a centralised process).

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 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, and informed consent).*
- *National ethics committees should work together in the assessment of a single multinational study, 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 and informed consent.*
- *There is a need to promote the cooperation and networking among the EC 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 / certification system (without duplication in countries where defined standards already exists) for ethics committee 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 / certification system could be placed under the umbrella of DG Health and Consumers (DG SANCO). This does not raise issues regarding their independence, as ethics committees should be primarily independent from sponsors, rather than from public bodies).*

(The NIHR CRN CC (the UK ECRIN partner) supports a one-stop shop for application, but does not support the concept of a single opinion at the EU level for either the CTA or ethical approval).

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 of the situation and there is a need for an unequivocal definition of amendments, and for change in the SUSAR reporting system.*
- *The ethics committees should have access to the EudraVigilance database, and there should be an open access to safety data.*
- *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 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…).*
- *Some arguments are in favour of an immediate 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 their national legislation. On the other hand, one can be afraid that poorly developed pan-European legislation in other areas may cause harm to clinical research. Whereas some ECRIN participants (DCRIN in Denmark, INSERM in France) would favour an immediate extension of the scope of the legislation, other participants (NIHR CRN CC in the UK) rather prefer to focus on clinical trials on medicinal products. We therefore 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 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 study; 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 others. 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 pharmacoepidemiology study with or without diagnostic intervention highlights the need for a smooth transition in the regulatory requirements, with a risk-based approach to regulation.*

(The NIHR CRN CC (UK ECRIN partner) does not support the extension of the Directive to all areas of clinical research).

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, although some representatives (NIHR CRN CC in the UK) express reservations, and/or consider that a Directive coupled to clear guidance to ensure unambiguous interpretation would be sufficient (KKSN, the ECRIN partner in Germany).*
- *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 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?

- *Regulatory requirements are currently similar for a phase 2 study and for a pharmacoepidemiology study with diagnostic intervention, or for a head-to-head comparison of marketed drugs.*
- *There is a need to agree on the definition of risk: hazard to participants, hazard to data, hazard to public health ?*
- *There is a need to agree on risk categories: how many categories, which boundaries ? This system should not be too complex, as complexity may lead to divergent interpretation.*

- *There is a need to define a procedure for the assessment of risk by the sponsor/investigator, and for its validation (this should probably be the role of the ethics committees).*
- *There is a need to define which processes should be affected by the level of risk ? (expedited ethical review, submission / notification to CA, requirement for a sponsor, for insurance, safety reporting, monitoring, inspections…),*
- *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, without waiting for a new Directive or Regulation.*

Consultation item 10

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

- *Multiple sponsors and flexible sponsorship arrangements should be allowed, however they should be bound by a consortium agreement, with a "principal" sponsor, a single Eudract number, a single protocol (including amendments), and a single database.*
- *There is a need to make a clear difference between:*
  - *sharing legal and penal responsibility (liability, indemnity, data ownership, IP, inspection) (referred to as joint sponsorship in the UK)*
  - *and task delegation (submission to CA and EC, vigilance, monitoring, etc…) that merely requires a task delegation contract (and sometimes referred to as co-sponsorship in the UK).*
- *There is a need for a clear framework for this co-sponsorship. Sharing some responsibilities based on geography (one sponsor per area / 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 vs. co-sponsorship) depending on the nature of trial (national vs. multinational, type of trial). Public institutions should be able to select the best adapted solution for each 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 if possible to replace the current EU Directive by a Regulation (however the NIHR CRN CC (the UK ECRIN partner) does not agree with the idea of a Regulation).*
- *In the long term, this new legislation should cover all the categories of clinical research, as the protection of participants should be the same as far as they take risks, and as there is a need to run multinational studies other than clinical trials on medicinal products, including genotype/phenotype studies etc…).*
- *We propose to start with a revised legislation for clinical trials on medicinal products that, if it 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).*

(The NIHR CRN CC (the UK ECRIN partner) does not agree with this idea of extending the EU legislation to other categories of clinical research).

Consultation item 13

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

- *No, we disagree on this option, and the same rules should apply to commercial and non-commercial studies as far as they have the same level of risk.*
- *Data from non-commercial studies should be useable for registration purposes.*
- *Regulatory requirements should be adapted to the risk, not to the commercial or non-commercial objective of the study.*
- *In turn, academic institutions acting as sponsors in clinical trials, especially multinational trials, should be supported by the appropriate infrastructure.*

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 is an excellent initiative, however clinical research in all patients populations, including geriatric populations and all type of intervention should also benefit from improvements like transparency, support measures, infrastructure, networks etc, should be developed for all categories of clinical research, in any population and in any disease area.*

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 when the temporarily incapacitated patient recovers his/her ability to consent, with data 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?

- *ECRIN 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 for capacity building, and for enforcement and supervision of GCP.*

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 (and 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 trial protocol with the 20 WHO items before inclusion of the first patient, 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 GCP rules*
- *This enforcement can be achieved in different ways depending on the sponsor:*
  - *EMEA submission and inspections for the registration studies,*
  - *and through funding bodies (EU and national funding agencies), the WHO, and journal editors for non-commercial studies.*

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 study, 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).*
- *Need for measures to prevent __fraud and misconduct__*
- *Need to plan an __assessment of the impact__ of the new legislation to follow its main objectives, with the development of a system to continuously monitor the relevant metrics on the clinical research activity and quality:*
  - *protection of participants*
  - *quality of studies*
  - *harmonisation and facilitation of multinational studies*
  - *attractiveness for industry trials*
  - *competitiveness of European research.*