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From: Stephane Berghmans [SBerghmans@esf.org]
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To: ENTR /F/2 PHARMACEUTICALS
Cc: Liselotte Højgaard; Roger Bouillon; FUEHRING Stefan (ENTR)
Subject: ASSESSMENT OF THE FUNCTIONING OF THE "CLINICAL TRIALS DIRECTIVE"
2001/20/EC- PUBLIC CONSULTATION
Attachments: IDCT FL report.pdf; Report IDCT workshop Nov 09.pdf

Dear Madam/Sir,

The European Medical Research Councils (EMRC) would like to thank the European Commission and DG Enterprise and Industry in particular for the opportunity that is given through this public consultation to offer our assessment of the application of Directive 2001/20/EC.

The EMRC, the membership organisation for all the Medical Research Councils in Europe under the European Science Foundation (ESF, an independent, non-governmental organisation, the members of which are 79 national funding agencies, research performing agencies, academies and learned societies from 30 countries), has made public its position on the functioning of the 'Clinical Trials Directive' 2001/20/EC in a Forward Look report entitled 'Investigator-Driven Clinical Trials' published in March 2009 (see attached document).

Investigator-Driven Clinical Trials (IDCT) form a key part of patient-oriented clinical research, the basis for continually improving patient care. Such research is under strain in Europe for a multiplicity of reasons, and because of this the EMRC and ESF undertook a Forward Look exercise. Forward Looks are foresight exercises that enable Europe's scientific community, in interaction with policy makers, to develop medium to long-term views and analyses of future research developments with the aim of defining research agendas at national and European level. This IDCT Forward Look represents what is probably the most comprehensive examination of IDCT in Europe in recent years. A thorough analysis of the problems faced by academic investigators conducting IDCT was carried out through a series of workshops covering different themes and attended by active and acknowledged experts in the field.

The Forward Look resulted in 25 recommendations of which five were ranked as top priorities listed below. Recommendation 4 specifically addresses the functioning of the 'Clinical Trials Directive' as does indirectly recommendation 3. These recommendations are better detailed in section 9 (Implementation Plan).

1. To improve the education, training and career structure and opportunities for scientists involved in patient-oriented clinical research.
2. To increase levels of funding for IDCT.
3. To adopt a 'risk-based' approach to the regulation of IDCT.
4. To streamline procedures for obtaining authorisation for IDCT.
5. To ensure that IDCT are carried out with an appropriate number of patients to produce statistically reliable results – that the trials are 'correctly powered'.

Relevant analysis regarding the impact of the 'Clinical Trials Directive' can be found in section 2 (Categories and Design of Investigator-Driven Clinical Trials) where a pertinent example is the statement that "within the EU directive on clinical trials of medicinal products, the definition of 'intervention' is unclear and open to interpretation. There is a grey area between 'interventional' and 'observational' studies ... This lack of common definition makes it complicated and often unnecessarily bureaucratic to organise IDCT." Recommendation is therefore made "that regulators devise a better classification of clinical studies to facilitate the coordination of studies and to prevent problems generated by different national

interpretations. This revision needs to better define the border between interventional and observational studies, especially for diagnostic interventions”.

Scrutiny into the functioning of the ‘Clinical Trials Directive’ is also important in section 3 (Regulatory and Legal Issues, Intellectual Property Rights and Data Sharing) where it is for example stated that “the directive failed to discriminate between different categories of research, which resulted in the lack of an appropriate system for risk assessment for different categories of clinical trials. One consequence of this is that regulations aimed at protecting patients in research that is considered to carry a high risk often need to be applied to ‘low risk’ research. This results in unnecessarily cumbersome bureaucracy which, in extreme cases, could deter the investigator from launching a trial. Furthermore, the infrastructure, funding and administrative support required to address this bureaucracy are generally lacking”. The report goes on with the following recommendation: “We recommend that regulators minimise requirements (submission to ethics committee) for studies whose risk is similar to usual care, and to use a broad risk-based categorisation. For example:

- Level A – low risk (such as non-interventional pathophysiology, imaging)
 - Level B – similar to usual care (equivalent to most phase IV clinical trials)
 - Level C – moderate risk (most phase III clinical trials)
 - Level D – high risk (most phase I–II drug trials, gene or cell therapy)
- and to bear in mind to reduce the administrative burden”.

Finally, section 10 of the report (Conclusions) summarises the EMRC position: “Regulations governing clinical research are ripe for review. They need to be revised and simplified but without compromising patient protection. A risk-based approach to the categorisation and management of clinical trials should be implemented as part of an overhaul of the EU Clinical Trials Directive of 2001.”

These are only examples of the detailed analysis performed in this foresight exercise and we urge you to further examine the attached IDCT Forward Look report. Important elements were also reiterated and emphasised in a workshop entitled ‘Can we facilitate multinational investigator-driven clinical trials?’ and organised by DG Research (hosted by Dr. Draghia-Akli) on 10 November 2009 in Brussels (see attached report).

We stay at your disposal to further discuss the position of the EMRC, of our member organisations and of the European medical research community.

Best regards,
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