

Statement
of the European Group on Ethics in Science and New Technologies (EGE)
on the Proposal for a
Regulation of the European Parliament and the Council on Clinical Trials on
Medicinal Products for Human Use, and repealing Directive 2001/20/EC
(COM 2012) 369 final

The European Commission launched a new proposal for a Regulation of the European Parliament and the Council on Clinical Trials on Medicinal Products for Human Use, on July 17th, 2012. The purpose of the proposal aims *“at achieving an internal market as regards clinical trials and medicinal products for human use”* while at the same time setting *“high standards of quality and safety for medicinal products”*. Further streamlining the process through a regulation should increase the European Union’s competitiveness in the field of clinical research, thereby positively impacting on new and innovative treatment and medicines. As noted in the explanatory memorandum, the Clinical Trials Directive has been one of the most criticised pieces of EU-legislation in the area of pharmaceuticals. It has been suggested that it has caused an additional bureaucracy and increased expenses and workload to a variety of stakeholders, and decrease in the number of clinical trials in Europe. Other commentators are of the view that it has improved the safety of patients and research participants in Europe.

The European Group of Ethics in Science and New Technologies (EGE) appreciates the objective of the Commission to harmonise and fast-track the clinical trial process with a view to bringing new medicines to the market. The EGE has, however, some concerns regarding the draft regulation, namely concerning

- (1) the marginalisation of research ethics committees
- (2) the nomination process for the reporting member state
- (3) the narrow grounds upon which another member state can disagree with the reporting member state
- (4) the timelines for review and authorisation which in our view are simply unrealistic.

We raise these concerns in order to facilitate a robust examination of the draft regulation by the European Parliament and the Council.

1. The assessment of a clinical trial has been split into two parts, with Part II dealing directly with issues of ethical concern including informed consent, compensation and rewarding issues, recruitment of research participants, data protection, and competence of research personnel, suitability of trial sites, use of samples, areas that have been traditionally considered to belong to the competence of the Member States. Aspects covered by Part I contain information essential to an ethically sound evaluation of the proposed clinical trial e.g. sample size, randomisation, comparator, its clinical and statistical relevance. Evaluation of these aspects is crucial for the protection of research participants from harm and unnecessary risks, aspects that are at the core of ethical evaluation of medical research. Moreover, in order to safeguard the interest of clinical trials involving vulnerable groups, children, incapacitated persons, patients with mental illness, and research in emergency situations independent, multi-disciplinary ethical evaluation of clinical trial proposals is required. The EGE is aware that many Member States already have specific legislation concerning the involvement of such groups in

clinical trials and more broadly clinical research. The draft regulation as currently drafted would effectively transfer authority in these matters from the MS to the reporting Member State. The EGE also notes that article 30 and article 31 in reference to incapacitated adults and minors respectively, provide for an investigator to take under consideration a refusal to participate or a withdrawal by an individual. It is the view of the EGE that any "explicit" wish in relation to either participation or withdrawal by an incapacitated adult or a minor must be respected.

2. The proposal for a Regulation does not refer to ethics committees but rather leaves it to the Member State concerned to determine the appropriate body or bodies to be involved in this assessment, indicating that it would be a matter of internal organisation within each Member State. The EGE is deeply concerned that any reference to the notion of 'ethics committee' will disappear out of the European legal framework for clinical trials and question the validity of omitting a globally accepted mechanism for safeguarding the rights of research participants and investigators alike. Multi-disciplinary evaluation of clinical research was established in the second version of the Helsinki Declaration in 1975, and most recently in 2008, has subsequently been incorporated into other legally binding documents such as the Council of Europe Convention on Biomedicine (CETS164) and its Additional Protocol on Biomedical Research (CETS 195). Many member states of the EU have already ratified the Convention of Biomedicine, and 22 member states of the Council of Europe have signed the Additional Protocol on Biomedical Research. The Clinical Trials Directive is also the basis for a number of additional regulations, so the repealing of this Directive will involve a series of amendments in the present legislative framework in Europe and guidance given by the EMA. For example in the guidance published by the EMA for the good clinical practice the size, composition, and duties of ethics committees evaluating clinical trials have been fully described (ICH Topic E 6 (R1) Guideline for Good Clinical Practice: Step 5: Note for guidance on Good Clinical Practice. July 2002 CPMP/ICH/135/95).
3. The EGE wishes to emphasize that changing the structure of ethical evaluation of Clinical Trials is likely to hamper the marketing authorisation process of new medicines, and, instead of increasing competitiveness of Europe, it may adversely affect it. A proper review process of each trial by at least one independent, multi-disciplinary ethics committee is a requirement for getting a new drug into market in accordance with the regulations of other marketing authorities such as FDA of the United States. Official rules of the FDA¹ require that "the [Foreign clinical] studies be conducted in accordance with good clinical practice (GCP), including review and approval by an independent ethics committee (IEC)"². The European Medicines Agency has also set similar requirements for trials conducted outside the EU/EEA³.
4. The ten days allotted to the competent bodies to assess the ethical aspects of a trial is too short to assess the compliance with the eight requirements enumerated in article 7 §1, even if it were to be taken that the timeframe refers to working days. Unrealistic timelines will undoubtedly and unfairly contribute to the perception (rather than an evidence base) that research ethics committees delay the commencement of clinical trials. The EGE agrees with the sentiments expressed in the Consultation paper that it

¹ Federal Register/Vol. 73, No. 82/Monday, April 28, 2008/Rules and Regulations

² <http://www.gpo.gov/fdsys/pkg/FR-2008-04-28/pdf/E8-9200.pdf#page=1>

³ Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities. EMA/121340/2011

would be *'worthwhile considering how cooperation and exchange amongst national ethics committees, as well as procedural best practices, could be promoted in order to improve the ethical review of a clinical trial'*. We should not lose sight of the fact that the majority of ethics committees in Member States operate on the basis of voluntariness and in order to ensure robust ethical evaluation, it is important that well functioning committees are appropriately resourced and trained. This will allow ethics committees to work efficiently in partnership with investigators and sponsors.

5. The EGE has emphasized the importance of ethical review of research in its previous opinions, n°25 in Nov. 17, 2009 concerning Ethics of Synthetic Biology, n°22 in July 13, 2007 on human Embryonic Stem Cells in FP7 Research Projects, n°21 in January 17, 2007 on Nanomedicine, n°19 in March 16, 2004 on Umbilical Cord Blood Banking, n°17 in February 04, 2003 on Clinical Research in Developing Countries, n°15 in November 14, 2000 on Human Stem Cell Research and Use, n°13 in July 30, 1999 on Healthcare in the Information Society, n°11 in July 21, 1998 on Human Tissue Banking, n°10 in December 11, 1997 on Ethical Aspects of FP5, and n°4 in December 13, 1994 on Gene Therapy. While multi-discipline ethical review is considered as an essential part of this type of biomedical research, it would be logical to require the same in clinical trials.
6. In the Proposal, the sponsor of the trial is vested with the task of identifying which MS should act as the reporting MS for the assessment of Part 1 of the clinical trial proposal. Other member states may only comment on issues relating to Part I to the Reporting Member State before it gives the assessment report of the trial. This raises a number of additional concerns: namely it could lead to a situation which promotes "ethics shopping". Furthermore, this could lead to a lack of capacity building amongst research ethics committees in relation to clinical trial evaluation.
7. In relation to the assessment process, the EGE notes that the grounds upon which a MS can object to a trial are very narrow, i.e. If there is a significant difference in normal clinical practice between the Member State and the reporting MS which might lead to a trial subject receiving inferior treatment or where the trial infringes national laws in relation to the use of human/animal cells. This could prove problematic, as there may very well be other ethically valid reasons a MS may have objections to a particular proposal. For example differences in e.g. antibiotic resistance of bacteria might make a study ethically relevant in one country but might do more harm than benefit in another. Thus, it would be important that a collaborative and constructive mechanism could be found to ensure that the concerns of all MS in which a trial is to take place will be taken into account by the Reporting MS in its evaluation.
8. The EGE welcomes the inclusion of provisions concerning emergency research in the draft proposal. Clinical research in this area is necessary in order to provide improved and evidence based treatment to patients in such situations. The EGE notes that there are a number of different national policies in operation in relation to this matter. Harmonising requirements for consent for research in emergency situations should serve to protect the interests of vulnerable patients with the aim of improving the outcomes for patients who require emergency treatment.
9. There has been criticism of the 2001 Directive in that it increased bureaucracy and an increase in staff costs, number of paper copies, thereby introducing delays into the approval system. It is not clear to the EGE how the documentation required under the draft regulation is less onerous.

10. The draft regulation proposes that the European Commission will launch a portal that would act as a repository for all documentation pertaining to a clinical trial proposal with the intention of reducing the amount of paperwork necessary for a review. It is unclear how such portal might interact with the already established EudraCT system and the EGE suggests some consideration might be given to modifying the existing system to perform both functions. In the interest of transparency, the EGE supports the efforts to make information on clinical trials accessible to the public.

The EGE is supportive of a harmonisation of clinical trial evaluation first and foremost in the interests of patients accessing effective innovative medicines in a timely manner and also to enhance the European Union competitive performance in the clinical trial arena. However, it is our view that marginalising the role of research ethics evaluation achieves neither of those objectives. In view of these comments, the EGE recommends the EU Institutions to

- **Explicitly provide for research ethics committee evaluation of proposals in the interests of protecting the rights of research participants**
- **Give consideration to how best to avoid any type of ethics shopping, which may weaken the legitimacy of the evaluation e.g. by rotating the reporting member state function**
- **Consider expanding the grounds upon which a MS can disagree with the Reporting MS in the interests of building consensus and respecting ethical subsidiarity**
- **Set realistic timelines which should serve to expedite the process while allowing a robust consideration of the issues.**

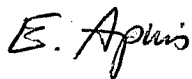
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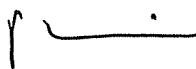
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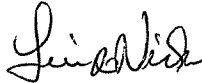
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