Mihaela Matei
Erwin J. O. Kompanje
Andrew I. R. Maas
David K. Menon
Francois Lemaire

Clinical research into the ICU: clouds at the horizon, once again

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M. Matei · E. J. O. Kompanje · A. I. R. Maas ·
D. K. Menon · F. Lemaire (✉)
Paris, France
e-mail: f.lemaire@numericable.com

Remember, it was back in 2001: a directive, drafted by the European Commission in Brussels, intended to give all EU Member States the same legislation for clinical trials on medicines [1]. The intent was legitimate, as the situation at that time in European countries was indeed chaotic. A working group of the ESICM published in this journal a striking picture of the diversity of the rules then governing human research [2]. An international working group, initiated by the Vienna School of Clinical Research published several articles describing the difficulties with the regulations of the directive in the practice of emergency and critical care research [3–5]. However, the European legislators forgot to mention the case of research made in emergency situations, where the patient cannot himself consent and his/her family is not around. Such research, though so necessary, was menaced to soon become unlawful. The directive was transposed in all EU Member States before the end of 2004. The Commission turned a blind eye to countries like France that continued to authorize the waiver or deferral of consent in emergency situations. The UK adopted a similar law in 2005 [6].

In July 2012, the EU Commission [7] proposed a *regulation* which would replace the directive 2001/20. The alleged rationale for revising directive 2001/20 is that the implementation of the European legislation has

resulted in useless bureaucracy and finally, in harm to clinical research, which many investigators and sponsors have denounced. The legal form of a regulation has to be implemented directly in all national laws with no adaptation, as opposed to a directive. Regulation has been chosen by the Commission in order to ensure that there will be consistency in application across the EU. The main objective of the proposed regulation is to simplify and speed up the process of authorization and conduction of clinical trials on medicines. To achieve that, sponsors will submit their research projects via a European portal, one unique reporting Member State will evaluate the dossier, and a single piece of advice (authorization or rejection) will be issued, no matter the number of “concerned” Member States. Approval times will be reduced (?). Ethical review of projects will remain in the Member States’ domain and competence. All these provisions sound reasonable.

Deferred consent in emergency situations is possible in the new proposal, as it states that ‘due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition, it is impossible to obtain prior informed consent from the subject and it is impossible to supply prior information to the subject’. However, there is also a major threat to research conducted in emergency situations. While authorizing the start of such research without initial consent, article 32 of the proposal limits the scope of this provision to situations where “the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject” (Table 1). In the context of the proposed regulation, it means that deferred consent will be accepted only when research will apply to authorized drugs. In other words, emergency research on new and innovative drugs will no longer be possible, which will constitute a major step backward for those countries that can today carry out such research.

The proposal for a clinical trials regulation is now under examination by the European Parliament. The

Table 1 Article 32 of the proposal

Directive 2001/20/CE	Proposal of regulation (EU Commission, July 2012)	Comments
No specific provisions for emergency research. Accordingly, waiver (or deferral) of consent is forbidden	<p>Article 32</p> <p>“...informed consent may be obtained after the start of the clinical trial to continue the clinical trial and information on the clinical trial may be given after the start of the clinical trial provided that all of the following conditions are fulfilled:</p> <p>(a) due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition, it is impossible to obtain prior informed consent from the subject and it is impossible to supply prior information to the subject;</p> <p>(b) no legal representative is available;</p> <p>(c) the subject has not previously expressed objections known to the investigator;</p> <p>(d) the research relates directly to a medical condition which causes the impossibility to obtain prior informed consent and to supply prior information;</p> <p>(e) the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject”</p>	<p>A great improvement from directive 2001/20; when the regulation is voted on (and included in national legislations), a clinical trial in emergency situations will be allowed to start without prior consent. Concerns include:</p> <p>(a) too restrictive; impossibility to consent may be caused by other conditions, for instance, sedation</p> <p>(b) should a legal representative be put on the spot, he could be unable to grant an informed consent (due to emotional stress or because of a too short window of inclusion; example: cardiac arrest)</p> <p>(d) too restrictive: impossibility to consent could be caused by another (pre-existing) medical condition, like encephalopathy)</p> <p>(e) <i>minimal risk</i> research, in the context of this regulation, means research on authorized drugs only</p>

report of the Environment Commission highlighted the issue and proposed a replacement of the condition of minimal risk by the more pertinent risk/benefit balance. This amendment has been accepted and voted on by the ENVI Commission at the end of May. We hope that the plenary EU Parliament will vote it also next Autumn.

The ESICM members and leadership should commit themselves to convincing all European MPs they can reach that banning research in precisely the most

devastating diseases is just nonsense. The provision calling for application of the risk/benefit balance in emergency situations must be supported and voted for by European lawmakers.

Conflicts of interest On behalf of all authors, the corresponding author declares no conflict of interest.

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