ICU MANAGEMENT & PRACTICE

ICU Volume 5 - Issue 1 - Spring 2005 - Europe

The EU's Clinical Trials Directive: The Potential for Inconsistent

Ethical Practices in Clinical Trials

Author

Henry J. Silverman, *MD, MA*

Department of Medicine

University of Maryland

School of Medicine

Baltimore, *MD*

Correspondence

hsilverm@medicine.umaryland.edu

This article describes the lack of specification of the European Union's (EU) Clinical Trials Directive regarding proxy consent and safeguards for vulnerable subjects. This failing could lead to inconsistencies in the way member states implement ethical standards in recruitment for clinical trials.

Introduction

The EU Clinical Trials Directive seeks to ensure consistency regarding the conduct of clinical trials involving new drugs in Europe (Directive 2001/20/EC). The Directive's goal is to provide an environment for conducting clinical research that protects research subjects without hampering the discovering of new essential medicines. The Member States had until May 2004 to incorporate the Directive into domestic legislation.

The Directive provides guidance regarding the protection of clinical trial subjects. It also gives further guidance for adult persons who are incapable of giving informed consent, because such incapacitated individuals represent a vulnerable class of subjects who "should be given special protection" (Directive 2001/20/EC). Specifically, the Directive discusses the identification of individuals who could provide proxy consent for vulnerable subjects, and additional safeguards to minimize the risk of harm and the potential exploitation of incapacitated subjects' inability to provide consent.

The Problem

Despite several commendable directives, the EU Directive lacks specification or complete guidance regarding proxy consent and essential safeguards for vulnerable subjects. Such a situation could lead to inconsistencies in the way member states implement ethical standards for the EU clinical trials directive. The potential for lack of harmonization in the ethical conduct of clinical trials could lead to confusion among sponsors, clinical research organizations, investigators, and others, thus creating an adverse perception of the EU as a desirable place in which to conduct clinical research.

This article will describe the exact nature of the lack of specification of the EU Directive regarding the protection of vulnerable subjects enrolled in research. Such identification might help Member States incorporate more uniform guidelines in its subsequent regulations.

EU Directive's Guidance for Vulnerable Subjects

The EU Directive, consistent with previous ethics guidelines (National Bioethics Advisory Committee 1998; Tri-Council Policy Statement 1998; Council for Europe 1997; Council for International Organizations of Medical Sciences 2002) states that respect for persons entails that persons with diminished autonomy require special protection and such protection entails obtaining "appropriate" proxy consent for their participation in clinical trials. Accordingly, the Directive requires the written consent of a legally authorized individual and refers back to existing national law. The

Directive recognizes that proxy consent might involve either a legal person (i.e. previously appointed through a legal process) or a natural person (i.e. a family member or close friend). Hence, the law of a Member State could give automatic legal authority to family members or close friends (i.e. without a prior legal process). Such a law would enable previously healthy persons, who become acutely and temporarily incapacitated to participate in clinical trials, e.g. patients with sepsis, strokes, trauma, or with a myocardial infarction.

The EU Directive does not specify the identity of natural persons. On one hand, such ambiguity allows individual Member States to adopt regulations informed by their different local conditions. On the other hand, such ambiguity could lead Member States to adopt approaches to proxy consent that differ greatly in the range of persons that could qualify as proxies. For example, the Austrian Drug Act does not allow family members to be automatically authorized to provide proxy consent for incapacitated individuals. The law in The Netherlands would empower only a legal representative, a spouse, or life companion to provide consent for incapacitated persons to participate in research. This list would exclude many persons who are unmarried, divorced, or widowed and without a life companion from participating in research. Such individuals might have parents or adult children who might be ethically appropriate proxies. In contrast, regulations in the United Kingdom and France are less restrictive and would even allow a physician to provide proxy consent for research participation. It is difficult to understand how such “third parties” can provide valid consent for incapacitated persons, as ethically appropriate proxy consent should either “represent the presumed will of the subject” (Directive 2001/20/EC) or know what would be in the best interests of the subject (Silverman et al. 2004).

Beyond the issue of proxy consent, the EU directive appropriately endorses other mechanisms to safeguard the rights and welfare of incapacitated individuals. These include the requirements for assent, dissent, the necessity requirement, and the subject-condition requirement. The necessity requirement would allow the participation of incapacitated subjects in clinical trials only if their enrolment is scientifically necessary. For example, the condition being studied causes incapacity in all persons, such as severe head trauma, or the research cannot be conducted in competent subjects with the same disorder. To enrol incapacitated subjects when it is not scientifically necessary raises the concern that such individuals are being targeted because of their easy availability or their inability to protect themselves. The subject condition requirement entails that the research must involve a condition from which the subject suffers.

The EU Directive, however, fails to mention safeguards that other guidelines have recommended for all research studies (National Bioethics Advisory Commission 1998). These include the requirement for investigators to outline a plan to assess the capacity of potential subjects when groups that might include incapacitated subjects are included in the study’s recruitment plans, for example, for patients receiving mechanical ventilation or individuals with mild to moderate schizophrenia. For subjects previously enrolled in research via proxy consent, several research ethics guidelines recommend that there be a mechanism to obtain the informed consent of such subjects if and when they regain competency (Tri-Council Policy Statement 1998; Council for International Organizations of Medical Sciences 2002).

Finally, the EU Directive is silent regarding further safeguards for research involving non-therapeutic procedures associated with more than minimal risk. Such safeguards could require the presence of an independent person to perform capacity assessments and the presence of an independent consent monitor, who could witness the informed consent process (Silverman et al. 2004). Finally, other ethics guidelines differ as to whether research that is greater than minimal risk should be prohibited (National Bioethics Advisory Committee 1998; Tri-Council Policy Statement 1998; Council for Europe 1997). The EU Directive is noncommittal on this issue and could lead Member States to adopt varying guidelines for such research.

A final problematic issue involves research performed in the emergency setting. In such situations involving incapacitated individuals, there might be insufficient time to obtain consent from legally authorized individuals due to

the narrow time window that usually exists for the administration of the investigational agent or intervention. The EU Directive fails to address this situation. Many fear that such silence will preclude potentially beneficial research in the emergency setting. As an alternative, many Member States have endorsed conditions under which such research may proceed with a waiver of informed consent (Silverman et al. 2004). However, such conditions differ greatly between Members States and could lead to further inconsistencies in the conduct of such research.

Conclusion

The EU Directive’s lack of specification and incomplete guidance regarding proxy consent and essential safeguards devolves too heavy a reliance on the diverse views of individual Member States as well as those of individual research ethics committees. Such a situation might lead to inadequate and inconsistent safeguards, thus making research ethically problematic (Silverman et al. 2001). A lack of clarity regarding research in the emergency setting might also lead to inconsistent and contradictory approaches. The potential for lack of harmonization in the ethical conduct of clinical trials among the Member States would lead to confusion among those who sponsor, oversee, and conduct research in the EU and will create an adverse perception of the EU as a desirable place in which to conduct clinical research.

Published on : Thu, 15 Aug 2013