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The European Union Directive on Clinical Research: present status of implementation in EU member states' legislations with regard to the incompetent patient

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Introduction

A European-wide response is slowly emerging to the European Union Directive on Clinical Research (2001/20/CE) establishing good practice in the conduct of clinical trials on medicinal products [1]. The Directive was to have been incorporated and made effective in member states' national laws by 1 May 2004. Among many other aspects of this wide-ranging Directive passed by the European Parliament on 4 April 2001 is the requirement for prior informed consent by a legal representative for research involving incompetent patients. A preliminary survey conducted by this group in 2002 demonstrated that many states did not possess clear definitions for a legal representative in matters of health, and in the absence of a waiver of informed consent none could validly recruit patients to clinical trials in emergency situations. The Directive therefore had the potential to make clinical research very difficult in intensive care, and impossible in emergency situations such as cardiopulmonary resuscitation. We now report current progress among member states in implementing the Directive.

Modifications to national legislation

A new law or an amendment to existing law has already been incorporated in national statutes or is in the process of approval in The Netherlands, France, Belgium, Italy, Denmark, Germany, Austria, and Spain (Table 1). In other countries discussions and proposals are still not complete. In some countries the proposals are limited to drug research (as was intended by the Directive); in others (Belgium, France, The Netherlands, the United Kingdom) its scope has been broadened to include all types of research (epidemiology, genetics, pathophysiology, and observational studies).

National responses to the requirements of the Directive concerning incapacity

In addition to the generic issues of research ethics, intensive care specialists must contend with difficulties in obtaining informed consent when undertaking clinical research, since critical illness and its treatment usually either impair or abolish competence and autonomy. The most important of these is the issue of competence and the requirement for surrogate consent or assent. The other special circumstance is the degree of urgency required to provide treatment or, in this context, to recruit patients for clinical trials such as when there is insufficient time to obtain consent as in the case of cardiopulmonary resuscitation.

Incompetence and the appointment of a legal representative

In circumstances in which patients lack the capacity to consent, have no legal guardian, and are not in an emergency situation most European countries have hitherto permitted surrogate consent from family members, although there may not have been a formal statute requiring familial assent. The Directive now makes it mandatory to clarify this matter and that the consent be granted by a "legal representative" defined according to national laws. The present responses across the EU to the Directive in the form of drafts or enacted legislation vary in extent and are inconsistent in content, reflecting the ill-ease of legislators all over Europe with the concept of surrogate consent for research. The following approaches have been adopted or are proposed:

In Belgium consent may be given by a legal representative designated in advance, or if there is no legal representative, by the spouse, partner, a child who has achieved majority, or a parent. This would seem to be a pragmatic and reasonable proposal. Similarly, Spanish law states that, "if the subject is not able to take decisions due to his/her physical or mental health and he/she has no legal representative, the consent will be granted by persons connected to him/her by family reasons or by fact."

In France consent may be given by a previously designated surrogate or a family member. However, the law now states that if the research has the potential to "interfere seriously with patient's bodily integrity" authorization is required from a judge. Ethics committees analyzing research protocols will decide whether this provision needs to be applied.

In The Netherlands consent may be given by a legal representative previously designated or, if not, by the subject's spouse or companion in life (which is different and less liberal than for the surrogate consent for treatment [2]. This provision has now been submitted for revision by the Dutch Parliament. All protocols of research without *direct benefit* are sent for approval to a "central" (national) committee, the CCMO.

In England and Wales it is proposed that consent may be given by a "personal" legal representative (someone with a "close personal relationship") if such a person is available or, if not, by a "professional representative," who could be a physician; interestingly, the British draft suggests that the physician in charge will determine who should be regarded as the potential subject's legal representative [United Kingdom Department of Health, "The medicines for human use (clinical trials)," 2004 regulations]. The identification and designation of the legal representative is rarely explicitly mentioned in the regulations of other countries.

In Scotland (which, although part of the UK, has its own legal system) the legal representative is identified on the basis of a cascade of relatives, male being given precedence over female at each level [Adults with Incapacity (Scotland) Act, 2000.]

In Italy the concept and responsibilities of the legal representative may be conferred on regional authorities; while still under discussion, it appears that Italian lawmakers are favoring a kind of "institutional" representative, as in England in Wales.

Table 1 Current state of implementation the EU Directive on Clinical Research (2001/20/EC) into the member states' laws (October 2004)

	Date of law	Drug research only	Emergency research			Incapacity to consent	
			Waiver of consent	Deferred consent	Only with direct benefit	Surrogate	Comments
Austria	April 2004	Yes	Yes	Yes	Yes	Yes	Surrogate designated by a judge. Research with medical devices are allowed without direct consent.
Belgium	April 2004	No	Yes	Yes	No	Yes	–
Czech Republic	May 2003	Yes	No	No		Yes	Surrogate designated by a judge.
Denmark	May 2003	No	Yes	Yes	Yes	Yes	Waiver of consent for emergency not applicable now for drugs trials, but this is not yet still unsettled.
France	July 2004	No	Yes	Yes	No	Yes	If "serious risk," assent is granted by a judge. In research without direct benefit no risk greater than minimal is allowed.
Germany	April 2004	Yes[a]	Yes	Yes	Yes	Yes	Surrogate designated by a judge.
Greece	May 2004	Yes	No	No		Yes	Waiver of consent for emergency not applicable now for drugs trials, but this is not yet still unsettled. Research on medical devices without consent is allowed.
Ireland	May 2004	Yes	No	No		Yes	An attorney appointed by the hospital can give consent when no patient's relatives are available within a reasonable time. The physician responsible for the care of the patient must be consulted.
Italy	April 2003	Yes	Yes			Yes	The legal representative has not yet been defined; this could be left to regional authorities.
The Netherlands	1998	No	Yes	Yes	Yes	Yes	Only the spouse or "life companion" may act as surrogate.
Norway	–		Yes	Yes	Yes	Yes	–
Portugal	–	Yes	No	No	No	?	–
Spain	February 2004	Yes	Yes	Yes	No	Yes	Waiver of consent is allowed for emergency research if no therapeutic alternatives in clinical practice are available, the patient is unable to give consent, and no surrogate is available; however, as soon as the patient recovers competence, or the legal representative is available, deferred consent is compulsory.
England, Wales	April 2004	Yes	No	No[b]		Yes	The physician responsible for care or a person appointed by the hospital ("professional representative") can give surrogate consent when patient's relatives ("personal" LR) are not available within reasonable time.
Scotland	April 2004	Yes	No	No		Yes	The physician responsible for care or a person appointed by the hospital can give surrogate consent when guardian, or welfare attorney, or patient's relatives are not available within reasonable time.

[a]Extension to all types of research is currently under consideration
[b]If "serious risk," assent required a judge

In Germany and Austria surrogates have been designated by a *judge*, a provision usually considered to be unfavorable. In Austria surrogate consent is allowed for drug research, but as the scope of the Directive is limited to drugs, the previous obligation of direct consent for trials with medical devices has not been lifted [3]. This therefore prevents Austrian researchers from undertaking studies of medical devices in incompetent patients, although the health care system accepts evidence of benefit for medical devices tested in this way in other countries.

The Clinical Trials Directive also has an impact on other research and health care legislation. The United Kingdom, for example, is currently trying to integrate the requirements of the Directive with the Human Tissue Bill (http://www.parliament.the-stationery-office.co.uk/pa/ld200304/ldbills/094/2004094.htm) and the Mental Capacity Bill (http://www.publications.parliament.uk/pa/cm200304/cmbills/120/2004120.pdf). [4]. Similarly, in France the recently updated law on bioethics now rules that research using blood or tissue samples obtained in usual care can be used for research purposes provided information is given to the patient and he/she does not object. In doing so this type of research—on samples, not on patients—is not covered by the Directive.

The context of emergency research

Even if a legal representative is defined in law and in person, this does not deal with the problem of undertaking clinical research in the context of emergency medical care. The Directive fails to identify emergency medical care as requiring special consideration, a major omission since it is clearly impossible to obtain informed consent for research in these circumstances [5]. European specialists in emergency medicine have stated that the implementation of the Directive in their countries will put all emergency research on hold [6, 7, 8]. In the United Kingdom, for example, resuscitation research has come to a halt. A strict definition of "emergency" research (or medical care) is also required. Various approaches have been adopted to ameliorate the effects of the Directive in this respect:

Austria, Belgium, France, The Netherlands, Germany, and Spain have chosen to maintain the possibility of a waiver of consent that they had previously, even though the Directive would appear to make this invalid. These countries argue that a waiver can be applied if the research brings some "direct benefit" to study patients. For example, the Dutch law says that emergency research can proceed with a waiver of consent if "the research may be of direct benefit to the subject" [2]. France, however, which had had such a provision since 1988, abolished it as its new draft law suppresses the distinction the previous law made between research with and without direct individual benefit [9]. Similarly, Germany allows a waiver of patient consent if "the treatment is necessary to save his life, restore his health or ease his pain."

The Austrian law, similar to the federal regulation in the United States, proposes that the public be informed of the clinical trial in appropriate manner [3].

The British draft proposals have tried to interpret the Directive strictly and in consequence are considering various possibilities for applying prior surrogate assent from an individual empowered to act as a legal representative for incapacitated patients. Proposals initially included paramedics, or the clinician responsible for the care of the patient. The revised proposals allow for the appointment of an individual by each hospital to act in this capacity.

Denmark proposes to allow a waiver of consent if "the trial will in the long run improve the patient's health condition." This provision, however, does not apply to trials with pharmaceuticals.

Italy has translated and closely applied the Directive, without regard to the emergency situation.

Several countries require that the researchers obtain deferred consent if the patient regains consciousness (e.g., Belgium, France, The Netherlands). Some extend this provision to a surrogate who may be identified after inclusion of the patient in the trial (Belgium, The Netherlands). France has added the possibility that a patient who would have refused participation in the trial if conscious at the time of inclusion may prevent utilization of the data collected from him when he was incapacitated.

Industrial vs. institutional research

In addition to the two key aspects of incompetence and emergency research, the Directive also applies special conditions to sponsors of clinical trials. The Directive has been written from the perspective of trials funded by pharmaceutical firms and dealing with innovative drugs (phase 1, 2 or 3). Institutional sponsors [10, 11] and investigators claim today that the national laws drafted according to the Directive will add considerable bureaucratic paperwork and will ultimately harm clinical research. The Medical Research Council in the United Kingdom has published the most comprehensive (and most critical) analysis of the Directive ["MRC response to the MHRA consultation letter on the medicine for human use (clinical trials)," 2003 regulations 2003 (MLX287), and draft legislation"] from the point of view of institutional sponsors.

Detailed guidance on interpreting the Directive

European Commission working groups have produced and displayed on the EU website (http://pharmacos.eudra.org/F2) five "detailed guidance" documents which complete the Directive and will ultimately be incorporated into national regulations. These concern: (a) the request to the administrative authority for authorization of a trial, (b) the documentation and application format to an ethics committee, (c) the presentation of adverse reactions report, and (d) the database for SUSAR, the European clinical trials database.

Adaptation of these documents to non-drug research is obviously necessary, as well as to research dealing with marketed drugs already in routine use. In particular, the possibility of using a simplified Investigator Medicinal Product Dossier must be clarified. Another matter of concern is the intention of the European Commission to impose a single sponsor for multinational trials, as is it felt that only the pharmaceutical firms will be able to cope with such an expansive requirement. Finally, the possibility of overregulation and overinterpretation of these legal texts is very real.

Conclusion

It is the view of the intensive care community and the ESICM Task Force on a legislatia research on that progress in the care of critically ill patients is necessary for the benefit of public health, and that such progress requires continued research in acutely ill patients throughout their journey through the health care system. The EU Directive, although well-meaning in intent, has not taken into account the particular needs of research in the critically ill patient and in emergency circumstances. This is causing significant difficulty in incorporating Directive into national statutes. The diversity of national responses to the Directive could actually impede international research.

We therefore ask that European and national lawmakers take note of and accommodate in their proposals the particular needs and difficulties of clinical research in critically ill patients. If they do not do this, there is a very real risk that research in acutely ill patients will become impossible. To minimize the potential adverse impact that the Directive could have on medical progress and improvements in patient care legislators need to take into account the following points:

Definitions

A clear distinction in terms of the procedures for obtaining consent to research should be made between patients who require emergency treatment (e.g., cardiac arrest, shock), and the "typical" ICU patient receiving organ system support where time permits the acquisition of informed consent from a legal representative. The United Kingdom draft proposals, for example, consider defining emergency circumstances as those in which medical interventions are required within 8 h.

Waivers

A waiver of consent, subject to appropriate protection for the subjects, should be possible for emergency research. This is already formalized by several existing regulations, in the United States since 1996 and in some European states as well. The additional draft of the Bioethics Convention makes it possible. Belgium, The Netherlands, France, and Spain have already drafted provisions regulating waiver of consent in emergency situations.

Legal representatives

National laws must clearly define which persons may act as a "legal representative" for consent to research in incompetent patients: the simpler, the better. Such a person could either be a previously designated surrogate (which in most instances will be a rare event) or a family member. It is difficult to see how the judiciary can bring added protection to patients when acting as surrogate legal representatives for emergency research.

Sponsors

Regulations intended to control research conducted by international pharmaceutical companies must not impede institutional research, which more often involves observational studies into disease mechanisms or necessary further investigation of drugs that are already marketed.

Individual benefit

The concept of "direct individual benefit" of research continues to appear in national laws. Such a concept indicates a total misunderstanding of the concepts of clinical research (i.e., the production of "generalizable knowledge") and usually leads to the interdiction of physiopathological ("observational") research. The misunderstanding also arises from a semantic confusion of "therapy," meaning drug treatment, and "therapeutic," implying "beneficial." Moreover, the idea that drug research can only be conducted if it is likely to benefit the individual patient is clearly unethical since it contradicts the essential principle of equipoise.

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