Informed consent of incapable (ICU) patients in Europe: existing laws and the EU Directive

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Purpose of the review

The new European legislation on good clinical practice in the conduct of clinical trials on drugs has raised serious concern that potentially lifesaving studies cannot be carried out in critically ill patients in Europe anymore after May 2004. The requirement of nominating a legal representative for obtaining informed consent before inclusion will deprive current and future patients of participation in research. The new legislation does not differentiate between patients who are incompetent because of a psychiatric illness or dementia and patients who are incapacitated owing to an emergency situation. All those patients may be enrolled in a clinical trial only after informed consent has been granted by a legal representative.

Relevant findings

Recent publications regarding the new European legislation manifest an outcry by intensive care specialists, emergency medicine specialists, traumatologists, and specialists of other related disciplines concerned about the proposed active withholding of potentially beneficial therapies for this very unfortunate group of patients. Many authors, although acknowledging the ethical principle of autonomy, express that in the field of emergency medicine not all criteria of autonomy may be met. The Declaration of Helsinki requires that even the best prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research. There is agreement among the authors that critically ill patients should not be deprived from the benefits of research.

Summary

Many groundbreaking therapies will not be scientifically evaluated anymore, and thus beneficial treatments in fatal diseases will be prevented. The European legislation is asked to adapt the Directive to promote research in critically ill patients.

Keywords

European Directive 2001/20/EC, clinical research, intensive care medicine, emergency medicine, critically ill patient, temporarily incapacitated patient, informed consent, legal representative, waiver of consent

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Introduction

The "Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use" [1] was officially adopted on April 4, 2001. The Member States had until May 2004 to incorporate the Directive into domestic legislation. Most of the Member States had complied and published new drug laws until then, but some could not meet the time frame [2]. The aims of the Directive were to "simplify and harmonize" the conduct of clinical trials in Europe and thus creating an environment stimulating research in Europe and making Europe competitive again. The major changes are the now Europe-wide requirement for multicenter clinical trials to establish a procedure for the adoption of a single opinion of an ethics committee for that Member State, the clear-cut definition of the term sponsor of a clinical trial, and the requirement of obtaining informed consent of the legal representative before including a patient not capable of providing informed consent him- or herself in a clinical trial. This last requirement could severely impair future research in critically ill patients as it does not differentiate between patients who are incompetent because of dementia or psychiatric illness and patients who in an emergency situation as they are temporarily incapable owing to a trauma, a myocardial infarction, or sepsis.

The patient who is incapable of giving informed consent: the requirements of the Directive

The Directive points out that there should be given special protection to patients who are incapable of giving legal consent to clinical trials. It elaborates further that, in the case of persons incapable of giving informed consent other than children, "such as persons with dementia, psychiatric patients etc." inclusion should be on an even more restrictive basis. In Article 5, it requires furthermore that such persons have received information according to their capacity of understanding regarding the trial, the risks, and the benefits; in addition, the ex-

plicit wish of the subjects who are capable of forming an opinion and assessing this information is considered by the investigator.

To increase patient protection, the Directive does require the written consent of the patient's legal representative and further states that the notion of a legal representative should refer back to existing national law. The Directive does not expressly refer to the emergency patient or the patient in the ICU.

What is the intention of the Directive?

This legislation has major implications for any research in intensive care and emergency medicine that has not been realized in the intensive care community.

Reading the above-mentioned requirements, one can only conclude that the Directive seems to have only patients in mind who have some kind of mental disorder and thus legally are incapacitated. The Directive does not refer to the temporarily incapacitated adult patient. There is no mention of the patient who acutely loses the capability to consent, *eg,* the patient with a myocardial infarction or sepsis, the trauma patient.

The Directive does not address the patient who does not have a legal representative. Considering this, one could argue that a clinical trial including such patients because of the lack of a legal representative is strictly forbidden!

However, it is beyond every power of imagination that in the whole of Europe, there should not be clinical trials in the field of emergency medicine. It is not feasible to deprive European patients from the benefits of such clinical research. If the intentions were, in fact, to exclude European patients from emergency trials, it would be a foregone conclusion to withhold treatments that are the result of such research. It would definitely be not ethical to go on and use drugs, medical devices, therapies without participating in their research, especially if the research has been carried out in countries with a not so developed legal framework for clinical trials and patient protection. In times of increasing globalization, one cannot draw a wall around a region [3].

The historic background

Physicians do know very well what the legal requirements for treating their patients are; they are well aware of how to obtain consent from their patients and which formalities are necessary if the patients are not capable of giving consent because of their condition or disease. It is therefore astonishing that the awareness concerning the legal requirements for research is rather low. Regulations concerning research are different with respect to consent and also in particular regarding the risks to research participants and the benefit of the research for the individual patient. Additionally, the situation is varying worldwide and in the individual European Member States and also differs, for example, as far as drug research, research on medical devices or surgical methods are concerned. There exists no regulation at the European level.

The driving force behind the Directive has been the pharmaceutical industry and the idea of creating a European internal market for medicinal investigational products [4]. Apparently the deputies of the competent authorities of the single European Member States contributing to the legislation in Brussels have merely been composed of representatives who are not overseeing the whole range of medical research. Otherwise it is not easy to understand that the "unrepresented" patient, the patient in an emergency situation, has been left out and not addressed by the Directive, but neither have medical experts, researchers in intensive care, and the respective scientific societies been involved from early on or they simply ignored the threat. Also ethics committees and patient representatives should have a professional interest that acutely incapacitated patients are not deprived of potentially effective treatment [5•,6•]. There has been no lobbying.

The "outcry" came rather late: After the publication of the Directive in the *Official Journal of the European Parliament and of the Council* in April 2001, some articles appeared in the international medical journals, all of them lamenting the situation [7,8,9•,10].

The legal representative/ waiver of consent

As mentioned previously, the Directive has not addressed the special situation of the patient without representative, and strictly following this, we can conclude that trials including patients who have no legal representative are not possible. However, the fact that the notion of legal representative is broader in the wording of the Directive leaves also another interpretation: According to the Directive, a legal representative is not only a typical custodian or guardian appointed by court, "but may include natural or legal persons, an authority and/or body provided for by national law" [11].

As we know from the literature, some nations have solved this problem in a particular way. In the Netherlands, some persons are eligible to function as legal representative: a spouse, a life companion, a legal representative, or a person authorized by the patient him- or herself. However, these seemingly thoughtful regulations do not cover the whole situation in a satisfactory way. The Dutch law recognizes only the spouse or life companion as a legal representative; because it is directed at persons living in the same household, it leaves out certain persons from being legal representative, such as unmarried adults without a companion and divorced or widowed adults with parents, and thus deprives such persons of participating in clinical trials [9•].

In Austria, because of the time-consuming procedure of appointing a legal representative and because of a certain number of requirements that have to be fulfilled, the former drug act had foreseen a waiver of consent. This regulation would still be in harmony with the ideas of the Directive [12]. The new Austrian drug act [13] still foresees the possibility of a waiver of consent if additional protections of the rights and welfare of the patients are provided, including public disclosure to the community in which the research will be conducted. Other European Member States (Belgium, Denmark, France, Germany and the Netherlands) also either upheld their previous regulations concerning the inclusion of patients in an emergency situation with a waiver of consent or foresee one now: There are situations in emergency research in which the ethical principle of autonomy can simply not be met in a narrow therapeutic time window without jeopardizing potential therapeutic benefits for the patients.

Even the United States had taken such an approach. In 1996, the authorities waived the general requirement for informed consent for a strictly limited class of research that may be carried out in subjects who are in need of emergency therapy because of a life-threatening situation and where available treatments are unproven or unsatisfactory [14].

Beyond that, it is not feasible to think that a third party can give real "consent" for another person. Because it is impossible for the patient to give consent him- or herself, a surrogate is necessary. However, surrogate consent is nothing but an instrument to control, an instrument the way ethics committees or other bodies exist to supervise research in protecting the integrity and the dignity of the patient but also in support of the investigator.

Furthermore, as it is the obligation of investigator and the ethics committee to follow the presumed will of the patient, how could an appointed legal representative who might be a stranger to the patient know his or her wishes or preferences in regard to participation in a clinical research project [15]?

The Directive does not have a commitment to the patient in an emergency situation. Many authors criticize this fact and express the fear that such research will not be possible anymore in Europe and that those patients will be deprived of potentially favorable therapies [16•]. There are only two solutions: a legally sound and Europe-wide simple procedure for nominating a legal representative or a waiver of consent.

What argues in favor of a waiver of consent is the fact that there is an additional multitude of requirements that have to be met before a patient can be included in a trial [17••,18••]. These multifarious prerequisites prevent irresponsible or inconsiderate research in such a vulnerable patient group:

- the requirement that such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods
- the requirement that this research has to relate directly to a life-threatening or debilitating clinical condition from which the incapacitated adult suffers
- the requirement that the clinical trial has to be designed to minimize pain, discomfort, fear, and other foreseeable risk in relation to the disease and developmental stage
- the requirement that the risk threshold and the degree of distress shall be specially defined and constantly monitored
- the requirement that an ethics committee with expertise in the relevant disease and the patient population concerned or after taking advice in clinical, ethical, and psychosocial questions in the field of the relevant disease and patient population has endorsed the protocol
- the requirement that the interests of the patient always prevail over those of science and society
- the requirement that there are grounds for expecting that administering the medical product to be tested will produce a benefit to the patient that outweighs the risks or has no risk at all.

Last but not least, one has to consider that scientifically unsound research is *ipso facto* unethical in that it may expose individuals to risks for no purpose at all [19]. Including only patients who are able to give informed consent personally or are represented by a legal representative in clinical trials of severe diseases might lead to an important selection bias, such as that the included patients are not representative of the typical patient with the researched disease or condition such as stroke and myocardial infarction. Results of those trials may not be comparable on an international scale [20•]. This emphasizes the need for an amendment or clarification regarding waivers of consent for research.

Conclusion

Most critically ill patients are unable to give informed consent. The new European legislation does not differentiate between patients who are incapacitated for a long time and patients who are temporarily incapacitated owing to an emergency situation requiring consent of the legal representative for all of them. Normally patients who are temporarily incapacitated do not have a legal representative. Furthermore, the Directive makes a reference to national law for the nomination of the legal

representative, thus resulting in a wide variation of possible legal constructions, which are not comparable.

For those patients, a waiver of consent in combination with the other requirements of the Directive would be an ethically acceptable possibility for not depriving such persons from participating in potentially beneficial research. Patients do need protection from unethical and illegal research procedures, but it has to be emphasized that they do also need to be protected from the deprivation of potentially beneficial treatments.

The European legislation is asked to adapt the Directive to promote such research in critically ill patients.

References and recommended reading

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- •• Of outstanding interest

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