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REVIEW

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Medical research in emergency research in the European Union member states: tensions between theory and practice

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Abstract In almost all of the European Union member states, prior consent by a legal representative is used as a substitute for informed patient consent for non-urgent medical research. Deferred (patient and/or proxy) consent is accepted as a substitute in acute emergency research in approximately half of the member states. In 12 European Union member states emergency research is not mentioned in national law. Medical research in the European Union is covered by the Clinical Trial Directive 2001/20/EC. A proposal for a regulation by the European Commission is currently being examined by the European Parliament and the Council and will replace Directive 2001/20/EC. Deferred patient and/or proxy consent is allowed in the proposed regulation, but does not fit completely in the practice of emergency research. For example, deferred consent is only possible when legal representatives are not available. This criterion will delay inclusion of patients in acute life-threatening conditions in short time frames. As the regulation shall be binding in its entirety in all member states, emergency research in acute situations is still not possible as it should be.

Keywords Emergency research · Deferred consent · Informed consent · EU Directive 2001/20/EC · Autonomy

Introduction

A proposal for a regulation by the European Commission that is currently being examined by the European Parliament and the Council and will replace Directive 2001/20/EC [1] states: "This regulation should provide clear rules concerning informed consent in emergency situations." Notwithstanding this extremely laudable aim, there are concerns about the clarity of the regulations, whether daily research practice in European intensive care units complies with their requirements, and indeed whether such compliance is universally possible.

In the European Union/European Environment Agency (EU/EEA), approximately 4,400 clinical trials are applied for every year. Approximately 60 % are sponsored by the pharmaceutical industry and approximately 24 % concern multinational clinical trials, performed in at least two member states. Clinical trials, as defined in 'European Union Directive 2001/20/EC of the European Parliament and the Council of 4 April 2001' are investigations of medicine in humans, where the medicines are applied outside normal clinical practice on the basis of a research protocol [1]. The aim of the European Union 2001/20/EC clinical trial directive was to simplify and harmonize the conduct of clinical trials, intended to create an environment that would stimulate clinical research in European member states. This directive has realized important improvements in the safety and ethical

soundness of clinical trials in the EU and in the reliability of clinical trials data. However, the directive is one of the most heavily criticized items of regulation in the EU in the area of pharmaceuticals, especially with regard to research in incapacitated patients [2–13]. Mental incapacity is an inherent characteristic of research in emergency situations, common to acute critically ill patients admitted to the intensive care unit. The provisions of Directive 2001/20/EC appear to have hampered the conduct of clinical trials in Europe, rather than stimulating them. Indeed, it could be argued that the directive had a significant negative impact on the development of much needed novel therapies for life-threatening conditions such as traumatic brain injury, cardiac arrest and stroke. Given this context, the action by the European Commission to revise this directive represented a substantial opportunity. In July 2012, the European Commission forwarded a proposal for a regulation of the European Parliament and the Council on clinical trails on medicinal products for human use, repealing Directive 2001/20/EC. In this report, we aim to summarize the existing European and national legislation to discus tensions between theory and practice, and to reflect on the new situation which will result following acceptance of the proposed new European regulation.

Consent in the Directive 2001/20/EC

In line with Article 3(2)a of the Charter of Fundamental Rights of the European Union any intervention in the field of medicine and biology cannot be performed without free and informed consent of the person concerned. Article 4 of the Directive 2001/20/EC states: "In the case of other persons incapable of giving their consent…the written consent of the patient's legal representative, given in cooperation with the treating doctor, is necessary before participation in any such clinical trial." The rules on the protection of subjects and on free and informed consent have been discussed extensively in the legislative process leading to Directive 2001/20/EC. The intent of this wording was to provide incapacitated subjects additional protection. It would appear likely that the population targeted primarily were chronic psychiatric patients. In practice the phrasing had direct adverse consequences for emergency research. Specifically the obligation to obtain written consent by the patient's legal representative has prevented much research in emergency settings [4, 15, 16]. Moreover, the use of the wording "legal representative" has created problems. In some countries this has been interpreted as requiring a court order as to which the legal representative is, in others proxy consent was considered acceptable. From a practical perspective, many studies have replaced the terminology of legal representatives in their study protocols by legally acceptable representative, thus also including proxies. Concerns existed that the restriction in wording might end emergency research in acute life-threatening situations, and indeed substantial problems have ensued in some member states.

Emergency research and research using medicinal products in incapacitated patients

Emergency situations relate to cases where a patient has suffered a sudden life-threatening medical condition due to severe and acute illness. Severe traumatic brain injury, severe forms of stroke (such as subarachnoid haemorrhage, intracerebral haemorrhage, brain stem infarction), myocardial infarction with circulatory arrest and other cardiac emergencies, and severe septic shock are all conditions necessitating immediate medical intervention within short time frames [14]. Depressed level of consciousness due to the disease, the depression of consciousness by essential medication (e.g. the use of sedative drugs to facilitate mechanical ventilation in traumatic brain injury and sepsis), and/or the absence of an immediately available legal representative render it impossible to obtain informed consent from the subject or its representative prior to the intervention.

Specific ethical issues pertaining to the evaluation of pharmaceutical agents in emergency situations include the emergency nature of the research, short therapeutic windows, the incapacity of the patients to consent before inclusion, and a risk–benefit ratio based on the concept that in relation to the severity of the acute condition, significant adverse side effects may be acceptable. These divergent aspects require specific expertise and the different ways in which European directives have been translated into national legislation have resulted in a wide variation in approaches and decisions by research ethics committees (RECs) in different member states. RECs must evaluate and mandate the medical research protocols. As legislation differs in the EU member states, national RECs have different methods and different kinds of protocols to evaluate.

Consent for research using medicinal products in incapacitated patients and in emergency situations

Several solutions have been adopted in practice for meeting the requirements on informed consent: Legal representatives (proxies) can give consent before inclusion in research, or the patient and/or proxy consent can be deferred for some time or consent can even be

waived. An independent physician can give his/her consent for inclusion in a trial, or patient/proxy consent can be presumed. Table 1 and Fig. 1 present an overview of accepted approaches in EU member states. Deferred proxy consent appears to be the preferred substitute for informed patient consent in emergency critical care research. In 12 member states, however, emergency research is not mentioned in national law. In almost all of the member states, prior consent by a legal representative is used as a substitute for informed patient consent for non-urgent research and deferred (patient and/or proxy) consent is accepted as a substitute in acute emergency research in approximately half of the member states.

Consent in the revised proposal (July 2012)

The proposed regulation from July 2012 [1] does not, with the exception of the issue of clinical trials in emergency situations, substantially change the rules with respect to requirements for informed consent. In contrast to Directive 2001/20/EC, the proposed regulation provides guidance for informed consent in emergency situations. The proposal specifically states: "…the regulation should set clear rules whereby patients in emergency situations may be enrolled in a clinical trial under very strict conditions. This clinical trial should relate directly to the medical condition, which causes the impossibility of the patient to give informed consent. Any previously expressed objection by the patient must be respected, and informed consent from the subject or the legal representative should be sought as soon as possible" (pp. 18–19 of the proposal). The provisions of clinical trials in emergency situations are described in Article 32 of the proposal (pp. 47–48). 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 five conditions are fulfilled:

1. As a result of 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
2. No legal representative is available
3. The subject has not previously expressed objections known to the investigator
4. The research relates directly to a medical condition which makes it impossible to obtain prior informed consent and to supply prior information
5. The clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject.

After inclusion in the clinical trial and start of the administration of the experimental agent and other study procedures, in case of incapacitated patients:

1. "The informed consent shall be obtained as soon as possible from the legal representative and the information shall be given as soon as possible to the subject"
2. "Informed consent…shall be obtained as soon as possible from the legal representative or the subject, whichever is sooner and the information referred to…shall be given as soon as possible to the legal representative or the subject, whichever is sooner"
3. When "informed consent has been obtained from the legal representative, informed consent to continue the trial shall be obtained from the subject as soon as it is capable of giving informed consent".

These provisions represent a substantial advance over the currently existing legislation, with specific recognition of the specific aspects of emergency research and research in incapacitated patients. It is good news that the principle of deferred consent in emergency situations is acceptable, especially in cases where no legal representative is available, but also in cases in which the therapeutic time frame is very short and there is no time to inform the overwhelmed relatives in a proper way. It is good news that research projects will be able to be submitted for ethical review via a central European portal, thus accelerating and facilitating harmonization of decisions. Final evaluation and decisions will, however, remain the responsibility and competence of member states. Despite these advances, some clouds remain on the horizon [16]. Potential problems may result from the clause that demands minimal risk, interactions with European data protection requirements, and the failure to explicitly recognise that capacity may be lost because of essential and unavoidable therapy as well as disease.

First, potential problems may result from the restricting clause that "the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject". However, this formulation of the clause takes no account of extreme disease severity in critically ill patients, which makes the use of interventions with greater potential side effects justifiable. To quote Shakespeare: "Diseases desperate grown By desperate appliance are reliev'd, Or not at all." [*Hamlet* IV. iii. 9]. Few treatments in an emergency setting in critically ill patients can be considered without risk; therefore, the requirement of "a minimal risk" would appear impractical and makes emergency research on new drugs not possible in patients life-threatening situations. We urge researchers to use the elegant component analysis, as proposed by Weijer and Miller [17, 18]. Component analysis represents a systematic approach to the ethical analysis of risks and potential benefits in clinical research and is supported by acceptable

Table 1 Overview of accepted approaches to consent in EU member states

EU member state	Form of consent for research in incapacitated patients	Form of consent in emergency research	References
Austria	Consent by legal representative	Deferred consent	§ 43(1)3 and § 43a. (1), Gesamte Rechtsvorschrift für Arzneimittelgesetz, Fssung vom 14.05.2013
Belgium	Consent by legal representative	Deferred consent	Chapter 5, art. 8; Chapter 6, art.9; Wet inzake experimenten op de menselijke persoon, 7 mei 2004
Bulgaria	Consent by legal representative	Waiver of consent	Art 96(4), 101(1), 101(2), Law on the Medicinal Products in Human Medicine
Cyprus	Presumed patient consent, unless it is obvious from previously expressed wishes that he/she would have refused	Presumed patient consent, unless it is obvious from previously expressed wishes that he/she would have refused	Part II, Sects. 13 and 14, The Safeguarding and Protection of the Patient's Rights Law, 2004
Czech Republic	Consent by legal representatives	Deferred consent	Section 52 (7)–(9), Act No. 378/2007 Sb. Of 6 December 2007 on Pharmaceuticals and on Amendments to Some Related Arts (the Act on Pharmaceuticals)
Denmark	Consent by legal representative	Deferred consent (does not apply to research with medicinal products)	Part 5, Art. 18(2), Art 20 (1) (2) (3), Act on Biomedical research Ethics Committee System and Processing of Biomedical Research Projects (11.02.2009)
Estonia	Consent by legal representative	Emergency research not mentioned in law	§ 91(2)(3), Medicinal Products Act (16 December 2004); § 13, subsection 8, Mental Health Act (1997, 2002)
Finland	Consent by legal representative	Prior written proxy consent	Chapter 2, Sects. 6 and 7, Medical Research Act 1999, no. 488/1999
France	Consent by legal representative	Deferred consent	Article 1, Law No. 2012-300 'Loi Jardé'; Article L.1122-1-2, French Public Health Code
Germany	Consent by legal representative	Deferred consent	§ 41. 1(1-2), Gesetz über den Verkehr nit Arzneimitteln (Arzneimittelgesetz – AMG)
Greece	Consent by legal representative	Emergency research not mentioned in law	Guide for research ethics committees, chapter 4, IV, directed to Directive 2001/20/EC and Oviedo Convention
Hungary	Consent by legal representative	Emergency research not mentioned in law	§ 6. (1)–(6), Decree 24/200 EUM of the Minister of Health relating to the implementation of good clinical practice in the conduct of clinical trials on investigational medicinal products for human use
Ireland	Consent by legal representative	Emergency research not mentioned in law	Art. 7 (b), Control of clinical trials act, 1987. No. 28/1987; S.I. No. 190 of 2004 European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, 2004, Schedule 1, part 1, 1.(4), part 5
Italy	Consent by legal representative	Deferred consent	Section 5, Legislative Decree no. 211 of 24 June 2003 Transposition of Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for clinical use
Latvia	Consent by legal representative	Deferred consent	Art. 31.3; 33.1–33.9, Art. 34, Regulations on clinical trials, Cabinet Regulations No. 289, 23 March 2010
Lithuania	Written patient consent	Emergency research not mentioned in law	Art. 5, 8, Republic of Lithuania law on ethics of biomedical research 11 May, 2000 No. VIII–1679

Table 1 continued

EU member state	Form of consent for research in incapacitated patients	Form of consent in emergency research	References
Luxembourg	Consent by legal representative	Emergency research not mentioned in law	Art. 5, Réglement grand-ducal du 30 mai 2005 relatif à l'application de bonnes pratiques cliniques dans la conduite d'essais cliniques de médicaments a usage humain (Recueil de Legislation A-No 84, 22 juin 2005)
Malta	Consent by legal representative	Emergency research not mentioned in law	Art 4(b), Art. 4(d) Art 6 (a–i), Malta-Medicines Act 2003 (Act no. III of 2003)
Netherlands	Consent by legal representative	Deferred consent	Section 6: 1,4, Regulations on medical research involving human subjects (Medical research (Human Subjects) Act)
Poland	Consent by legal representative	Emergency research not mentioned in law	Art 25, Act of Medical Profession of 5 December 1996; Chapter 2a, Article 37b.2.2, Article 37 f.1, Article 37i., Act of 6 September 2001 [Pharmaceutical Law]
Portugal	Consent by legal representative	Emergency research not mentioned in law	Article 10, Decree Law no 97/94; Article 8, Law 46/2004 of 19 August 2004
Romania	Consent by legal representative	Emergency research not mentioned in law	Law 336/2002
Slovakia	Consent by legal representative	Deferred consent	§13Sub-paragraph (5), §13sub-paragraph (6) and §41sub-paragraph (2) of Law No. 277/1994 Collection of the laws On Healthcare, Slovak Republic-Regulations on Ethics and Research
Slovenia	Consent by legal representative	Deferred consent	No specific law regulating biomedical research on human subjects. Provisions related are found in the Law on Medical Practice, art. 47 and Draft additional Protocol to the Convention on Human Rights and Biomedicin, on Biomedical Research. Steering Committee on Bioethics (CDBI), Strasbourg 2002 [12], 1-14. (Art. 17) For emergency research, in Slovenia, the provision of Article 20 of the Oviedo Convention is followed
Spain	Consent by legal representative	Emergency research not mentioned in law	Article 4, 2. Law 14/2007, of 3 July, on Biomedical Research
Sweden	Consent by legal representative	Emergency research not mentioned in law	Section 20–22, The Act Concerning the Ethical Review of Research Involving Humans (2003; 460)
UK	Consent by legal representative	Deferred consent	Statutory Instruments 2006 No. 2984, The Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations 2006; Statutory instruments, 2004 No. 1031, The Medicines for Human Use (Clinical trials) regulations 2004, Schedule 1, Part 5

arguments. Weijer and Miller [17] state: "Component analysis ensures, through the proper application of clinical equipoise, that the sum of risks and potential benefits of therapeutic procedures in a clinical trial are roughly similar to that which a patient would receive in clinical practice". This approach is also recommended by the VISEAR working group in response to restrictions in the EU Directive 2001/20/EC [19].

Secondly, in explicitly stating that research is only permissible if "The research relates directly to a medical condition which causes the impossibility to obtain prior informed consent and to supply prior information," the revised regulation ignores the fact that therapeutic sedation, with subsequent loss of capacity, may contribute to or cause the inability to obtain consent. For example, severe pneumonia may not, in itself, impair capacity. However, the need to provide mechanical ventilator support usually predicates the need for sedatives to facilitate tracheal intubation and ensure patient comfort. In many instances, such sedation may make it impossible to communicate in a way that allows true informed consent. The treatments that we need for pneumonia with

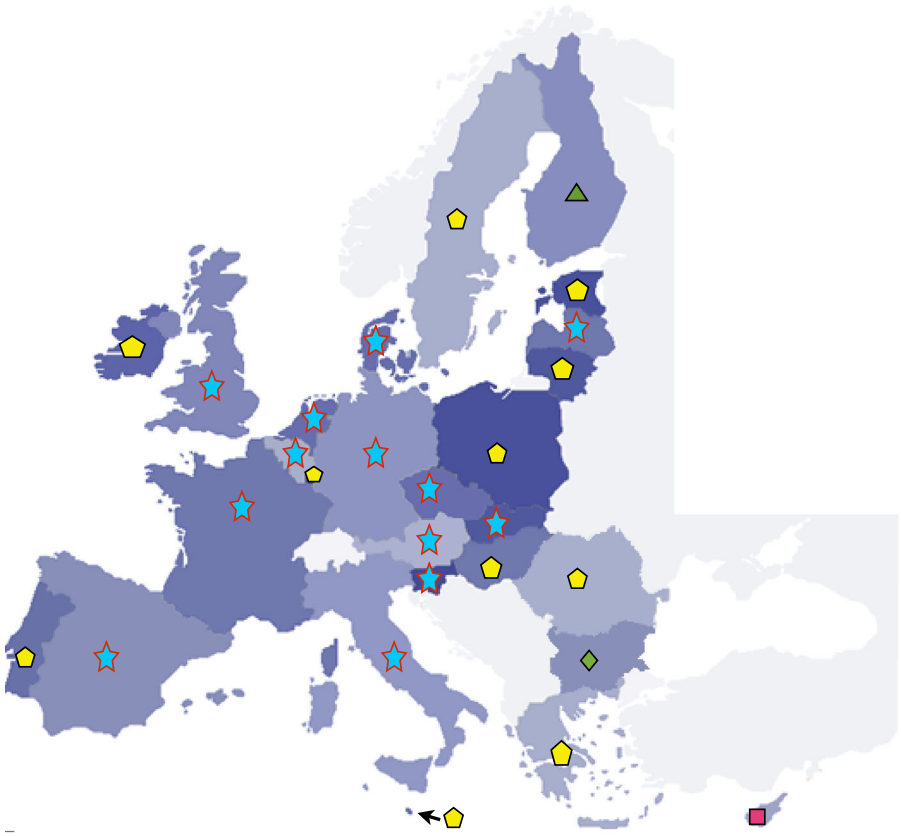

Fig. 1 Forms of consent for research on medicinal products in incapacitated patients in emergency situations in the European (*star* deferred(patient/proxy) consent, *pentagon* emergency research not mentioned in law, *triangle* prior written proxy consent, *square* presumed patient consent, *diamond* independent physician consent)

severe respiratory failure may be completely different from those used in less severe pneumonia, and proscribing the conduct of research to develop and test novel therapies in this and other similar contexts unfairly consigns patients with these diseases to have little or no development of therapeutic advances.

Discussion

The text on emergency research in the proposal is an improvement, but still several aspects are impractical and can form a major threat to emergency research [15, 16]. Following the wording of the proposal, emergency research on new drugs is not always possible and patients in life-threatening situations cannot be included in research when a relative is present in the hospital, and when there is no time to inform the overwhelmed relatives [20–27]. Delayed consent is acceptable from the research participant's perspective [28]. However, most relatives want to have some form of involvement in the decision [29]. Relatives of critically ill patients fear study-related harm or discomfort for the patient, but are motivated to consent by the potential benefit and by altruism [30].

The process of obtaining proxy consent in an emergency situation contains three phases. First, information about the emergency critical care trial is provided. Second, the investigator or physician in charge asks the proxies for consent. Third, the proxies consent or refuse [25]. Several authors state that the emotional nature of the emergency situation limited the validity of surrogate consent. Given the complexities of informed consent documents, a larger proportion of proxies might fail to comprehend an actual protocol for an emergency trial [31]. Given the time pressure and the emotionally charged situation, comprehension may be less than optimal [32]. Patients enter critical care in physiologic crisis, whereas their relatives enter it in a psychological crisis [33]. Uncertainty as to whether the patient will survive also has a profound influence on the proxies' reactions, actions and strategies [34]. In these cases, deferred consent is ethically valid. Inform the relatives only then when they can comprehend the given information.

In almost all of the EU member states, prior consent by a legal representative is used as a substitute for informed patient consent for non-urgent medical research. Deferred (patient and/or proxy) consent is accepted as a substitute in acute emergency research in approximately half of the member states. In 12 member states emergency research is not mentioned in national law. Deferred patient and/or proxy consent is allowed in the proposed regulation from July 2012, but does not fit completely in the practice of emergency research [15, 16]. Deferred consent is only possible when legal representatives are not available. This criterion will delay inclusion of patients in acute life-threatening conditions in short time frames. The proposed regulation shall enter into force 2 years after its adoption by the Parliament and on the 20th day following that of its publication in the *Official Journal of the European Union*. The regulation shall be binding in its entirety and directly applicable in all member states. There is much work to be done by the different member states to incorporate the new rules into their national regulations, as of this moment, regulations are not harmonized. The confusion concerning emergency research was initially caused by a lack of clarity in the Directive 2001/20/EC. Furthermore, emergency research in acute situations is still not possible as it should be.

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