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Review article

# Evolution of European Union legislation on emergency research[☆]

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ABSTRACT

*Aim:* Emergency research is necessary to prevent exposure of patients to unvalidated clinical practice (nonmaleficence), and to improve the dismal prognosis of disorders requiring emergent treatment such as cardiac arrest (beneficence). Regulations that govern clinical research should conform to bioethical principles of respect for nonmaleficence, beneficence, autonomy, and justice. Our objectives are to review the evolution of European Union (EU) legislation on emergency research, and to identify potentially remaining problems.
*Data sources:* EU legislative sources on clinical research and medical literature describing the impact of EU Regulations on emergency research.
*Results:* Article 5 of EU Directive 2001/20/EC required consent before enrolment in a research study to ensure the autonomy of potentially incapacitated research subjects. However, obtaining such consent is often impossible in emergency situations. Directive 2001/20/EC was criticized for potentially preventing emergency research. Several EU Member States addressed this problem by permitting deferred consent. International ethical guidelines supporting deferred consent were also cited by Good Clinical Practice Directive 2005/28/EC. However, Directive 2001/20/EC was not revised to achieve harmonization of EU emergency research, thus resulting in ongoing "*ambiguity*" as regards to emergency research legitimacy. This will be definitively addressed by applying EU Regulation No. 536/2014 and repealing Directive 2001/20/EC. The new EU Regulation permits using deferred consent under clearly specified conditions, and may foster emergency research that evaluates interventions posing minimal risk relative to standard practice.
*Conclusions:* Legislation related to emergency research in Europe has evolved to increase concordance with bioethical principles so as to increase evidence-based improvements in emergency care.

## 1. Introduction

Enrolment in a randomized clinical trial usually requires a priori consent. Regulations that govern consent for clinical research are grounded in four basic ethical principles that constitute the framework of biomedical research ethics: nonmaleficence, beneficence, respect for autonomy, and justice.[1,2] The principle of nonmaleficence specifies abstention from causing harm to patients and, in medical ethics, is equivalent to the Hippocratic maxim "Primum non nocere".[2] The principle of beneficence refers to maximizing the patient's welfare.[2] Autonomy, derived from the Greek autos (self) and nomos (rule), is defined on the basis of liberty and agency. Liberty refers to absence of external control of behaviour and agency to the capacity for intentional action. Respect for individual autonomy is expressed via informed patient or proxy/legal representative (LR) consent obtained before enrolment in a clinical study (i.e. pre-enrolment or prior consent). Principles of justice can be examined using different approaches (e.g. utilitarian, libertarian, egalitarian, communitarian theories, theories of capabilities, and well-being theories). A common core to most of these approaches relates to the equality of rights to health and health care and the practical difficulties of allocating, rationing, and setting priorities.[2]

It is difficult to conduct prospective emergency research that adheres to fundamental principles of bioethics because of the inherent need to quickly establish diagnosis, verify study eligibility and initiate study intervention as well as standard care. A characteristic example pertains to out-of-hospital cardiac arrest (OHCA), which

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is common and debilitating. In Europe, the incidence of emergency medical service-treated, out-of-hospital cardiac arrest varies within 17–51 per 100,000 person-years.[3–6] Observational studies can be conducted without informed consent but cannot establish a causal relationship between use of an intervention and subsequent outcome.[7] Adequately powered randomized clinical trials must be conducted to test commonly used therapies with uncertain efficacy[8] or new, potentially beneficial treatments. Improvements in outcomes after OHCA that have occurred over the past 15 years suggest that effective treatments exist.[4–6]

The conduct of emergency research/OHCA clinical trials clearly accords with nonmaleficience, beneficence, and justice (if clinical equipoise is assumed). Regarding respect of autonomy, deferred consent may constitute an ethically acceptable alternative.[2,9–13] After inclusion in the research study, the patient or his/her proxy/LR are informed as soon as possible and their consent for continued research participation is requested. Proxies (relatives, spouse, and close friends, i.e. "family" in a broad sense) and/or LRs may be designated by nation-specific laws exhibiting variability or appointed through a legal process.[14,15]

Deferred consent has been criticized for the absence of legal definition of consent for procedures that have occurred previously.[16,17] However, deferred consent may ensure respect of family autonomy until the emergency research participant regains decision-making capacity. Family autonomy is generally considered as "the best possible substitute" to the individual autonomy of an incapacitated patient.

A possibly improved alternative to deferred consent could be exception to informed consent (EFIC) with prior community consultation, and in conjunction with the option for community members to opt out from an EFIC study by wearing "NO STUDY" bracelets.[18] Emergency research involving EFIC [19, Appendix I] or deferred consent,[20] and collectively, exception to pre-enrolment consent seems generally acceptable by the public in North America and the European Union (EU),[21–28] particularly when research interventions pose minimal risk.[23,28] A relevant analysis of prior randomized clinical trial data showed that pre-enrolment consent-associated delays in investigational treatments may hamper their benefit to patients, or even increase the risk of death.[29]

EU legislation now includes specific provisions for deferred consent [20, Appendix II], after a 15 year-long period of repeated and often-criticized changes. The purpose of this paper is to review these changes and their impact on EU emergency research.

## 2. EU legislative sources

In the EU, there are currently three sources of applicable legislation for the consideration of clinical research proposals by Research Ethics Committees (RECs). These sources include (a) the EU Directives 2001/20/EC[30] and 2005/28/EC [or Good Clinical Practice (GCP) Directive[31]], (b) the Oviedo Convention[32] and its related Additional Protocol on Biomedical Research,[33] and (c) national legislations – sections pertaining to deferred consent have been provided in the supplement of a recent article.[34] EU Directives 2001/20/EC and 2005/28/EC were to be incorporated into national legislations of EU Member States within 2004 and 2006, respectively.

## 3. The directives system and the barrier of prior consent

Article 5 of EU Directive 2001/20/EC sets out seven prerequisite conditions for the inclusion of incapacitated adults in clinical trials (Appendix III). The first condition was pre-enrolment obtainment of a (valid) proxy/LR informed consent. However, it is widely accepted that it is impossible to obtain such consent in emergency research, due in part to the limited time frames for the initiation of the (tested) treatment(s).[9,14,35–46]

Directive 2001/20/EC has also been characterized as an important, comprehensive document, primarily aimed at harmonizing and fostering clinical research in Europe.[37] However, the strict application of pre-enrolment consent would have resulted in a complete halt of EU clinical emergency and resuscitation research.[14,38,42–46] The response of the scientific community resulted in the publication of several scholarly articles that described this major problem, defined its dimensions, and proposed measures of amelioration and/or definitive solutions.[9,14,35–48] For example, it was repeatedly argued that the inability to conduct potentially beneficial research in the emergency setting would result in the exposure of many incapacitated patients to the hazards of unvalidated clinical practice.[14,36–38,42] This counteracts the principles of nonmaleficence and beneficence.[1,2,14]

Regarding emergency research, the Vienna Initiative to Save European Academic Research[46] recommended that "Article 5(a) be construed purposively or amended if necessary (by extension, waiver, or deferral) to permit and harmonize emergency research involving incapacitated persons where treatment must be commenced as a matter of urgency." Notably, paragraph 5.2.3 of a Consultation Letter on clinical trials regulations[49] [published on May 1, 2003 by the Medicines Control Agency of the United Kingdom (UK)] included the following interpretation: "There is no intention in the Directive (2001/20/EC), or the implementing Regulations, to prevent such emergency research being carried out."

Recital 8 and Article 3 of the GCP Directive (Appendix IV) respectively cite the International Conference on Harmonization (ICH) consensus paper[12] and the Helsinki Declaration.[10,11] More specifically, recital 8 states that the "*ICH consensus paper should be taken into account*" (for clinical trial conduct), whereas Article 3 states that "*Clinical trials shall be conducted in accordance with the Declaration of Helsinki...*" (see also Appendix IV and relevant Notes). Notably, both documents/policy statements address the impossibility of obtaining pre-enrolment informed consent in emergency research [Paragraph 4.8.15 of ICH Topic E 6 (R1)[12] and Paragraph 30 of the Helsinki Declaration[11]]. The cornerstone of these provisions comprises the possibility of research to proceed, under the obligation of the researcher's seeking deferred consent.

The citation of the ICH consensus paper and the Helsinki Declaration by the GCP Directive as "whole documents" (that is without the exclusion of any part of their texts) is consistent with the above-cited, UK interpretation of Directive 2001/20/EC[49] (i.e. that there was no intentional prevention of emergency research). Furthermore, the rationale of the 2006 UK Amendment of Clinical Trial Regulations (aimed at permitting deferred consent in emergency research) is actually based on the GCP Directive [Paragraph 4.3,[50] Appendix V], and also, most importantly, cites European Commission correspondence with the UK which "*strongly implies that emergency situations are outside the scope of EU Directive 2001/20/EC*" [Paragraph 4.4,[50] Appendix V].

Provisions for emergency care research were already in-place before the publication date (i.e. April 9, 2005) of the GCP Directive in the national legislations of Austria, Belgium, France, Germany, Italy, the Netherlands, Norway, and Spain.[45] Multicenter studies in cardiac arrest employing deferred consent were conducted in several of the aforementioned countries; for example, the "*Thrombolysis during resuscitation for out-of-hospital cardiac arrest*" study[43,50,51] was performed from January 2004 to March 2006 in Austria, Belgium, France, Germany, Italy, the Netherlands, Norway, Spain, Sweden, and Switzerland.

By May 2004, EU Directive 2001/20/EC was incorporated into national law across the EU. However, its interpretation varied widely in the different Member States.[9,45] Notably, countries that applied the Directive in a more liberal manner (e.g. as detailed above for the UK) did not elicit any criticism from the Regulatory