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'Treat first, ask later?' Emergency research in acute neurology and neurotraumatology in the European Union

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"Treat first, what kills first" is an adage of the ATLS principles. We propose that "Treat first, ask later" is a defendable approach in emergency research on acutely incapacitated patients. However, this opinion is in conflict with new legislation resulting from the European Clinical Trial Directive 2001/20/EC. The European Union Member States have been instructed to adopt and publish the laws, regulations and administrative provisions necessary to comply with the directive before 1st May 2003, and they should apply these provisions at the latest in effect from 1st May 2004 [1]. The directive concerns a European-wide harmonisation of the provisions concerning clinical pharmacological trials, aiming at facilitation of multinational clinical research.

Acute neurological conditions such as severe traumatic brain injury and stroke, causing high mortality and morbidity, are major burdens to patients, their relatives and societies. An ethical imperative and a significant need for further research exits to develop and test the efficacy and safety of new therapeutic agents and strategies aimed at improving outcome. In the last two decades many randomised controlled clinical Phase III trials have been conducted in traumatic brain injury and stroke [2, 3]. Some of these have allowed waiver of consent.

Most patients with acute neurological conditions are acutely, and often for a longer period of time, incapacitated as a result of their cerebral injury; subsequently informed consent cannot be obtained from the subject. Most ethics committees have legally accepted that consent by legal representatives or those who are, according to national law, pragmatically acceptable as valid surrogates to informed consent by the patient himself in acute care research. In the US, authorities issued rules allowing waiver of consent under strict regulations for emergency research. In the new European legislation, however, emergency research under waiver of consent is not permitted. According to Article 3 (protection of clinical trial subjects) and Article 5 (clinical trials on incapacitated adults not able to give informed consent) of the directive, a clinical trial may only be undertaken if the subject or, when this person is not able to give informed consent, his legal representative has had the opportunity to understand the objectives, risks and inconveniences of the trial and has granted consent.

This process is time-consuming. Time windows in which neuroprotective agents may be effective are considered to be relatively short, showing a maximum of 3–6 h after onset. But clinical experience shows that, despite the desire for early treatment initiation, patient enrolment is very often delayed to the last hour of the time window. Reasons include mainly the consent process, but also delay created by the necessity of additional investigations such as a head CT scan, admission to the ICU and connection to life support and monitoring, and delays due to secondary referral. Relatives are rarely available in the first hours after an acute insult [4]. The experience of the National Acute Brain Injury Study: Hypothermia was that using witnessed-signed proxy consent resulted in low accrual and late achievement of target temperature [5]. One study including European countries shows a delay to secondary referrals of patients with traumatic brain injury up to 4 h [6].

Little is known about the validity, quality and ethics of proxy consent given in adult emergency settings but, in our experience, relatives are often not able to focus mentally during an emotionally charged event such as a relative's acute and severe injury or stroke. In a recent study, 70% of lay persons in the US would not object to being entered into an emergency study without providing prospective informed consent [7], and are altruistic in helping further acute research. In another study, 84% of patients felt that the physician should independently decide whether to include a patient with acute myocardial infarction in a trial, if the patient is too ill to be asked [8]. We believe that the consent process should be submissive to the severity of illness status in acute neurological care research. The ethical demand to avoid exploitation of incapacitated patients remains pertinent but, at the same time, it would be wrong to deprive current and future patients of the opportunity possibly to benefit from acute research within a short therapeutic time window. The strict regulations on prior consent in the EU directive will deprive many patients of this opportunity.

How the different Member States of the European Union will actually apply the provisions of the directive is currently uncertain. The EU Directive is a valuable document and deserves respect, but its strict regulations on prior written proxy consent in the case of acutely unconscious patients impede or even obviate emergency research Phase III trials in acute neurology and neurotraumatology in the European Union. The European Society of Intensive Care Medicine and the European Brain Injury Consortium have, among others, expressed their concern about the impact of the directive on emergency research in the EU [9, 10]. We believe that 'Treat first, ask later' is ethically defendable and desirable for emergency research in the field of acute neurology and acute neurotraumatology. Protection of individual patients can be guaranteed by requiring evaluation and assent from an independent physician, not otherwise involved in the study conduct or treatment of the patient.

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