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EDITORIAL

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The inability to consent in critical care research: emergency or impairment of cognitive function?

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Obtaining consent for participation in a research trial from people who cannot consent has always been the nightmare of clinician–researchers working in intensive care units (ICUs) – not to mention the lawmakers. In this issue of *Intensive Care Medicine*, Dr Sheila Harvey and colleagues have addressed this topic from a UK perspective [1]. From data collected during the PAC-man study they published earlier [2], they demonstrate how frequently this actually happens: out of the 498 patients they included, only 13 (2.6%) were able to consent! Their study was designed in such a way that they could further assess the process of surrogate consent. Indeed, their conclusions are important: assent granted by relatives was obtained in 81% of 485 incompetent patients. Relatives could not be identified in only 18 patients. These figures are even better than those (8%) provided in 34 French ICUs by Elie Azoulay et al. [3]. When survivors were asked later to re-consent, 93% of them (175) accepted, with only six refusals. This is good news, which certainly will consolidate the views and arguments of those who plead for the feasibility and legitimacy of proxy consent/assent in the realm of human research. Another fascinating piece of information in this paper is the way the consent process, as implemented in the UK, is dissected and controlled step by step: the chain of possibilities starts from the patient's consent, when possible, which, as showed in the study is rare; if not, relatives', when available; if not, inclusion of the patient in the trial; then, relatives' assent, when/if they show up; if patient regains ultimately mental competency, his consent is requested; if he dies or never regains consciousness, authorization to use the data is required from a central national ethics board (MREC).

However, is such a process in line with current practice in other countries, especially in continental Europe, after the implementation of directive 2001/20/CE [4]? The answer is not simple. The reasons why patients cannot consent for themselves fall into two main categories: first, impairment of cognitive functions, and second, emergency.

Let us first consider the situations where patients have a major mental impairment, such as encephalopathy, coma or deep sedation, all situations encountered every day in ICUs. Most clinical trials proposed to these patients have nothing to do with emergency, many of them starting days or sometimes weeks after admission, with large windows for inclusion. But, as patients cannot consent for themselves, they constitute a "vulnerable population", needing special and reinforced protection. Even though the declaration of Helsinki, back in 1964, somewhat watering down the Nuremberg code (Article 1: "The voluntary consent of the human subject is absolutely essential . . ."), recognized surrogate consent in such cases, it had no legal binding value. National legislations were never at ease with this concept. Actually, before the implementation of directive 2001/20, in 2004, most European legislations did not have any specific provisions for surrogate consent for clinical research, but used general regulations or legislation applied to patient care. It was also the case in the US where the "ARDSnet controversy" revealed that family consent had been used during the ARMA trial [5, 6] with no solid legal foundation. Silverman showed that only California and Virginia have currently a specific state legislation on surrogate con-

sent for research [7]. It is certainly the merit of this otherwise so disparaged directive that all European lawmakers have been obliged to propose some substance to the vague and rather esoteric concept of "legal representative". And, finally, at least in this field, the result is not so bad: most legislations of EU member states have merely recognized that the family is the "natural" legal representative of any incompetent patient, even when they tried to propose a system by which any person could designate in advance his chosen representative, which in fact they rarely do. In the study by Dr Harvey and colleagues, an agreement to the proposed research by relatives was obtained in four fifths of all cases, a comforting finding. And, more importantly, when patients themselves regained mental competence, they massively confirmed the decision made earlier on their behalf, contrary to the evidence some other researchers have produced [8, 9]. This legal frame has been recently introduced in the UK. It combines the provisions of the Medicines for Human Use (Clinical Trial) regulation of 2004 and the Mental Incapacity Act of 2005 [10]. Accordingly, when a patient is incompetent, a trial can proceed only after a "legal representative" has given an informed consent. Coats and Shakur pointed out that ". . . it was the first time in UK law that one adult could consent on the behalf of another"[1]. But the UK legislation went further: that legal representative (LR) is called a "personal LR", when he or she is a next of kin. When there is no one available to play that role, a "professional LR" may intervene, who can be either the physician "responsible for the treatment" or another person nominated by the "relevant health care provider". This is a quite unique procedure in this field, since physicians are usually seen as biased in favour of research and not as independent patients' advocates. For instance, in Germany, the surrogate decision-maker is designated by a judge [4]!

Moreover, the second situation where patients cannot consent for themselves is even more problematic. It is when a study needs to be started without delay, in emergency: think of a cardiac arrest outside the hospital. If research has to be done in such a context, which seems quite obvious for the sake of public health, inclusion should be done at once, on the spot, by the emergency rescue team, without waiting for any surrogate decision-maker to show up or be identified [11, 12]. The US Code of Federal Regulation introduced in 1996 a set of provisions allowing a waiver of consent for emergency research, provided some additional procedures are fulfilled [13]. The French had by law such a possibility since 1988, which was maintained after 2004. Similarly, the Belgians, the Germans and the Dutch introduced or maintained a "deferred consent" clause in their legislation after they implemented directive 2001/20. However, the provision allowing waiver of consent in emergency situations contradicted the directive, which did not foresee such a possibility, to the great dissatisfaction of investigators, who complained loudly [14, 15, 16, 17]. Apparently, this was more an oversight by European lawmakers than a deliberate attempt at suppressing emergency research, as directive 2005/28 soft-pedalled on the ban on the waiver of consent in emergency situations[2]. But in the meantime, the opportunity to allow a waiver of consent in emergency situation was initially missed by British legislators, who did not consider any departure from the directive [18]. They rather tried to imagine a system by which a surrogate assent could be given by a person on the scene but not involved in the trial, such as a paramedic [10]. It was no surprise that such a weird proposal was immediately criticized, on the grounds that the paramedics themselves would most certainly be reluctant to play that role, and that they could hardly be seen as absolutely independent from the investigators or the sponsors. A recent common briefing from the MRC, the Royal College of Physicians, the Academy of Medical Sciences and the Wellcome Trust[3] indicates that an amendment on the consenting process for emergency research is currently under discussion and could become effective by 2007.

Most current European legislations allow a "deferred" consent more than a mere waiver. They usually recommend that assent or consent be required once the next of kin shows up or when the patient regains consciousness [4]. The study by Harvey et al. shows convincingly that the whole process is workable. However, the discussion of their paper rightly mentions that it could be seen as cynical to ask the patient's consent once he has already been included. This is why the investigators should give him the possibility to withdraw the data obtained when he was unconscious and unable to refuse his participation. Even though specialists in biostatistics argue that data suppression, by introducing a selection bias, could jeopardize the balance between trial arms and ultimately ruin the study [19], it seems difficult not to recognize and respect a patient's restored autonomy. It is the price investigators have to pay for society to accept that research be performed without consent, a major violation of a paramount tenet of research ethics since Nuremberg.

[1] Similarly in France, legislation on human research back in 1988 scratched the jurisprudence on "*Nul ne peut consentir pour autrui*", once thought to be set in stone

[2] Whereas 10: "The detailed rules adopted by Member States pursuant to Article 3(1) of Directive 2001/20/EC, to protect from abuse individuals who are incapable of giving their informed consent should also cover individuals temporarily incapable of giving their informed consent, as in emergency situations."

[3] Access 29-06-2006: http://www.mrc.ac.uk/pdf-mental_capacity_amendments_final.pdf#xml=http://www.mrc.ac.uk/scripts/texis.exe/webinator/search/xml.txt?query=mental+capacity+bill&pr=mrcall&order=r&cq=&id=44a0cc362

No information is provided in this paper as to the window during which relatives' assent could be obtained. We know only that it was granted by relatives of 81% of 485 patients unable to consent. It is not specified whether proxies were consulted before or after randomisation, hence making it difficult to know which category of "vulnerable population" the investigators were dealing with. When the time frame is measured in minutes, so defining a "true" emergency, patients' consent should be waived or delayed, as proposed by Kompanje et al. for traumatic brain injury [20]. Waiving consent in emergency research has been shown to improve and speed the inclusion rate in the CRASH trial [21], or even to be the only way to make it possible [22].

The clarification of the nature of patients' inability to consent (alteration of cognitive capacities or emergency situation?) and determination of the size of the window for inclusion are probably the first steps when designing a trial dealing with incompetent patients, in order to identify the right legal and ethical frame.

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