

F. Lemaire
L. Blanch
S. L. Cohen
C. Sprung
Working Group on Ethics¹

Informed consent for research purposes in intensive care patients in Europe – part I

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F. Lemaire
Service de Réanimation Médicale,
Hôpital Henri Mondor,
51, avenue du Marechal de Lattre de
Tassigny,
F-94010 Créteil, France
FAX: +33(1) 42 07 99 43

L. Blanch
Intensive Care Department,
Hospital de Sabadell, Parc Taulí s/n,
E-08208 Sabadell, Spain
FAX: +34 (3) 723 3863

S. L. Cohen
UCL Medical School,
The Rayne Institute,
5 University Street,
London WC1E 6JJ, UK
FAX: +44 (171) 209 6211

C. Sprung
Department of Anesthesiology
and Critical Care
Medicine, Hadassah University Hospital,
P. O. Box 12000, Jerusalem, Israel 91120
FAX: +972 (24) 30349

¹ Members of the Working Group on Ethics: R. Abizanda (Spain), A. Armaganidis (Greece), F. Blin (France), G. Conti (Italy), W. Dick (Germany), L. Dragsted (Denmark), J. Eklund (Sweden), R. J. Kahn[†] (Belgium), J. R. Le Gall (France), D. Matamis (Greece), N. Mutz (Austria), A. Net (Spain), A. Paes Cardoso (Portugal), S. Ruyter (Norway), H. P. Schuster (Germany) P. M. Suter (Switzerland), J. Takala (Finland), L. G. Thijs (The Netherlands), J. L. Vincent (Belgium), T. Woodcock (UK)

Modern medicine has progressed rapidly during the past decades, largely due to clinical investigation. It is easy to demonstrate that rapid developments and improvements in the care of critically ill patients are rooted in extensive clinical research. But, since the Nuremberg code, clinical investigation is recognized as acceptable only if an informed consent is granted by the patient subjected to this research. In the “Code”, informed consent is defined as follows: *“The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent, should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision”*. Accordingly, the five attributes of an informed consent are:

1. Disclosure of information;
2. Legal competency;

3. Voluntariness;
4. Understanding of the patient;
5. Decision making [1, 2].

This basic principle, cornerstone of any statement in bioethics, has been repeatedly reaffirmed since World War II, after the Nuremberg code, from the declaration of the World Medical Association (Tokyo 1964, revised at Helsinki 1975) to the guidelines issued by CIOMS and WHO (Geneva 1993). In contrast to the initial Nuremberg declaration, the more recent texts state strongly that the “good of Society” should *never* prevail over the interest and welfare of any particular human being. These documents also now separate research with and without direct benefit to the patient. In most international recommendations and European or National regulations, research without direct benefit to the patient is not allowed if he cannot himself consent to this research. It is also widely recognised that all patients taking part in research benefit, including those randomised to receive placebo rather than the experimental therapy, if all receive at least current treatments and more clini-

cal and/or biological surveillance, and a chance to obtain a potentially more efficacious treatment.

Though such declarations were never openly challenged or rebutted, systematic and widespread implementation of informed consent started recently and slowly in Europe, with noticeable differences from country to country; some countries have a more paternalistic attitude, and others put more emphasis on patient's autonomy. However, it is probably fair to recognize that most, if not all, clinical investigations performed in Europe are done at present according to the Helsinki-Tokyo ethical concepts. The reasons for overwhelming emergence of the informed consent procurement policy all over Europe are many: the effects of hospital, medical associations or scientific research bodies regulations, the editorial policy of medical journals (through the uniform requirements, issued by the so-called Vancouver group of editors), the growing "consumerist" attitude of European patients and families, the requirements of international drug companies for enrolling patients in multicenter trials, some recently issued laws in several countries on the protection of subjects submitted to biomedical research (France 1988, Spain 1990, Portugal 1994), and also, the prominence of North American standards and attitudes in medicine. It must be clear at this point that the trend to recognize patient autonomy and for control medical investigation is not intended to promote or facilitate medical research, but to protect the concerned individuals.

We are concerned that inappropriate legislation on consent may deprive critically ill patients in intensive care of the benefits of research. Admittedly, consent to any kind of biomedical research must be "informed" and voluntary, which implies disclosure of information, competency, understanding and decision making capacity. Most ICU patients are sedated or unconscious, in shock, sepsis, etc. They are frequently stressed, due to their disease, treatment and distressing environment. Even when they look *conscious*, they may not be *competent* de facto, despite they are still legally capable. Mental impairment, for instance, is one of the criteria for determining sepsis. It is important to define who should assess the level of competence of ICU patients, especially for research procedures. This judgement should in theory be provided by a person who is independent of the physicians taking direct care of the patient, but this judgement is usually made by the attending ICU doctors. It is recommended there be a separation of duties between the responsible ICU physician and investigator, and that they should not be the same individual.

Emergencies constitute another situation where consent cannot be obtained, due to the urgent need to treat, and, if planned, to start a research protocol. Cardiac arrest (outside the hospital) is the paradigm situation where consent cannot be asked from the patient and relatives, rarely present at the scene of the accident, and

not likely to accept and understand any information on a research protocol. However, intensivists strongly believe there is an ethical obligation to perform research in these situations, to improve patients' care and outcome. If research in these patients is not performed, there will never be any improvement in their treatment or the saving of their lives.

Physicians working in intensive care units and/or emergency departments and/or pre-hospital emergency medicine may be faced with many situations where a direct, informed consent cannot be obtained from incompetent patients. Two distinct and very specific situations may actually be present in critical care and emergency medicine.

1. Assent obtained from a surrogate

In the United Kingdom, Switzerland and the United States, when a patient is declared incompetent, assent to research is obtained from a surrogate. Although the Nuremberg code stated that "the voluntary consent is absolutely essential", the declaration of Helsinki admitted the consent, or, better, the *assent*, given by a surrogate in case of "physical or mental incapacity" (proxy assent). In the French Huriet law (1988), relatives "when present" can give a consent to a research protocol (therapeutic) in case of "emergency" (Art. L 209-9). The ethical basis for the surrogate consent is a concept of "substituted" judgement, where the surrogate is supposed to choose what the patient would have chosen himself, if competent. In doing so, he assumes the patient's choice from previous knowledge of the patient. Practically, this concept is sound, since surrogate consent is better than no consent at all. At least, it provides an obligation for the physician to explain to a person independent from the research team the expected risks and benefits (full disclosure) of the research. A most important benefit of surrogate consent is that it will allow the surrogate to refuse consent to the research if that is their view of the patient's wishes. Moreover, this systematic approach has a strong didactic value, both for the investigator and the family. Ideally, the surrogate should be designed by the patient himself in advance (advanced directive). If not, and when possible, designation of the proper surrogate could be asked to the patient at admission, and identification of this surrogate written in the medical record. When a patient is incompetent at entry, and in the absence of any advanced directive, the surrogate can be identified by the attending staff.

Identification of the proper surrogate may be difficult in some families, and determining who is the most appropriate for the patient's best interests is not always easy. Also, the best surrogate is not necessarily the closest relative and may not be a relative at all. But, basi-

cally, it is not different from identifying the relatives or friends with whom the responsible doctors discuss the daily treatment plans, as they do routinely. Some countries, or states (in the United States), have formalised a hierarchy of surrogate decision makers, patient's spouse, child, parent, etc. (Spain, Greece, Portugal). In many others, the family has no legal power of attorney to discuss these matters with doctors. They may theoretically obtain a legal proxy designated by a judge. The surrogate may or may not be a family member (Germany).

We are concerned and have past experience that *judicial appointment of a surrogate* proves too slow and cumbersome to permit research in these urgent situations in intensive care, and under these circumstances patients will be denied possible benefit from new types of therapy.

2. The presumed consent or waiver of consent

Research may be conducted without asking consent from a patient in emergency situations, faced with life-threatening events requiring immediate treatment, unable to communicate, and if there is no time to search for relatives or any legal representatives. In such clearly delineated circumstances, it is more and more accepted that research may be started without obtaining consent [3]. A new proposal of the Federal Drug Administration (FDA) would permit physicians to carry out research with a waiver of informed consent under certain well defined circumstances [4, 5].

This situation is seen as identical to the need to treat the patient according to his presumed "best interest", but, clearly, such an application of the "therapeutic privilege" applies to research only when it can benefit the patient himself.

Stringent additional conditions are needed:

- Research must have been planned in advance, and approved by an independent ethics committee, who should critically examine the scientific as well as the ethical bases for this research.
- The research involves no more than minimal risk for the subjects
- Patients or proxy will receive relevant *information* after recovery. If needed, consent will be asked for the continuation of the study.

In such conditions, a waiver of consent is acceptable, according to many existing laws or regulations: the US Department of Health and Human Services rules and regulations, the US FDA regulations, the British "Manual for research ethics Committee", the French Huriet law, the recommendation R 90-3 of the European Ministry Council, the draft convention of bioethics of the Council of Europe [6], etc. Accordingly, the doctor-researcher

acts in the "best interest" of his patient, according to a concept of "presumed" consent.

Present situation in Europe

At present, the situation in Europe is rather confused, varying from country to country and evolving rapidly. At the level of European organisations, a corpus of recommendations is slowly arising, which should progressively apply to all the member states. The recommendation R90-3 of the Committee of Ministers of the Council of Europe, after reaffirming the general necessity of informed consent for clinical experimentation, stated that medical research can be carried out in emergency situations ("where a patient is unable to give a prior consent"), when some conditions are fulfilled: research planned in advance, approved by an ethics committee, and have some possible direct benefit for the patient. Research on patients legally responsible but transiently incompetent – most ICU patients – was not considered here, but it is certainly possible, as done in France when using the Huriet Law, to classify most ICU situations as "emergency".

The new proposal of the Council of Europe, through its steering committee on bioethics (July 1994, modified June 1996 [6] and formally approved in November 1996) states:

Article 6 (protection of persons not able to consent):

1. «An intervention may only be carried out on a person who does not have the capacity to consent, for his or her *direct benefit*».

3. «Where, *according to law*, an adult does not have the capacity to consent to an intervention because of a mental disability, *a disease or for similar reasons*, the intervention may only be carried out with the authorisation of his or her *representative* or an authority or a person or body provided for by law».

Article 8 (emergency situations):

«When, because of an emergency situation, the consent cannot be obtained, any medically necessary *intervention*^a may be carried out immediately for the benefit of the health of the individual concerned».

^a *intervention* here means treatment *and* research

Role of the European Society of Intensive Care Medicine (ESICM)

A Society of professionals, such as the ESICM, has not only the goal of developing scientifically sound research and good clinical practice, it is also committed to the promotion of ethical considerations in patient care and research. To achieve this, the Society has a strong influence, by controlling the access to scientific communication in the meetings it organises or sponsors, and to publication in its official journal. The Declaration of Helsinki-Tokyo (World Medical Association 1964, revised 1975) has already stated that «1.8: . . . *Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication*». This obligation was later reaffirmed in the “Universal requirement for manuscripts submitted to biomedical journals”, by the “Vancouver group” of editors [7]. The Society has also the responsibility to explain to our national and European representatives the specificity of our discipline and patients, the necessity of performing clinical investigation for the patient’s sake, and the limitation and difficulties of the present laws and regulations.

Recommendations

1. Clinical research in intensive care medicine is essential for the quality of patient care, improvement of therapies and outcome. Universal rules guiding human experimentation (Nuremberg code, Helsinki-Tokyo recommendations) apply fully to intensive care medicine, especially those concerning beneficence and non-maleficence, acceptance of protocols by institutional review boards (ethics committee), scientific quality of protocols and the search for informed consent.

2. Due to their disease (cerebral dysfunction, coma, circulation impairment, hypoxia) or environmental factors (stress, sleep deprivation, sedation, etc.), most ICU patients are generally considered *incompetent*, in terms of understanding a research protocol and decision-making capacity, even when they are conscious and though they are still *legally capable*.

3. As it would be unfair and certainly unethical to deny these patients, in case of permanent or temporary incompetence, the potential benefit of research for themselves and others with the same disease, consent, or rather “assent”, should be obtained from *surrogates*. According to national regulations and laws, the surrogate may be determined by law, or designated by the patient himself in advance. However, advance directives are not very frequent in Europe at present. In most situations, the proper surrogate is actually identified by the responsible doctors among the members of family,

friends, or relatives visiting this patient. This named surrogate must be recorded in the patient’s notes.

4. We firmly object to the designation of surrogates by court, in case of temporary loss of competence, as totally unrealistic. It would actually result in a ban on biomedical research and progress in intensive care medicine.

5. Only in cases of emergency, a waiver of consent may be accepted (“emergency clause”). Some essential conditions should be required:

- The subject is in a life-threatening situation requiring immediate treatment.
- Informed consent cannot be obtained from the subject because of an inability to communicate with him or her.
- Time is insufficient to obtain consent from the subject’s legal representatives.
- Personal benefit for the patient should be expected.
- Minimal risks beyond standard therapy. In this situation, minimal risk is the increment of risk the research presents to the patients rather than the risk it would present to normal individuals [8].
- Detailed information must subsequently be given to the patient or to surrogate.
- Protocol approved in advance by an institutional review board.

We believe that the majority of ICU research falls into these categories and should continue with consent of a surrogate or when meeting the emergency conditions without obtaining the prior consent of either the patient or a surrogate. In such cases, it may be desirable to obtain deferred consent, i. e. consent from the patient retrospectively after recovery.

6. Efforts at obtaining consent, even from a surrogate, has an enormous didactic value, both for the medical team and society. It is the role and duty of the ESICM to validate, implement and control the use of these recommendations. Specifically, clinical investigation which would not comply with universal ethical rules and this ESICM policy should not be sponsored by the “Society”, presented at its meetings, or published in its journal. It is also the role of the ESICM to explain to the European authorities the specificity of intensive care medicine, the necessity of performing clinical research and the difficulties we face. We, as specialists in intensive care medicine, should describe our patients as highly vulnerable, but who must not be denied the benefits of therapeutic research. Our Society should promote and stimulate research on the assessment of competency of acutely ill patients, and on the expected role of surrogates.

The questionnaire will be published in the next issue.