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POINT OF VIEW

How to protect incompetent clinical research subjects involved in critical care or emergency settings

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ABSTRACT

Clinical research is an essential component of medical activity, and this is also true in intensive care. Adequate information and consent are universally considered necessary for the protection of research subjects. However, in emergency situations, the majority of critical patients are unable to consent and a valid legal representative is often unavailable. The situation is even more complex in Italy, where the relevant legislation fails to specify how investigators should manage research in emergency or critical care setting when it involves incompetent patients who do not have an appointed legal representative. While special measures for the protection of incompetent subjects during emergency research are necessary, not allowing such research at all dooms critically ill patients to receive non-evidence-based treatments without the prospect of improvement. The recently-issued EU Regulation n. 536/2014 will probably help shed light on this situation. Indeed, it specifically addresses the issue of "research in emergency situations" and introduces detailed rules aimed at protecting patients while allowing research.

In this article, we argue that obtaining informed consent during emergency research on incompetent subjects in unrealistic, and that in most cases substituted judgment on the part of a proxy carries major flaws. Strict criteria in evaluating the risk-benefit ratio of proposed intervention and a careful evaluation of the trial by a local or national Research Ethics Committee are perhaps the most practicable solution.

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Emergency research in incompetent patients is a common but problematic issue. Due to the large sample size required, multicenter studies are usually necessary. Such studies have to overcome center and country variability in the approval process. In Italy, the level of this variability is striking and Italian Research Ethics Committee (RECs) often take opposite

Comment in p. 389.

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decisions based only on the different interpretation of the current law, as we will discuss further on.

This raises important issues in relation to research in critical care or emergency settings, when involving temporarily incompetent patients (*e.g.* comatose patients), or highly distressed patients that cannot rapidly provide a truly informed consent. The aim of this paper is to present the current legal framework in Italy, compare it with the recent developments in European Union legislation and discuss such developing regulation.

Information and consent in emergency research

Clinical research is an essential component of medical activity, even in emergency situations. Effective therapies mean better outcomes and reduced morbidity and mortality; these goals can be achieved only by means of research. Not allowing such studies stops progress in knowledge, condemning critically ill patients to receive inferior non-evidence based treatments, without any prospect of improvement. Critically ill patients should be protected from such undesirable lack of evidence.

In order to also protect subjects involved in research studies, adequate information and subsequent valid consent are mandatory both in the international context and in the European Union (EU) legal framework (see WMA Declaration of Helsinki, 2013, points 25-26 and Directive 2001/20/EC, articles 2.j and 3.2.b-d). Informed consent may be granted either by the patient or by the legal representative of the incompetent patient (see WMA Declaration of Helsinki, 2013, points 27-29 and EU Directive 2001/20/EC, articles 3, 4 and 5). These measures of protection work in non-critical settings (*e.g.* research on psychiatric patients or on incompetent patients with degenerative conditions). However, in emergency situations, the vast majority of patients are incompetent and legal representative are absent:[1] they cannot be adequately informed and are consequently unable to consent. In addition, as might be the case in cardiac arrest research, there is no time or opportunity for consent to be given.

The specific issues of clinical research on incompetent patients in emergency settings had not been addressed in the EU legal framework until April 2014, leading to uncertainty on the legal feasibility of such research[2].

The present situation in Italy

The European Directive 2001/20/EC will still be in force at least until May 2016. In Italy, such directive has been implemented by the Legislative Decree n. 211/2003,[3] whose art. 3 states that only the involved subject can give valid consent for research. According to art. 5, the "legal representative" is the only legal substitute for the incompetent patient; yet, the Decree fails to specify who is to be intended as legal representative in emergencies.

According to Italian law, in case of incompetent adults, the legal representative is a legal guardian specifically appointed by the Court — a process which optimistically takes weeks. How then could be possible to involve incompetent adults in emergency research when a legal guardian is not available, as indeed happens in most cases?

A possible, extreme solution is to consider every form of research on the incompetent adults forbidden.[4]

Yet, this construct makes emergency clinical research in adult incompetent persons impossible *at all*, unless there is a previously appointed legal substitute (as in case of previous mental impairment). This deprives critically ill patients of evidence-based improvements in care and is clearly unethical.

An alternative solution is to consider that the protection measure of legal representation, as it has been developed in the Italian legal order, does not cover emergency situations, in the absence of a previously appointed legal substitute.[5] As a consequence, art. 5, lett. a) of the Legislative Decree n. 200/2007 should not apply to emergency situations. On the contrary, according to art. 4 of the same Decree,[6]

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the point 4.8.15 of the Annex I to the Ministerial Decree 15.7.1997, which implemented the GCP CPMP/ICH/135/1995 in Italy, must be considered applicable:

"When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favorable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested".

This means that currently the destiny of a research protocol in emergencies depends on a case by case evaluation of the local REC. The REC has to assess if the special measures provided in the protocol are adequate for the protection of the rights, safety and well-being of the perspective subjects. The aim can be achieved through:

— measures concerning the "acceptability" of the risk/benefit ratio — involving the study design, limitation of inherent risks, necessity of a second expert opinion, stress on the investigator responsibility, use of more strict inclusion criteria etc., or

— measures concerning the participation of the perspective subjects — involving the information and assent of the person even partially competent, the respect of any previously expressed objection by the patient, a proxy consent, the delayed consent.

In the absence of other applicable regulatory requirements, this evaluation totally relies on the RECs' discretion.

Things are changing: the EU scenario

On April 2014 the European Parliament and the Council issued EU Regulation n. 536/2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. The new regulation shall apply no earlier than 28 May 2016 (see art. 99 in the Appendix). The Recital (36) states:

"This Regulation should provide for *clear rules* concerning informed consent in emergency situations. (…) For such cases, intervention within an ongoing clinical trial, which has already been approved, may be pertinent. However, in certain emergency situations, it is not possible to obtain informed consent prior to the intervention. This Regulation should therefore set clear rules whereby such patients may be enrolled in the clinical trial under very strict conditions".

Accordingly, the new regulation provides special protection measures at art. 10 and 35 (Appendix) and it mostly seems in line with art. 30 of the WMA Declaration of Helsinki, 2013, setting four fundamental principles:

1. good clinical research must be promoted, even on incompetent subjects and in emergency situations, in order to meet health needs and priorities of this group of patients;
2. clinical research in this setting requires special protection measures, including: a) a strict relationship between the clinical trial and the medical condition which causes the patient's incompetence, b) the necessity to conduct the clinical trial in emergency situations; c) the expectations of benefits and of only minimal risks or burdens for the perspective subjects.
3. informed consent from the subject or from a legally designated representative should be sought as soon as possible (delayed consent).
4. the clinical trial should have been previously reviewed by a REC.

Protecting incompetent patients through informed consent?

Two kinds of measures are currently used in order to protect the subjects of clinical research.

The first kind of protective measures relate to the acceptability of the risk/benefit ratio of the study design. They may give answers to the need of reasonably balancing the promotion of scientifically sound and clinically relevant re-

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search and the physical protection of incompetent patients involved in clinical research. The second kind of protection measures concern the involvement of the participants and the protection of the identity of the research subjects and their rights to privacy and self-determination.

Both these kinds of measures have to be used, in line also with the EU Regulation n. 536/2014.

Yet, in case of emergency research on incompetent subjects, a *previously* collected informed consent is simply unfeasible (by definition, as the subjects are incompetent).

As for *deferred* consent, it is evident that consent can protect a patient only if given before an action is performed. Deferred consent can work only for the subsequent treatments and for the use of personal data. On the contrary, in prospective randomized protocols, after a potentially dangerous intervention (a drug has been administered, an operation has been performed), consent can have little space in practice in order to protect the patient. Collecting valid consent from next-of-kin is also problematic. In Italy, though this practice has no full legal value,[3, 6, 7] researchers often inform the relatives and take into account their reporting of the patient's wishes. This practice is often not feasible in emergencies due to several reasons; first, the time constraints, as a next-of-kin is usually unavailable in the therapeutic window frametime;[8] second, different family members could give different versions of the patient's wishes and/or may fail to accurately report them;[9] third, emotional stress can significantly bias the decision of relatives in emergency situations.[2, 10]

Protecting incompetent patients through risk/benefit ratio evaluation: the role of RECs

We believe that measures regarding the acceptability of the risk/benefit ratio of the study design can protect the incompetent subjects of emergency trials much more than information and consent. Regulation EU n. 536/2014 sets suitable rules for this aim. In fact, Article 31 (Clinical trials on incapacitated subjects) and Article 32 (Clinical trials on minors) state that clinical trials may be conducted only where — among other conditions — there are scientific grounds for expecting that participation in the clinical trial (1) will produce a direct benefit for the subject concerned outweighing the risks and burdens involved; or (2) […] will pose only minimal risk to, and will impose minimal burden on the subject concerned in comparison with the standard treatment of the minor's condition. On the contrary, in Article 35 (Clinical trials in emergency situations) the two standards of "direct clinically relevant benefit for the subject" and "minimal risk to, and minimal burden on, the subject in comparison with the standard treatment" are both mandatory for the subject's inclusion. These two strict prerequisites are designed to protect the incompetent subject of emergency research, when he/she cannot decide (he/she is incompetent) and a guardian is not (yet) available. The role of the REC here is crucial as it has the task to verify that the clinical trial design really respects these requirements.

As a matter of fact, an efficient local REC can provide a much better evaluation of the planned intervention, by ensuring effective protection of research subjects and promoting good clinical research in emergency settings. All REC's members should be experienced professionals who should be able to evaluate all the relevant issues related to protocol safety and have sufficient time for adequate discussion. No other people, and surely not the subject's relatives pressed in an emergency situation, can make a better evaluation. Yet, such a Committee should work in close contact with the research clinicians.

At present, in Italy, most RECs do good pre-emptive work: they examine the different aspects of the protocol, the information sheets and the insurance issues. But after that, the task of optimal performance and protocol adherence is left to the clinicians.

Our proposal is to trust clinicians: those who perform clinical research have specific legal and moral responsibilities. But, at the same time, we think that the strengthened criteria verified by the RECs in evaluating the design of an emergency trial involving incompetent subjects should be sufficient for the inclusion (Figure 1).

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The problem of multicenter trials (and multiple RECs)

But again: what to do in multicenter trials, where many centers (and many RECs) are involved? How can agreement be reached?

In a recent document,[11] the Italian National Committee for Bioethics expressed hopes for a significant legislative change in Italy, which could enable multicenter emergency research on incompetent patients, provided that:

1. the clinical trial has been approved by an *Ad-Hoc* National REC composed by expert clinicians, lawyers, patients' representatives, bioethicists;
2. if a patient has not previously refused to be involved in medical research, he/she has to be promptly enrolled;
3. deferred consent is used for subsequent treatments and for permission to use previously gathered data;
4. publication of negative results is recommended.

The proposal of the National Committee for Bioethics is open to challenge. The main problem is to assemble expert members in different disciplines who are able to represent the different working realities (university and big city hospitals, little community hospitals in rural areas). Moreover, to evaluate all multicenter studies regarding emergency and involving temporarily unable patients, this "*ad-hoc* national REC" should have adequate number of planned meetings: a dire challenge, also from an economic point of view. Another problem is that such a committee could be perceived as too far away and disconnected from researchers.

On the other hand, this solution could ensure a more balanced equilibrium between the local interests (autonomy of local REC) and the community interests (the possibility to perform phase III studies).

We will wait and see how the scenario will evolve, hoping for a clearer set of rules that allow critically ill patients in emergency conditions or in intensive care unit to receive the best treatment, based on the best available research data.

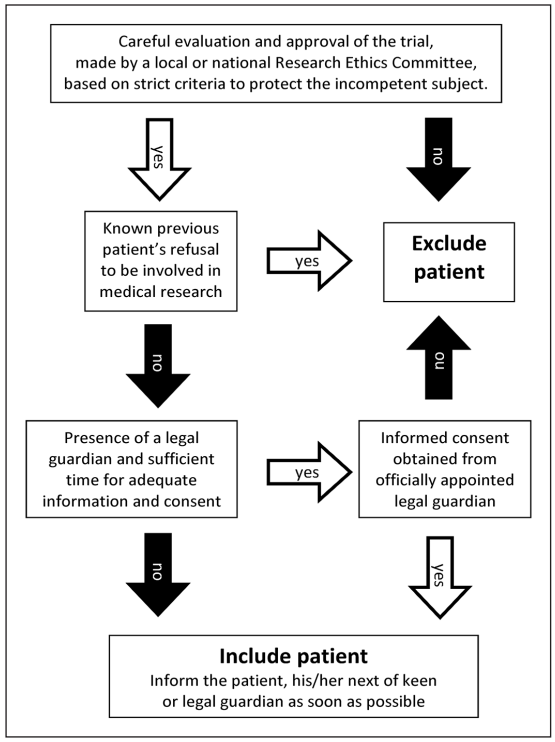

Figure 1.—Flowchart for management of incompetent patients eligible for emergency clinical trial.

Key messages

— Clinical research is an essential component of medical activity; it has to always be guaranteed, both for individual and social interests, even in emergency conditions.

— Adequate information and consent are unfeasible in critically-ill patients and a legal representative is often not promptly available.

— Special measures for the protection of incompetent patients have to be harmonized with the possibility to conduct research in emergencies, in order to reach evidence based treatments.

— The careful evaluation and approval of the trial by the competent Ethics Committee appears as the best solution, together with surveillance during trial progress and the timely consent collection from patient.

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Appendix

EU Regulation n. 536/2014 on clinical trials on medicinal products for human use, repealing Directive 2001/20/EC

Article 10 — Specific considerations for vulnerable populations

1. (…)
2. Where the subjects are incapacitated subjects, specific consideration shall be given to the assessment of the application for authorisation of a clinical trial on the basis of expertise in the relevant disease and the patient population concerned or after taking advice on clinical, ethical and psychosocial questions in the field of the relevant disease and the patient population concerned.

Article 35 — Clinical trials in emergency situations

1. By way of derogation from points (b) and (c) of Article 28(1), from points (a) and (b) of Article 31(1) and from points (a) and (b) of Article 32(1), informed consent to participate in a clinical trial may be obtained, and information on the clinical trial may be given, after the decision to include the subject in the clinical trial, provided that this decision is taken at the time of the first intervention on the subject, in accordance with the protocol for that clinical trial" and that all of the following conditions are fulfilled:
   (a) due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition, the subject is unable to provide prior informed consent and to receive prior information on the clinical trial;
   (b) there are scientific grounds to expect that participation of the subject in the clinical trial will have the potential to produce a direct clinically relevant benefit for the subject resulting in a measurable health-related improvement alleviating the suffering and/or improving the health of the subject, or in the diagnosis of its condition;
   (c) it is not possible within the therapeutic window to supply all prior information to and obtain prior informed consent from his or her legally designated representative;
   (d) the investigator certifies that he or she is not aware of any objections to participate in the clinical trial previously expressed by the subject;
   (e) the clinical trial relates directly to the subject's medical condition because of which it is not possible within the therapeutic window to obtain prior informed consent from the subject or from his or her legally designated representative and to supply prior information, and the clinical trial is of such a nature that it may be conducted exclusively in emergency situations;
   (f) the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject in comparison with the standard treatment of the subject's condition.
3. Following an intervention pursuant to paragraph 1, informed consent in accordance with Article 29 shall be sought to continue the participation of the subject in the clinical trial, and information on the clinical trial shall be given, in accordance with the following requirements: (a) regarding incapacitated subjects and minors, the informed consent shall be sought by the investigator from his or her legally designated representative without undue delay and the information referred to in Article 29(2) shall be given as soon as possible to the subject and to his or her legally designated representative; (b) regarding other subjects, the informed consent shall be sought by the investigator without undue delay from the subject or his or her legally designated representative, whichever is sooner and the information referred to in Article 29(2) shall be given as soon as possible to the subject or his or her legally designated representative, whichever is sooner. For the purposes of point (b), where informed consent has been obtained from the legally designated representative, informed consent to continue the participation in the clinical trial shall be obtained from the subject as soon as he or she is capable of giving informed consent.
4. If the subject or, where applicable, his or her legally designated representative does not give consent, he or she shall be informed of the right to object to the use of data obtained from the clinical trial.

Article 99 — Entry into force

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*. It shall apply as from six months after the publication of the notice referred to in Article 82(3), but in any event no earlier than 28 May 2016.

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