RESEARCH ETHICS

Medical research in clinical emergency settings in Europe

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Clinical emergencies necessitate immediate action to avert the danger to the patient's life or health. Emergency patients might be in greatest need of novel therapies, and even presumed willing to assume some risk, but research into emergency conditions should be conducted under commonly accepted principles that fulfil the scientific, ethical, and legal criteria. Such criteria already exist in the US, but are still under development in Europe.

This article introduces criteria upon which trials in emergency settings may be ethically and legally justified in Europe. Based on both legal texts and professional guidelines, the author has established seven conditions for emergency research, of which informed consent and its substitutes, as well as the conditions of direct benefit requirement and necessity, are considered most problematic and therefore analysed more closely. Other conditions include absence of alternative methods, scientific validity, and approval by an ethics committee.

Since the Nuremberg trials and the Nuremberg code¹, the requirement of free and informed consent has been accepted as the cornerstone of any medical research or experimentation involving human beings. Some claim that research on persons with diminished capacity to give consent should be conducted under very strict conditions only and never without the approval of the legal representative.² Medical experimentation on incapacitated persons has been questioned as a violation not only of personal autonomy but also of human rights.³ If research on children and mentally incapacitated persons with proxy consent is considered problematic, then what about medical research on unconscious patients who enter the emergency and accident department without anyone accompanying them who can state either their identity or their views on participating in research?

For example, British researchers at the Royal Bolton Hospital are investigating the effect of corticosteroids in case of significant head injuries.⁴ Treatment is begun within eight hours or as soon as possible in order for the treatment to have the hoped-for benefit. The trial has been designed as a randomised placebo controlled trial, where both the research group and the control group will receive the standard treatment, but in addition, the trial group will receive a 48 hour infusion of corticosteroids. Due to the nature of the patient population, all eligible patients will have a reduced level of consciousness and a personal informed consent is therefore out of the question. Most would agree that this kind of research should be conducted, but what are the conditions that define its ethical and legal acceptability and why?

Emergency settings appear not only with conditions that involve a severe trauma, but also in conditions such as cardiac arrest, acute congestive heart failure, sepsis or haemorrhage, stroke, or a drug overdose.⁵ These patients can hardly be expected to read a multipage information sheet stating the nature and purpose of the research as well as all the risks and benefits expected, even if conscious. Therefore, a standard informed consent procedure is on many occasions out of the question, even if it is always to be preferred. Emergency patients, at high risk of morbidity or death, might, however, be in greatest need of novel therapies and might be willing to assume some risk for a potential benefit. If this is done solely in the therapeutic interest of the particular patient, it is categorised as "innovative therapy" to differentiate it from

medical research carried out in the interest of future patients and accumulation of scientific knowledge.⁶ These practices have been recognised also in the Declaration of Helsinki.⁷ The administration of innovative therapy is not usually submitted for the prior approval of a research ethics committee, nor are the subjects always made aware of the innovative nature of the therapy, which has led to criticism both on the grounds of lack of respect for the self determination of the patients, and because of the danger it poses to public confidence.⁸ In order to encourage the medical profession to conduct research rather than performing individual experimental practices, the conditions for such research should be made clear and accessible.

Another example of an actual trial involving emergency conditions is a trial of intravenous magnesium sulphate as a potential neuroprotective agent in acute stroke, coordinated by the University of Glasgow.⁹ The inclusion criteria include a clinically diagnosed acute stroke with residual limb weakness, but do not exclude patients unable to give independent consent. On the contrary, special instructions for including incompetent patients to the trial are given to the research staff in case of failure in communication with the patients themselves or their relatives despite reasonable attempts having been made. The patients must be enrolled in the study within 12 hours of the stroke.

If the efficacy of the treatments on these conditions cannot be tested on healthy subjects and the nature of the condition undermines the capacity of the patient subjects themselves, the only options for research in this situation are either to gain informed consent from a legal representative, or to proceed with experimentation without any consent until such is available. In fact, trials in emergency situations have been conducted both in the US and in Europe using various consent designs.^{10–13} In the United States, the Food and Drug Administration (FDA) and the Department of Health and Human Services (HHS) gave out waivers of informed consent for emergency research on October 2, 1996.¹⁴ In Europe, such regulation is still under development. Nevertheless, the need for such research remains the same on both continents and therefore, an ethical and legal analysis on research in emergency settings is needed also in Europe.

INTERNATIONAL PROFESSIONAL AND GOOD PRACTICE GUIDELINES

Despite the inadequate level of detail, some guidance already exists concerning medical research in emergency settings, both globally and at the European level. The recently revised Declaration of Helsinki states¹⁵:

Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorised surrogate.

The Declaration of Helsinki states many of the conditions that are relevant when conducting research in emergency settings, although a global professional guideline obviously cannot be very specific. Some basic conditions can, however, be extracted from the text:

- 1) research cannot be conducted using other research participants capable of giving informed consent;
- 2) research shall be adequately planned and designed in a research protocol;
- 3) protocol shall be approved by an ethics committee for emergency conditions specifically;
- 4) informed consent is not obtainable:
 - a) from the participant him or herself when the circumstances for research are at hand,
 - b) from the participant him or herself previously,
 - c) from his or her legally authorised representative;
- 5) informed consent for continued participation in the trial shall be obtained from either the participant him or herself or the legally authorised representative as soon as possible.

All of the requirements listed above are necessary if research in emergency settings is to be ethically justified according to the Declaration of Helsinki. An almost identical list of criteria can be extracted from the International Conference on Harmonisation (ICH) good clinical practice (GCP) guidelines drafted as an international ethical and scientific quality standard for trials on medicinal products.¹⁶ Neither the declaration nor the ICH GCP guidelines, however, describe the nature of research that may be conducted without a proxy consent, that is, what kind of research may be conducted if the conditions above have been fulfilled. Additionally, as both the Declaration of Helsinki and the ICH GCP guidelines lack direct legal effect, more guidance should be sought from the Council of Europe Convention on Human Rights and Biomedicine.

COUNCIL OF EUROPE CONVENTION ON HUMAN RIGHTS AND BIOMEDICINE

The most prominent of the legal documents touching the area in the European context is the *Council of Europe Convention on Human Rights and Biomedicine*.¹⁷ Although it does not, in its present form, address emergency research specifically, most of the basic conditions set out above can also be extracted from the convention articles dealing with biomedical research (chapter V). More particularly, article 17 of the convention states provisions on the protection of persons not able to consent to research. The conditions include the authorisation of a representative, an authority, a person or a body provided by

law. Nevertheless, it seems that the drafters have not taken into account circumstances in which it is not possible to obtain consent from a representative because of lack of time; no mention of emergency biomedical research is made either in the text of the convention or in its explanatory memorandum.¹⁸ However, emergency situations in general (not limited to research) are addressed in article 8, where the rule of informed consent (article 5) has been waived. It states:

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

There are two ways in which this article can be interpreted. On the one hand, it could be argued that as the article is not combined with the provisions that deal with scientific research (chapter V), it should be interpreted in a narrow sense, thereby limiting its scope of application to non-experimental treatment situations only.¹⁹ On the other hand, the text of the article itself does not refer to standard clinical practice situations, but speaks of “any medically necessary intervention”, thereby covering the so called “innovative therapy” at the minimum and, according to an even broader interpretation, also procedures within a research protocol that may be considered as medically necessary although not part of standard therapy.^{20–22} The broader alternative is favoured in the *Draft Additional Protocol on Biomedical Research* given out for consultation on 18 July 2001, which allows medical research in emergencies under certain protective criteria presented below.²³ Yet another argument in favour of the more liberal interpretation is that the Council of Europe has, in its previous guidance, addressed research in emergency settings specifically. In principle 8 of the *Council of Europe Committee of Ministers’ Recommendation (90) 3*, three conditions for this kind of research have been given: 1) the research must have been planned to be carried out in the emergency in question; 2) the systematic research plan must have been approved by an ethics committee; and finally, 3) the research must be intended for the direct health benefit of the patient.²⁴

On the basis of the above, two additional points may be added to the criteria of research in emergency settings: 6) intervention shall be carried out for the direct health benefit of the patient, and 7) the intervention in question shall be medically necessary and unable to be delayed.

ANALYSIS OF THE EUROPEAN CRITERIA

In the following, I will examine some of the requirements for emergency research more closely. Conditions 1, 4, and 5 are all linked to the requirement of informed consent and therefore will be analysed under that heading, whereas conditions 6 and 7 will be dealt with under the subsequent title, direct benefit and necessity. As far as informed consent is concerned, the question of the person giving proxy consent is dependent on national legislation, and therefore cannot be answered here. Further, the requirements of a research protocol (condition 2) and an ethics committee review (condition 3) are mainly involved with the more general aspects of medical research and will therefore fall outside the scope of this article. Suffice it to say here, all research should be adequately planned, and a research protocol drawn up before its implementation, and deviations from the normal consent procedure always require a prior approval of an ethics committee, even if the research protocol has already been approved for non-urgent circumstances.^{25 26}

INFORMED CONSENT IN EMERGENCY SITUATIONS

One of the essential elements of informed consent is that it is voluntary and may always be freely withdrawn. Additionally,

articles 5 and 16 of the biomedicine convention state that in order to be valid, informed consent shall be free and informed, specific, and documented. They further state that information on the project shall include at least the purpose and nature of the intervention as well as its consequences and risks.

When a subject is capable of giving informed consent even though he or she has suffered a mild heart attack or a mild stroke, the starting point for such research is normal informed consent. However, even if the patient is competent to decide for him or herself (which may be hard to estimate reliably in the circumstances), some aspects of informed consent may still need to be considered, because the pain, stress, and anxiety suffered by the patient do not render the patient receptive to all the information that is pouring in. As informed consent by the patient him or herself is always preferred to the consent of a representative or, exceptionally, to waiving consent altogether, the information given to the patient in urgent circumstances should be particularly concise and understandable. All the information that is required in non-urgent circumstances may not be suitable here and may even confuse the patient. Therefore, the focus of informing the patient in a very anxious state should be on the core elements stated in the biomedicine convention: the purpose and nature of the intervention as well as its consequences and risks. The rest, however, should be explained to the patient at a later stage, when the patient's circumstances allow for a full disclosure. This solution could also prove useful in cases where informed consent is given by the representative of the patient, for example, in the case of research on asphyxiated neonates whose parents have just been informed of possible brain damage to the child.²⁷

Grim *et al* have, in fact, reported using a so called "two-stage consent" procedure, where the initial dose of the thrombolytic substance was given already in the ambulance to the patient suffering from acute myocardial infarction along with some preliminary information about the trial. The consent procedure was finalised at the hospital before administering the rest of the infusions when the patient was calmer and the research staff on hand to help in the process.⁴¹ In such a consent design, self determination of the subject is maximised even in challenging circumstances. Another problem appears if after giving the initial consent the patient does not remain conscious or the investigator wants to confirm the validity of consent from the patient's representative. Taking relatives or other representatives into the consent process is, however, a double-edged sword. If the patient is competent, giving decision making power to people other than the patient him or herself can be considered as a violation of self determination. On the other hand, if the suspicions as to competence are justified, the consent of the legal representative is necessary to validate the assent of the potentially incompetent subject. In any case, the wishes of the subject remain legally relevant, even if the legal representative is involved in the process. According to article 17 of the biomedicine convention, experimental procedures may never be performed if the person concerned objects, even if the subject is incompetent.

The form of consent is not explained in detail in the biomedicine convention, although the requirements for the consent to be specific and documented are stated. It seems, therefore, that a documented oral consent may be acceptable if the subject him or herself is not able to read or write because of his or her condition. In order to avoid any possible future conflict and to ensure the condition of documentation, it may be advisable to have an impartial person to witness the disclosure of information and the oral consent of the subject in addition to the signature of the investigator.

It is characteristic of emergency conditions that they appear abruptly and without prior warning. Therefore, the relevance of advance directives is rarely an issue to be discussed in this context. If, however, such a prior statement of the will of the patient is known to the investigating team or to the represen-

tative of the patient, it has to be taken into account (biomedicine convention, article 9). Although advance directives have been discussed extensively in connection with standard treatment and terminal care, there has not been very much discussion about their relevance to experimentation. Some hopes have been raised about their use in medical research. There are also voices, however, that take a more cautious view on their applicability.²⁸ Although it is questionable whether consent to research can be given in advance, for example, because of lack of sufficient information of the particular research protocol, it is clear that if a person has made an advance refusal of extraordinary measures for sustaining his or her life, he or she would most likely say no to research having the same aim. Just as an incompetent person has the right to refuse to take part in experimentation, so an advance refusal of medical research should always be treated with the same respect.

Whatever design for informed consent is used in emergency settings, it is of the utmost importance to use all means available to get a proper informed consent for continued participation in the trial either from the participant him or herself or from the patient's representative as soon as possible (condition 5). It is also to be remembered that the mere fact of a narrow therapeutic window does not justify proceeding without consent. The urgent nature of the research must relate to the condition of the potential participant, not to the interests of the investigating team in gathering a sufficient amount of evidence about a new treatment in a hurry, nor to lack of staff attempting to reach the potential representatives of the patient in time. Informed consent should not be compromised merely because there are not enough study nurses to make phone calls to relatives. More specifically, the intervention shall be carried out for the direct benefit of the patient, be medically necessary, and be unable to be delayed (conditions 6 and 7). In the following, these two conditions will be analysed more closely.

DIRECT BENEFIT AND NECESSITY

Medical research is activity aimed at collecting knowledge in order to develop new methods of treatment. Therefore, by definition, no promises about the superiority of an experimental therapy can be made to an individual participant. Setting any benchmarks on the level of potential benefit to the person is difficult.

One attempt to draw lines of this kind has been to divide research projects into non-therapeutic and therapeutic, depending on the likelihood of expected health benefit to the individual participant. This approach has, however, proven to be problematic, due to the fact that within one research project different groups of subjects may receive different types of treatment or even placebos. Again, each group may be subjected to various procedures, some of them conducted in the furtherance of patient health—for example, injections of potentially therapeutic substances, and some for purely scientific purposes—for example, measuring the absorption of the medicinal substance by additional blood samples.²⁹ Despite the controversy attached to the two categories, the protection of incompetent persons in the biomedicine convention is founded on a general rule that incompetent persons should only be allowed to participate in research that offers a potential health benefit to the individuals themselves, that is, therapeutic research, and non-therapeutic research should be conducted under exceptional circumstances only. In the biomedicine convention (article 17.1.ii), the first category has been formulated as:

Research on a person without the capacity to consent . . . may be undertaken only if . . . the results of the research have the potential to produce real and direct benefit to his or her health.

The next question which naturally arises is how to interpret this category: what is meant by the “results of the research”; what is a “real” and “direct” benefit to health and how likely shall the benefit be? One could argue that by connecting the direct health benefit requirement to the “results of the research”, the Council of Europe has not limited the health benefit to be gained directly from the research measures themselves, but from what can be deduced from additional scientific knowledge after the results have been analysed. A more conventional interpretation, however, is that “results of the research” refers to the direct physical or psychological results of the interventions involved in the study as a whole, and not to the results that the analysed data may bring about in the future, nor to any implications those results may have for the development of medicine.

What then is the meaning of a “real and direct” health benefit? It may be helpful to try to interpret these words starting from their antonyms, that is, from what they are not. Unreal health benefit could then be described as minimal, theoretical, or imaginary, such as the patient’s own assumption of superior treatment (for example, the placebo effect) or the benefit of a better monitoring of the patient’s condition. Indirect health benefit can better be understood in terms of the second category of “non-therapeutic” trials, which, using the language of the biomedicine convention, could be characterised as:

capable of conferring benefit . . . to other persons in the same age category or afflicted with the same disease or disorder or having the same condition.

Therefore, indirect health benefit could be described as a group benefit rather than benefit directed towards the individual him or herself. According to article 17 of the biomedicine convention, “non-therapeutic” trials on incompetent persons are only allowed if the risk and burden involved is kept to the minimum. This can be seen as an attempt to balance the risk-benefit calculus where the potential benefit is lacking, by equally reducing the risks involved.

In an emergency setting, an argument can be made that only research belonging to the first category is justified without informed consent. This is because the Council of Europe recommendation (90) 3 requires the element of direct benefit, and article 8 of the biomedicine convention refers to the element of medical necessity for the individual concerned. A health benefit conferred to others belonging to the same group does not fulfil either of the criteria. The question remains, whether even a direct benefit to the individual as described in article 17.1.ii of the biomedicine convention is sufficient to fulfil the criteria of “necessity”, which appears in recommendation (90) 3. Even if a measure, for example, removing a thorn, is beneficial to the individual, it does not make it necessary as such. The notion of necessity is connected to situations of life and death or serious permanent damage to health, together with a need for immediate action. As only a “direct health benefit” is generally required from research on incompetent patients with proxy consent, should not the standard for expected health benefit be lifted higher for research where proxy consent is not available?

According to the *Draft Additional Protocol on Biomedical Research to the Biomedicine Convention*, research in emergency clinical situations should only take place if 1) research of comparable effectiveness cannot be carried out on persons in non-emergency situations; 2) the research has been approved specifically for emergency situations by a competent body; 3) persons participating in the emergency research will be provided with all the relevant information as soon as it becomes possible, and 4) consent or authorisation for continued participation will be obtained as soon as reasonably possible (article 21). Otherwise the same conditions would apply

as in the case of protection of persons not able to consent to research in general (article 18, which has roughly the same wording as article 17 in the original convention). This solution leaves open the possibility of conducting even non-therapeutic research in emergency situations without consent, which can be criticised for the reasons stated above. If such provision is to be accepted, the level of risk should be lowered from minimal to virtually non-existent, in order to compensate for the lack of protection of proxy consent. Naturally, if a potential health benefit could be shown, higher risks could again be justified by the potential benefit involved.

CONCLUSION

Above, criteria have been created which would ethically and legally justify medical research in emergency situations. If this list of criteria is compared to the list used in the US, it can be seen that the US criteria take a much more comprehensive and detailed approach to research in emergency settings than the list that can be deduced from the Declaration of Helsinki, ICH GCP guidelines and the guidance given by the Council of Europe. Although there is slight variation in most aspects between the US and the European criteria, the most striking differences can be found in the procedural requirements. As in Europe, prior review by an ethics committee (institutional review board in the US) is of central importance. In addition, the US regulations insist that where emergency conditions apply an individual consultant to the committee must approve the study.³⁰ The most interesting aspect of the US waiver of consent in emergency settings, however, is the extent to which the researchers (or the sponsors) are required to involve the general public in their developmental work. The regulation requires setting up community consultation with the representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn. It further presupposes public disclosure of the investigation plan and its risks and expected benefits, prior to the initiation of the clinical investigation. The community consultation requirement has already raised some discussion as to how it should be interpreted.³¹

A similar waiver to the US criteria is hardly to be expected in Europe, but some activity in the area can be seen. The *Draft Additional Protocol on Biomedical Research to the Convention on Biomedicine and Human Rights* already suggests more detailed requirements as to medical research and human rights. Although some of the details in the draft additional protocol can be criticised, it conveys a positive attitude towards medical research in emergency clinical situations, at least within the Council of Europe. The same cannot be said of the new directive 2001/20/EC of the European Parliament and the council on clinical trials on medicinal products.³² The directive does not contain an exception for emergency circumstances, but requires the informed consent of a legal representative in all cases where trials are conducted on incapacitated adults not able to give informed consent.³³ Unless a person in the research hospital—physician or other personnel—is given the status of a legal representative, the difficulties in obtaining proxy consent remain. From a continental European legal perspective, I would consider it very problematic for hospital personnel to be designated legal representatives because of the built-in danger of partiality. Unless, however, the directive is amended prior to its national implementation, this would be the only foreseeable solution which would permit the continuation of emergency research for example, in the cases described in this article.

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