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ORIGINAL PAPER

Assessing the Ethics of Medical Research in Emergency Settings: How Do International Regulations Work in Practice?

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Abstract Different ethical principles conflict in research conducted in emergency research. Clinical care and its development should be based on research. Patients in critical clinical condition are in the greatest need of better medicines. The critical condition of the patient and the absence of a patient representative at the critical time period make it difficult and sometimes impossible to request an informed consent before the beginning of the trial. In an emergency, care decisions must be made in a short period of time, and the more time is wasted, the more the risk of death or severe tissue damage and incapacity increases. Consent requests take time, and so the time period before treatment might put the patient's life in jeopardy. Not requesting consent before a trial is also contradictory. A person should not be forced to participate in a trial against his or her will. Due to the dark history of medical research previously, international declarations and conventions have set up ethical principles for medical research. They emphasize the autonomy of the research participant—or his or her legal representative—to give a free and informed consent prior to the initiation of research. In the case of a critical emergency, the unconscious state of the patient, the emotional stress of family members or the lack of time to start life-sustaining measures may often restrict the possibilities of communicating with the patient or his/her representative. Therefore, written informed consent is difficult to achieve, and its voluntariness in emergency situations is, at best, open to question. The mortality of patients is high without clinical interventions in emergency research. Random selection of patients is difficult and requires

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extra work from personnel in the emergency rooms. Recruitment, information and asking for consent may also take time, postpone the initiation of treatment and increase the risk of death and irreversible tissue and organ damage, and therefore be risky for the patient. It is therefore essential that the health care professionals recruiting suitable research participants are well motivated and well trained. Medical research in an emergency setting should always be regarded as an exceptional situation requiring special provisions. Only such research should be done as cannot be done in other conditions. An independent body must approve the research protocol and the ways in which the consent of the participant or proxy are to be sought. In addition, the trial must be expected to result in direct and significant benefit for the research participants. If research without prior consent is not approved, the development of emergency care is threatened. On the other hand, if prior consent is not required, a person could be recruited into a clinical trial against his or her will. Doing good and avoiding harm, and respecting the autonomy of the patient are in conflict in the context of emergency medical research. To develop better medicines for patients experiencing acute medical emergencies, research into such conditions should be allowed. Research participants should have the possibility to participate or refuse to participate in research that may benefit them and other patients. The risk of irreversible damage occurring as the consequence of time delays for seeking consent is unacceptable. A prior wish about participation in clinical trials should be respected, if known. The conditions under which medical research in emergencies can be considered acceptable can be determined and agreed upon nationally and internationally.

Keywords Clinical trials · Emergency medicine · Ethics · International declarations · Legislation · Research

Introduction

Medical research in emergencies brings up several ethical dilemmas. Patients in emergency situations are often unconscious and in a critical, life-threatening condition. These conditions appear suddenly and unexpectedly, and often neither the patient nor the family members have been able to prepare for them. To keep the patient alive, immediate measures or medication are often necessary.

Medical research is a prerequisite for maintaining good clinical care and improving it further. Before new medicines can be introduced into clinical practice, their effectiveness and safety should be tested in research settings. Persons recruited into research studies should have the possibility to consent voluntarily or to refuse to participate, according to international conventions and declarations, such as the Nuremberg Code [1], The Declaration of Helsinki of the World Medical Association [2], International Ethical Guidelines for Biomedical Research Involving Human Subjects by CIOMS [3], and the Universal Declaration on Bioethics and Human Rights by UNESCO [4]. The Convention of Biomedicine of the Council of Europe (ETS 164) and its Additional Protocol on Medical Research (ETS 195) [5, 6], as well as Directive 20/2001/EU of Good Clinical Practice [7] set even more binding

provisions to the member states of the Council of Europe and European Union in the fields of biomedicine and clinical trials.

In emergency settings the patients themselves are often not able to consent to research if they are unconscious or in severe pain and therefore not able to evaluate independently and freely the benefits and risks of their participation. It is not always possible to get an authorization from the representative of the patient in emergency situations. Although the representative (often a family member) may be present in the emergency room, he or she may also be unable to give an authorization for research, i.e., receive information or evaluate risks or benefits. Asking the relatives to give written consent when they are distressed seems inhumane, especially in a situation where any delay may be harmful for the patient. While written consent is emphasized, it is sought even in these circumstances.

The requirements for informed consent are that the person is adequately informed, and that he or she understands the treatment or the procedures of the investigation procedure, its risks and benefits and consequences of participation in the research project. To fulfil the criteria of informed consent, the person needs to participate in the research voluntarily and without coercion. The signature of the patient or his/her representative in a patient information and consent form that has been previously accepted by an independent ethics committee is a prerequisite for the initiation of the study.

The Nuremberg Code

The strong emphasis on obtaining voluntary, informed consent in advance has its origins in a dark chapter in the history of medicine. Before and during the Second World War, lethal experiments were performed without the consent of research participants in many parts of the world. In the Nuremberg tribunal, 23 medical doctors were accused and 16 were convicted of crimes against humanity [8]. The Nuremberg Code, published as a part of the final document of the tribunal, emphasizes the voluntariness of the research participant to give an informed consent. This principle was mentioned first, and so it is considered the most important of all the requirements of medical research. According to the Nuremberg Code, the 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." To be able to give voluntary consent, the nature, duration, purpose of the experiment, methods, risks, and expected harms and benefits should be made known to the research participant. The researcher has the duty to tell this information to the research participant. The Code emphasizes the right of the research participant to withdraw consent at any stage of the research [1].

According to the Nuremberg Code the clinical trial has to meet other requirements also. The research needs to have scientific value, and the results cannot be achieved by other means, such as animal trials or cell cultures. Such

means should always precede human experimentation. Unnecessary suffering must be avoided, and expected benefits should always exceed risks. Researchers have to be sufficiently qualified to protect the rights and safety of the research participants during the trial [1].

The Nuremberg Code emphasizes the voluntary consent of the person, and therefore it cannot be applied directly to emergency research, although the principles of the Code do not necessarily conflict in an emergency. To do research also in these specific and exceptional situations, it has been necessary to devise new international rules that have been accepted internationally.

The Declaration of Helsinki [2]

The World Medical Association (WMA) was founded in 1948. One of the basic reasons for establishing the worldwide organisation of medical doctors was the Nuremberg trial and its consequences, i.e. the stigma and mistrust cast upon the medical profession as a whole. Soon after its foundation, WMA established the Committee on Medical Ethics, which started to form an international code of medical ethics concerning biomedical research. The Declaration that was agreed by national medical associations was signed at the WMA meeting in Helsinki in 1964. This Declaration has been revised five times, and discussion continues on the revisions of some of its articles [2].

The Helsinki Declaration stated that there are exceptional situations where informed consent cannot reasonably be obtained. In emergencies, according to the Declaration, there need to be other ways to ensure that research is performed in an acceptable way. The fact that the research is done without prior consent must be stated and reasoned in the protocol and approved as such by an independent review committee. Consent from a person should, however, be obtained from the individual or a legal representative as soon as possible.

The Helsinki Declaration, although binding on medical doctors only, has been widely accepted as an international document concerning medical research. It is a basis for national legislation and international conventions such as the Convention on Biomedicine of the Council of Europe, the CIOMS Guidelines on Biomedical Research and the UNESCO Declaration on Biomedicine.

The Convention on Human Rights and Biomedicine of the Council of Europe (ETS 164) and its Additional Protocol on Biomedical Research (ETS 195) [5, 6]

The Convention on Human Rights and Biomedicine (ETS 164) [5] and its Additional Protocol on Biomedical Research (ETS 195) [6] are the first and, as of now, the only binding international instruments concerning biomedical research. The member states of the Council of Europe that have signed and ratified the Convention are bound to respect its provisions.

The general rule for biomedical research trials is that the research participant him/herself must give free and informed consent for participation in the trial.

Additionally, there must be no alternative of comparable effectiveness to the research, the possible risks must be proportionate to the potential benefits, and a competent body and ethics committee must approve the research.

If the person concerned cannot give an informed consent, one may ask for authorization from his/her representative. The requirements for the authorization are similar to those for the consent of the research participant [5].

If research is done on persons not able to consent, it must meet further criteria. The results of the research must have the potential to produce real and direct benefit to the health of the research participant, the research must not be carried out if research of comparable effectiveness may be carried out on individuals capable of giving consent, and the necessary authorization must be given specifically and in writing. If potential direct benefit is not expected, the research should entail only minimal risk and minimal burden for the patient.

Article 8 of the convention lays out provision for emergency situations. If, because of an emergency situation, consent cannot be obtained, medically necessary intervention may be carried out for the benefit of the health of the individual concerned. However, any previously expressed wishes of the patient must be taken into account (Article 9). These articles can be interpreted also concerning medical research in emergencies.

According to the additional protocol on Biomedical Research (ETS 195), national law shall determine whether research can be done in emergency settings without prior consent or authorization. The research that is done must be approved for emergency situations. Consent or authorization for continued participation shall be requested as soon as possible, when the research participant recovers adequately to give his/her consent, or the legal representative can give the authorization or the consent on behalf of the research participant [6].

As of May 2007, twenty counties have ratified the Convention on Biomedicine, and fourteen additional countries have signed it. Four member states have ratified the Additional Protocol on Biomedical Research. Several member states of the Council of Europe that have not signed or ratified the convention are on the way of amending their legislation according to the provisions set up in the Convention.

Other International Instruments

CIOMS Guidelines on Biomedical Research [3] and the UNESCO Declaration on Biomedicine [4] state also that biomedical research in emergency situations must fulfil all of the requirements for research, and it must be designed and approved by an ethics committee exclusively for an emergency setting. Any waiver of informed consent must always be regarded as uncommon and exceptional, and these exceptions can be done only in accordance with the conditions and requirements set down by law. The research conducted on emergency patients is expected to bring direct benefit for the person concerned, and the expected benefit should be so significant that consent or authorization can be waived. Ethics Committees as well as the researcher must evaluate carefully if the urgency in the initiation of research makes it necessary to waive consent [3, 4].

The EU Directive on Clinical Trials (20/2001/EU) [7]

The directive of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (20/2001/EU) set up conditions for medicinal trials conducted in the European Union member states. While this directive was being prepared, debate on the provisions was intensive. The European Parliament made several amendments that made the interpretation of the directive, if possible, even more challenging. Special attention was drawn to and special conditions set up for minors and those not able to give consent. According to the Directive, research can only be done with a prior written, dated and signed informed consent or authorization of the research participant or his/her legal representative. This legal representative has to be defined by existing national law and may include natural or legal persons, an authority and/or a body provided for by national law [7].

In many countries a *legal representative* is a family member, e.g. in the case of minors, their parents or other guardians. A legal guardian, very often for guarding economical benefits, can also be nominated. If not specifically mentioned, these guardians have no authority to make decisions on the health or other personal issues of the patient. On the other hand, even if the patient cannot take responsibility for economic issues, he or she may be able to give consent on medical interventions, at least in part, or to name a person, a family member or a close friend that could make such decisions for him or her. This ability can be taken into consideration also when consent is sought for research.

In emergencies, this kind of legal representative may not, however, be available, or may be unable for other reasons (e.g., shock or trauma) to grant voluntary consent for research. Therefore, clinical trials cannot be performed in emergency settings in countries where the EU directive for clinical trials has been implemented. From 2004 on, clinical trials in emergency situations have practically ceased in EU member states.

In 2006, Denmark amended the law concerning clinical trials. This amendment states that, in emergency situations, a legal representative may be a unit of two doctors who are independent of the research project. This unit needs to consider the interest of the person concerned, estimate if more direct benefit than harm can be expected for the person not able to consent, evaluate that the trial is of significant worth, and after consideration give authorization for the research. The research protocol must be approved in an ethics committee as an emergency trial, and consent or authorization must be sought as soon as possible [9].

The Clinical Trials Directive emphasized children as an example of a specific patient group entitled to good care and better treatment possibilities. At the time the Directive was discussed in European countries and the European Parliament, about 50–90% of medicines used in paediatric hospitals had not been approved for use in children since the medicine had not been properly tested in these age groups [10]. Only five percent or less of clinical trials were conducted on children. When medicine has not been approved for use in children, the doses, safety and efficacy of the medicine may be questioned or thought unwarranted, and industry may not have

sufficient interest in developing optimal pharmaceutical forms for children. The Commission of Europe dealt with this problem in broad international discussions and approved a new Commission Directive [11] to promote medicinal trials conducted on children in member states. In this directive, the Commission sets the conditions by which new medicines may be studied for the benefit of children and specifies the kinds of benefits research sponsors or the institutions carrying out the research may get and the ways in which studies may be directed. This Commission Directive came into force in January 2007 [12]. Whether Europe follows the development seen in the United States [13], where the number of medicinal trials conducted on children has increased [14], and whether more medicines will be approved for children of different ages and in different clinical conditions in the future, remains to be seen.

Still, the children in the most urgent need of new medicines are newborns in neonatal intensive care. Up to 90% of their medicines have not been studied properly in research settings. Research in neonatal intensive care conditions has even more situational complexity: often the only person present and able to grant consent is the father, who is not necessarily the legal guardian of the neonate (e.g., if the parents are not married). Giving adequate information about the research and preparing for consenting before the child is born could be used in situations where a very premature birth is expected. However, many other clinical conditions may arise suddenly without predictive signs, preventing parents from being adequately informed or prepared.

Impact of International Instruments on Clinical Trials on Emergency Medicine

International declarations have certainly improved trust in medical research after the shocking revelations of the unauthorized, unethical and inhuman research trials that were conducted before and during the Second World War. Since then declarations have formed a strong ethical basis for more binding conventions and national legislation. Although every country does not have legislation on biomedical research or on clinical trials, international instruments set standards for the medical profession and also for the publication of research. For example, scientific journals have made prior evaluation by an independent ethics committee a necessary requirement for the publication of the results of research on humans. Ethics committees evaluate research trials according to the provisions set up initially in these international instruments.

Although international instruments, guidelines and more binding instruments improve the quality of clinical research, they may reduce research activity, especially in areas where ethical principles conflict. The more detailed the articles, the more they can also affect the research activity. This may lead to treatments that are not adequately evaluated, and to less optimized clinical care. Clinical trials in emergency settings have practically ceased in European Union countries since 2004, when the Clinical Trials Directive 2001/20/EC came into force.

All of the international instruments emphasize the autonomy of the research participants. In emergency settings, it is difficult to determine whether the person has previously expressed any wishes about participation in medical research. Such a wish, if known, must be respected. How to obtain this information remains problematic.

Conclusion

Research conducted on persons not able to give consent must always be an exception and must receive special attention. It is difficult to ultimately judge if the subjects participating in emergency research would have freely chosen to do so, whether for their own benefit or for the benefit of others in the same clinical condition. Only few patients entering emerging rooms have expressed their prior wish to participate or not participate in clinical emergency trials. There must be strong arguments for conducting such research, for example, the expectation of a significant benefit for research participants or of the research resulting in an improved medicine or better clinical care for the specific condition. Without adequate research in settings where new treatment is compared with the best-proven treatment, patients and patient groups do not get better medicines or treatments. While biomedical research is the only way to develop better treatments and care for patients, should it be more an obligation to help cure, care and reduce the suffering of these patient groups as much as we can?

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