

Deferred proxy consent in emergency critical care research: Ethically valid and practically feasible

Tim C. Jansen, MD; Erwin J. O. Kompanje, PhD; Jan Bakker, MD, PhD

Important ethical aspects apply to the process of obtaining consent in emergency critical care research: the incapacity of almost all patients for giving informed consent and the emergency and life-threatening nature of the conditions involved, resulting in short therapeutic time frames. We argue that deferred proxy consent is the preferable substitute for informed patient consent in emergency critical care research. However, researchers can face two problems when using this consent procedure. First, can proxies give a valid judgment for consent or refusal in the acute phase of the life-threatening illness of their relative, and second, what should researchers do with already obtained data when study procedures are finished (e.g., because the patient has

died) before proxies can be informed and consent be sought? We propose approaching the relatives with information about the trial and asking them for consent only if it is ethically valid to do so. The first psychological distress may prohibit a complete understanding of the information, which is necessary for a true and valid informed proxy consent. In addition, we recommend using the study data if study procedures are finished before proxies can be informed and consent be sought, provided sufficient privacy measures have been applied. (Crit Care Med 2009; 37[Suppl.]: S65–S68)

KEY WORDS: proxy consent; informed consent; ethics; study design; methodology

The need for medical research programs involving critically ill patients is real and profound. However, involving this patient category in observational or interventional trials raises ethical, juridical, and practical concerns. Clinical trials in emergency and critical care settings frequently involve patients with acute catastrophic injuries or life-threatening illnesses causing loss of decision-making capacity and, given the emergency nature of the conditions, facing (very) short therapeutic time frames. Examples are hemorrhagic shock, septic shock, cardiac arrest, subarachnoid hemorrhage, trauma, and traumatic brain injury.

All clinical trials are subject to the ethical and juridical principles of good clinical practice and international and national regulations. The guiding ethical principles underlying clinical trials are respect for autonomy of the subject, protection against discomfort, harm, risk

and exploitation, and the prospect of potential benefit.

Informed consent in emergency critical care research can, given the emergency nature and severity of the condition or due to pharmacologic sedation, seldom be obtained from patients themselves. Delaying acute experimental treatment to obtain informed patient or proxy consent might jeopardize the trial results. Several solutions are in use for obtaining consent in emergency situations. Proxies (legal representatives) or an independent physician can give consent before inclusion in research, or (patient or proxy) consent can be deferred for some time, or consent can even be waived. The prospect of benefit can even be complicated by the equipoise underpinning the statistical null hypothesis of pharmacologic trials: the hope that an individual patient will benefit, being evenly certain as the chance of no benefit.

In this article, we will argue that using deferred proxy consent is the preferable substitute for informed patient consent in emergency critical care research. We will address two problems, which researchers can face when using deferred proxy consent. First, can proxies give a valid judgment for consent or refusal in the acute phase of the life-threatening illness of their relative? Second, what should researchers do with already obtained data when study procedures are

finished (e.g., because the patient has died) before proxies can be informed and consent be sought? We propose some recommendations regarding these two dilemmas.

The Concept of Proxy Consent

Most ethical committees in European countries consider consent by legal representatives valid. The moral basis for such proxy consent is restricted to the substituted judgment about inclusion into the trial. Theoretically, the proxy is supposed to act as the patient, if competent, would have decided. The question remains if the patient wants to be represented by relatives for inclusion in a trial. Roupie et al (1) found that only 41% of 1089 patients would want their spouse/partner to be their surrogate, whereas 28% wanted to be represented by the physician in charge of their care. Furthermore, many proxies do not seem to know what the patient's wishes are (2). For instance, Coppolino and Ackerson (3) concluded that surrogate decision makers for critical care research resulted in false-positive consent rates in up to 20%. In the study by Sulmasy et al (4), agreement between patients and proxies varied between 57% and 81%, depending on whether previous discussions had taken place on similar situations. It is unlikely that such existential discussions occur frequently in the target population, re-

From the Department of Intensive Care, Erasmus MC University Medical Center Rotterdam, Rotterdam, The Netherlands.

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For information regarding this article, E-mail: e.j.o.kompanje@erasmusmc.nl

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sulting in lack of evidence what their relative would have wanted in case of severe illness.

The Concept of Deferred (Proxy) Consent in Emergency Critical Care Research

Proxies are not always available in the first hours of hospital or intensive care admission or are too overwhelmed to understand the provided information to give a valid consent. This prompted investigators and ethical committees to use deferred proxy consent and waiver of consent in emergency critical care research facing short therapeutic windows. With deferred (proxy) consent, patients are included in the research without prior consent. After inclusion, the patient (deferred patient consent) or his/her representatives (deferred proxy consent) should be informed as soon as possible and subsequent consent should be requested. With waiver of consent, consent is waived at all. Emergency research without prior consent (deferred consent or waiver of consent) can be accepted morally on the principles of fairness, justice, and beneficence. Furthermore, the requirement for all patients to give written informed (proxy) consent before enrollment can result in a significant selection biases, such that research populations are not representative of the typical patient (5). A study searching for public views on emergency exception to informed consent found that 49% of 530 people believed that enrolling patients without prior consent in an emergency situation would be acceptable and 70% would not object to being entered into such a study without providing prospective informed consent (6).

The implementation of waiver or deferred consent strategies was successful in terms of enrollment rates and therapeutic windows: the adoption of waiver of consent in the National Acute Brain Injury Study—Hypothermia resulted in a higher enrollment and reduced the time between injury and treatment (7). In this study, relatives of only 11 of 113 patients arrived within 6 hrs of the injury. In the Corticosteroid Randomization After Significant Head Injury trial, mean time to randomization was significantly longer and patient recruitment higher in those hospitals where consent was required compared with those where it was not required (8). In a septic shock trial, the investigators could not contact the prox-

ies within the inclusion time in 74% of the cases, and these were included under waiver of consent (9).

Dilemma 1: Are Proxies Competent Enough During the Acute Phase of a Sudden and Unexpected Emergency Situation?

The emotional nature of an emergency situation has been shown to limit the reliability of proxy consent for clinical research (2, 10, 11). In addition, only 48% of 79 representatives of European Brain Injury Consortium-associated neurotrauma centers in 19 European countries felt that relatives could make a balanced decision in an emergency situation (12). Also in our own experience, the validity of informed consent and proxy consent given in an emergency situation is at least troubling. Therefore, under emergency circumstances, proxy consent does not always seem to secure proper patient/subject protection.

The process of obtaining consent for inclusion in an emergency critical care trial contains three phases. First, information about the trial is provided. Second, the investigator asks the proxies for consent. Third, the proxies give consent or refusal. However, when consent for clinical research is sought during an emergency situation, comprehension is generally less than optimal (13–16). Patients enter intensive care in physiologic crisis, whereas their families enter the intensive care in a psychological crisis (17). Admission to intensive care triggers a variety of emotional and psychological responses in the relatives that often manifest in the form of distress, anxiety, anger, guilt, and fear. Such responses can impede the ability of family members to exercise effective coping strategies (18). In many cases, relatives are so distressed or overwhelmed in the first chaotic phase of admission of their loved one that they cannot fully understand the information provided during the acute phase; at least their understanding is selective. They have a need for information about the diagnosis and prognosis (19), but most probably have no interest in the pros and cons of inclusion into a clinical trial. Uncertainty as to whether the patient will survive has a profound influence on the relative's reactions, actions, and strategies (20).

Decision-making competence is based on factual understanding, evidencing a choice (consent or refusal), and reason-

ing and appreciation of the situation. We argue that some family members in emotional distress are temporarily incompetent in these three points. Hence, relatives of a patient who is in a life-threatening situation can be temporarily incompetent for valid proxy consent during the acute phase.

Dilemma 2: What if Study Procedures are Finished Before Proxies Can be Informed and Consent be Sought? Use the Data or Not?

Clinicians and investigators may encounter another important practical and ethical problem when enrolling patients in a study under deferred (proxy) consent: should the researcher use the study data if study procedures are already finished before it was possible to inform proxies and ask consent? This includes the situation in which the patient has died early.

A Recently Finished Clinical Trial as an Example. The clinical importance of this dilemma is illustrated by the enrollment process of a recently completed Dutch multicentered, randomized controlled trial: early lactate-directed therapy in the intensive care unit—study (<http://www.clinicaltrials.gov/ct/show/NCT00270673?order=1>). In this clinical trial using deferred consent, which was approved by the local Ethics Committee referring to the Dutch revised “Medical Research in Human Subjects Act” (21), approximately 10% of the randomized patients died before consent could be sought (22), in comparison with an estimated overall study mortality rate of 40%. In another 5% of the enrolled patients, it was not possible to inform proxies and ask consent within the period of study procedures (72 hrs from randomization).

Ethical Considerations. The question is whether the arguments in favor of not using data are outweighed by the following arguments in favor of using data, which can be particularly important in the specific situation that a patient has died. First, not using these data will probably introduce selection bias, make randomization arms asymmetrical, and jeopardize trial results. Furthermore, the intention-to-treat principle implies that the primary analysis should include all randomized subjects (23). Second, the validity of proxy consent obtained from bereaved relatives can be ethically ques-

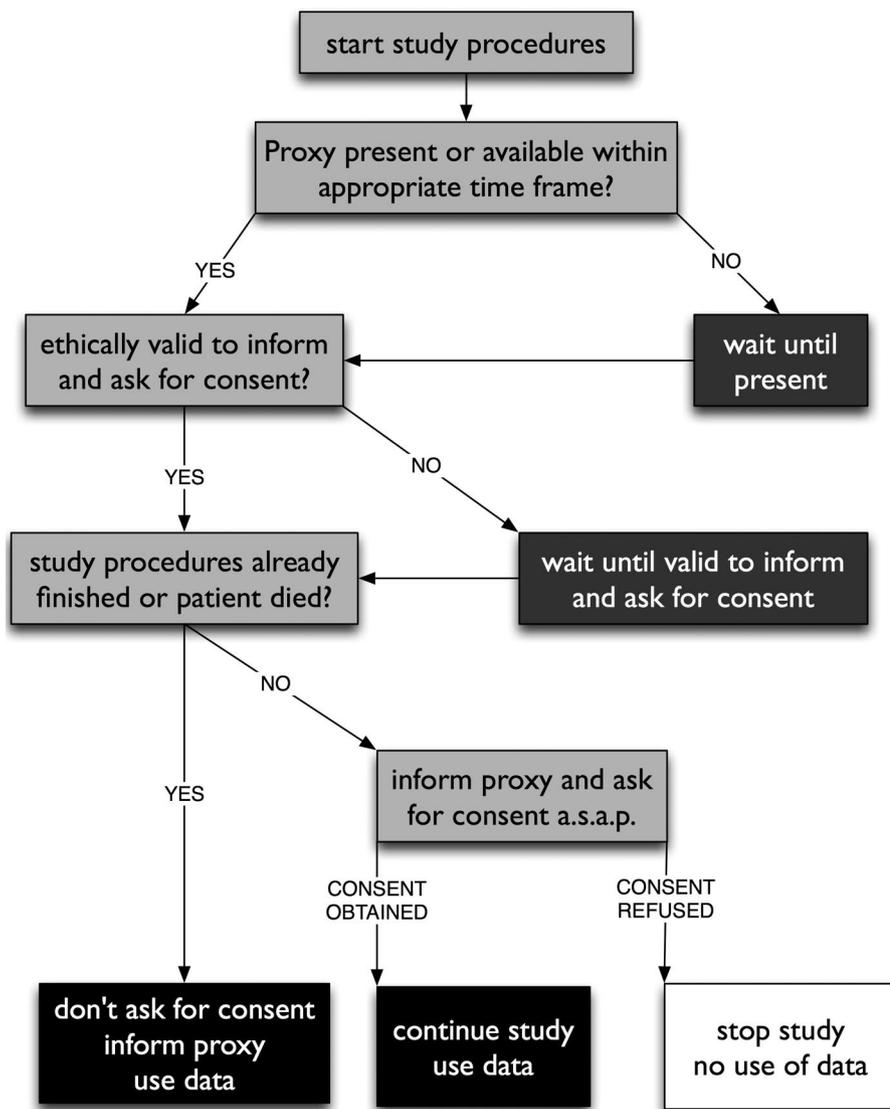


Figure 1. Proposed flow chart for use of proxy-deferred consent in emergency critical care research. We recommend this flow chart if 1) the emergency nature of the disease prevents *a priori* obtaining of informed consent and 2) patients are mentally incapacitated.

tioned. As already mentioned in dilemma 1, the risk exists that consent by relatives in emergency intensive care unit situations reflects rather a regimen of bureaucracy (consent is required, we need a signature), than true ethical concern (by obtaining consent the relatives act in the patient interest); how then can we value consent in the tragic situation in which the patient has died? Third, very few patients or relatives refuse consent for the use of already obtained data in emergency situations (22, 24–26). Furthermore, using data will not harm the patient or relatives, provided that appropriate confidentiality and privacy measures have been applied. Fourth, jeopardizing studies by not using data might harm future patients and society. Degrading a study in

this fashion also devalues the contribution made by subjects who do consent to take part in the study, which is an ethically undesirable consequence. Although this premise probably cannot provide an argument for including data when research subjects expressly deny consent, it does make an ethically valid case for including data where such explicit denial of consent does not exist. Fifth, since confronting bereaved relatives represents additional burden, which healthcare providers have the duty to relieve or prevent, it seems morally correct to adopt policies that prevent seeking consent from proxies after their relatives have died. Sixth, the individual's decision about the privacy of their medical information (whether made by the individual him/

herself or his/her proxy) is not absolutely binding if the processing is necessary and proportionate for “the protection of health” (Article 8 of the European Convention on Human Rights), if sufficient safeguards apply (EU Data Protection Directive), or if it is necessary and proportionate for the goals of medical research (UK Data Protection Act 1998). In a recent publication, (22) to prevent unauthorized use of this exception of the obligation to obtain consent, we proposed a time limit for the exception of 72 hrs (after start of study procedures). Only if a patient should die after this period and consent is not yet obtained, should data not be used.

Back to our Example. The Central Committee on Research Involving Human Subjects (CCMO, the Dutch national Ethics Committee) was asked for a judgment on the use of already obtained data from patients who died before consent could be sought. The Committee stated that this situation is comparable with the situation in which the research project has already been finished at the time that deferred consent can be sought. They judged that in such cases relatives should be notified about the research project (in line with the responsibility of a good healthcare provider), but that seeking consent was not useful anymore because of the lack of consequences. The proposed time limit of 72 hrs, as proposed in our recent publication (22), was unnecessary in view of this committee, as the representation of the patient by a relative ends when the patient dies. In these circumstances, family members also lose control over the patient files. In the Dutch law, the consent of the patient or his relatives primarily relates to the participation in the study and not to the use of the data collected in the study.

Recommendations

We propose approaching the relatives with information about the trial and asking them for consent only if it is ethically valid to do so. The first psychological distress may prohibit a complete understanding of the information, which is necessary for true and valid informed proxy consent. In addition, we recommend using the study data if study procedures are finished (including the situation in which a patient has died) before proxies can be informed and consent be sought, provided sufficient privacy measures have been applied. Using these two

recommendations, we have constructed a flow chart for the conduct of emergency critical care research in an ethically valid and practically feasible way (Fig. 1).

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