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Deferred consent in emergency intensive care research: what if the patient dies early? Use the data or not?

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Introduction

Respect for individual autonomy, expressed in the concept of informed consent, is the basic ethical principle in research with humans. Many ICU patients are unable to give consent as a consequence of mental incapacity, and this can be further complicated in emergency situations, in which treatment needs to be initiated without delay. Various approaches are used as surrogate to subject consent: waiver of consent, consent by an independent physician and deferred consent. Deferred consent involves randomization at the investigator's discretion according to criteria that have been explicit during ethical review of the protocol, followed by the request for patient's (deferred subject consent) or representative's (deferred proxy consent) informed consent in a later phase. Several emergency trials have used deferred consent [1, 2, 3, 4].

During the enrolment process in an ongoing Dutch multi-centre randomized controlled trial using deferred consent the situation arose that no deferred (subject or proxy) consent was obtained from patients who died early after start of the study. Should data of these patients be used or not? In this article we analyse this practical and ethical problem.

The "Early Lactate-Directed Therapy on the ICU" study as an example

To evaluate the efficacy of early lactate-directed therapy two of the authors (T.C.J., J.B.) are currently conducting a multi-centre trial. Patients eligible for inclusion are randomly allocated to either 8 h of early lactate-directed therapy or control group therapy. Since early timing of goal-directed therapy is essential [5, 6], patients are randomized immediately after the first available lactate level, resulting in a very short inclusion time window. The Ethics Committee approved the use of deferred consent, referring to the Dutch revised "Medical Research in Human Subjects Act" [7]. Study procedures are temporarily undertaken without consent, and, as soon as possible, written consent from the patient or legal representative is sought.

Until December 2006 we had collected data from 115 patients (Fig. 1). In 11.7% of cases (13/111) consent could not be obtained due to early death (< 72 h, before relatives could be approached). Given the predicted sample size of 350 patients, not using data of these patients would result in an additional requirement of 41 patients. In 2.7% of cases (3/111) relatives could not be identified, or contact was lost. In 2.7% (3/111) relatives refused

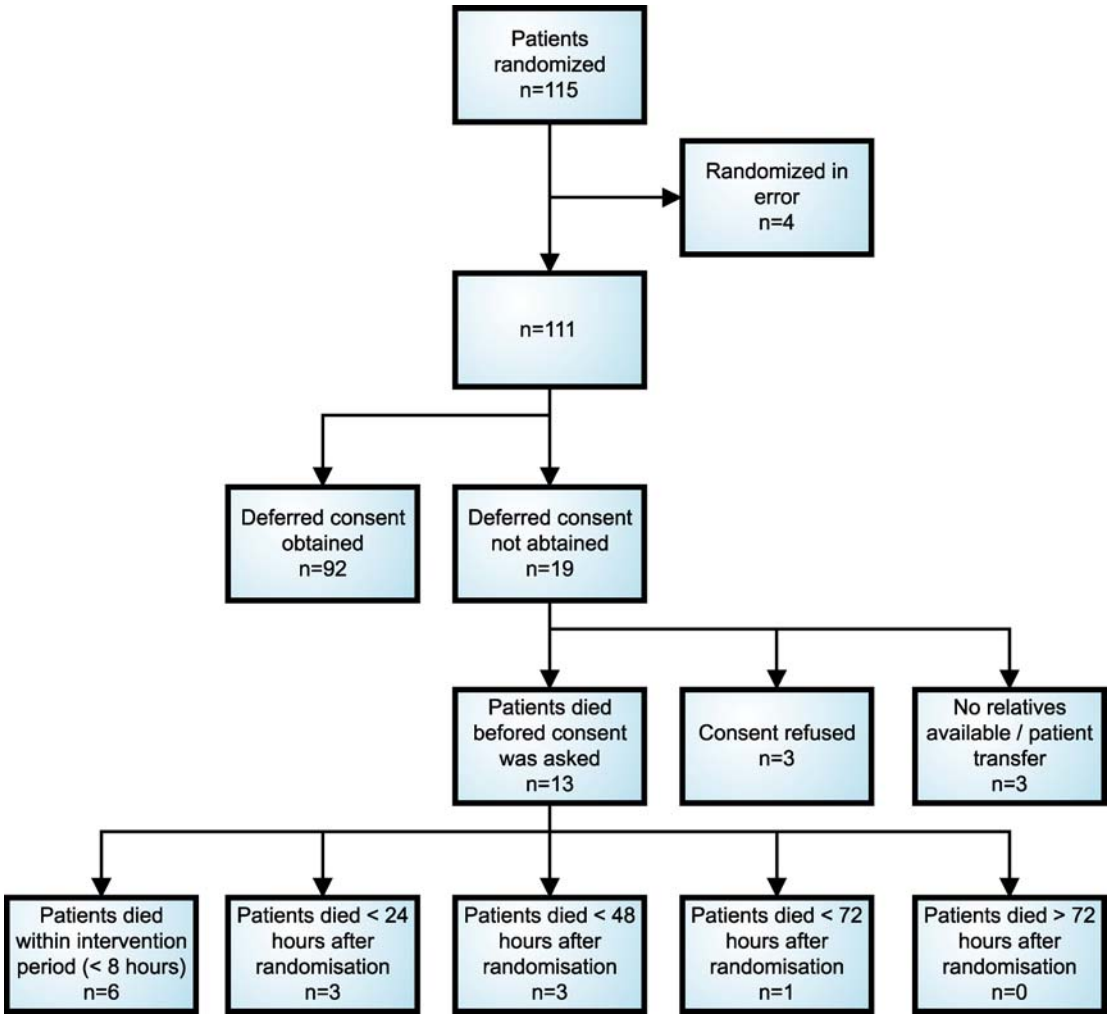

Fig. 1 Flow-chart of the process of deferred consent in enrolled patients in the "Early Lactate-Directed Therapy on the ICU" study (February–December 2006)

consent, and these patients were withdrawn from analysis. Median randomization-to-consent time was 1 day ($n = 92$, interquartile range 0–3 days).

The Ethics Committee of the coordinating centre was asked for a judgement on the use of already obtained data of patients who died before consent could be sought. Our proposal to use the data was rejected.

Previous experience in patients who died before obtained deferred consent

Some emergency studies using deferred consent have reported the use of data from patients who died early. In the PAC-man trial using deferred consent [2] consent was sought from patients who regained consciousness (deferred subject consent), regardless of whether relative's assent was obtained earlier. It was stated that "if the patient's died without regaining mental competency, the patient's data were included in the trial analysis" [8]. Fifty percent (249/500) of the patients died with obtained relative's assent (not consent) but without obtained subject deferred consent. Nine percent (45/500) died with neither relative's assent nor subject deferred consent. Data of these patients were included in the analysis. In another trial 74% of patients (220/300) were included under deferred consent [1] and were asked consent as soon as possible. This was done only in survivors, suggesting that if patients died before regaining consciousness, data were used [9]. As overall 28-day mortality was high (58%), a substantial part of the data were probably analysed without consent. In another trial [4], diligent attempts to contact the relative were made and an independent physician was consulted before it was deemed necessary to waive consent. If attempts to contact relatives continued to be unsuccessful, or if the patient died before relatives could be contacted, the institutional review board was notified, and data were used. Summarizing, in these studies [1, 2, 4], data were

used if the patient died before deferred consent was obtained, and reasonable efforts were made to obtain permission from a patient representative.

Ethical considerations

Guiding ethical principles for medical research are respect for patient autonomy, protection against discomfort, risk, harm and exploitation and the prospect of benefit. Taking our lactate study as point of departure for analysis, some questions remain:

Why is deferred consent necessary?

For optimal respect of patient's autonomy, seeking consent before study participation is preferable. Principle 1 of the Nuremberg Code states that the primary consideration in research is the subject's voluntary consent, which is "absolutely essential" (Military Tribunal, 1947, United States vs. Karl Brandt, "Trials of war criminals before the Nuremberg Military Tribunals under control counsil law no. 10: the medical case"). Unfortunately, in emergency ICU research this is often not possible, as illustrated by the PAC-man trial in which only 2.6% of patients could consent before starting the study [8]. Emergency research represents an exceptional situation in which the mechanisms of the consent process may need to be modified, but the social contract between researcher and research subject must be respected in order to provide a safeguard against unethical research. Despite the importance of the subject's voluntary consent or its various surrogate procedures, the question remains as to whether arguments in favour of *not using* data, are outweighed by the following arguments in favour of *using* data in such extraordinary case when patients die early and deferred consent would have to be sought from bereaved proxies.

Is proxy consent valid in emergency situations?

Uncertainty exists whether a substituted judgement on what a patient would have decided would concur with the patient's preferences. Some have shown that most patients confirmed the judgement made earlier by the relatives [8]. However, surrogate decision making for critical care research resulted in false-positive consent rates of 16–20% [10, 11]; a recent review showed overall inaccuracy of 32% [12]. The validity of proxy consent may be further reduced in emergency situations. Overwhelming emotions may decrease validity. Most proxies seem to make decisions based on what they hope will happen (benefit of therapy), not taking in consideration what is a real prospect (possible non-benefit and research-related burden) [13]. It is of ethical and fundamental concern that relatives cannot make balanced decisions in this period of uncertainty. If the risk exists that consent by relatives in emergency ICU situations reflects more a regime of bureaucracy (consent is required, we need a signature), rather than true ethical concern (by obtaining consent the relatives act in the patients interests) [14], how can we value consent in the tragic situation in which the patient has died?

Do we harm the patients by using the obtained data?

Can we estimate how many patients or relatives would refuse the use of data obtained in acute situations without consent? Two studies evaluating emergency therapies [15, 16] used waiver of consent with subsequent written notification. Survival hospital-discharge rates were 8% (43/538) and 17% (14/82). Only 0.4% (2/538) and 0% (0/82) were withdrawn at relatives request after written notification [17]. In the PAC-man trial 3.3% of survivors (6/181) refused consent [8]. In our lactate study 2.7% (3/111) of patients or relatives refused study participation after randomization. It seems that very few patients or relatives refuse consent for using already obtained data in emergency situations. Do we harm patient's interests by using data without consent? The data in our lactate-study, consisting of regular data as survival, consumption of health care resources, laboratory values and haemodynamics data, are patient-identifiable only by the principal investigator. Given privacy-respecting handling of data and thorough confidentiality, patient's interests are not harmed by using the data.

Would we introduce selection bias by not using the data?

Patients who die early are the most severely ill (100% mortality) and excluding them can reduce external validity, jeopardize the balance between study arms and influence the effect of the intervention as this may differ in patients who die early than in survivors or those who die later. The intention-to-treat principle, recommended in the ICH E9 [18], implies that the primary analysis should include all randomized subjects. Compliance with this principle would require complete follow-up of all subjects for study outcomes. Not using study data of patients who died early would thus hamper the intention-to-treat principle. Although the Registry of the Canadian Stroke Network used a different consent procedure than our study, it does show that important selection biases can be found if many patients died or left the hospital before they could be approached for consent [19]. The in-hospital mortality rate was much lower among enrolled patients (6.9%) than among those eligible for study participations but not enrolled (21.7%). Hence study patients were no longer representative of typical stroke patients. Other studies

showed that absolute requirements to obtain consent have led to selection biases in retrospective studies based on chart review [20, 21] and decreased enrolment in registries [22]. These concerns probably apply equally to the critical care/emergency medicine context, but additional data in this area would be useful. After completion of our lactate study we plan to compare study results including or excluding data from patients who died before deferred consent could be obtained. By doing this the hypothesis posed in this article will be tested, that not using these data will introduce selection bias, make randomization arms asymmetrical and jeopardize trial results.

Do future patients benefit from the obtained data?

Clinical research plays an important role in obtaining knowledge for improvement in therapy, patient safety and progress in medicine. Future patients will benefit from critical care research results of today. If data obtained in emergency ICU situations without consent cannot be used, and selection bias is thus introduced, study results may be ruined and future patients be harmed. 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. While this premise 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. Notwithstanding this discussion it should not be forgotten that the society's interests in medical progress may never overrule potential burden and risks for patients, as enshrined in the Nuremburg Code [23].

What is the burden for the relatives?

Health care providers have a prima facie duty to relieve and prevent suffering (harm, burden) of patients, their relatives and society. Confronting relatives again with the event that their loved one died on the ICU can be seen as harm or burden. Concerning our lactate study, the local Ethics Committee acknowledged this psychological burden. If we can say that confronting bereaved relatives represents additional burden, which we have the duty to relieve or prevent, it seems morally correct to adopt policies that prevent seeking deferred consent from proxy's after their relatives death. Extending the time period of seeking consent could theoretically reduce the burden. However, obtaining written consent a long time after the patient has died can be impractical (telephone consent is not allowed and it is questionable whether the agreeing relative will take effort to reply a request for written consent), and, more importantly, actively approaching relatives for seeking consent in a "fatal medical research case" would still be a real burden for the relatives.

Is the individual's (or proxy's) decision about the privacy of their medical information binding?

The individual's decision (whether made by the individual him/herself or his/her proxy) is not absolutely binding. In certain situations it is permissible to use personal information even though the individual has not allowed it. This point is supported by principles in ethics and law: (a) Article 8 of the European Convention on Human Rights permits personal information to be used without consent (even if the individual expressly objects) if the processing is necessary and proportionate for "the protection of health". This is generally understood to include some medical research projects. Additionally (b), the European Union Data Protection Directive allows member states to adopt laws which allow personal data to be processed for scientific purposes without consent provided sufficient safeguards apply. Lastly (c), the United Kingdom Data Protection Act of 1998 permits such processing if it is necessary and proportionate for the goals of medical research. Although there is little case law, the courts would likely consider the following factors when deciding whether the twin principles of necessity and proportionality have been met include: the practicality of seeking consent (or proxy consent), the importance of answering the research question, alternative ways of answering this question, the degree of anonymization of the data, the practicality of discarding individuals' data, the implications of discarding the data (selection bias) and the degree of distress caused to the individual or proxy by ignoring their wishes.

Deferring consent: how long do circumstances continue to prevent the giving of consent?

In the lactate trial study procedures were allowed for as long circumstances continue to prevent the giving of consent [7]. The local Ethics Committee interprets such a circumstance as physical absence of the patient's relative arguing that, as soon as relatives arrive, this circumstance is no longer valid, and hence consent should immediately be sought. Given that seeking proxy consent in emergency conditions is questionably valid (see "Is proxy consent valid in emergency situations?"), and it is a burden for the relatives to consent for their dead relative (see "What is the burden for the relatives?"), it could be seen in a way that in fact the circumstance continues that prevents the giving of consent.

To prevent investigators' abuse of this ongoing circumstance a time limit for seeking consent could be suggested. In a conducted survey among investigators active in

the field of traumatic brain injury, opinions concerning the most appropriate time for requesting proxy deferred consent, were investigated (Fig. 2). Peak preferences of time limits were "less than 24 h" and "no limit". Adding the percentages, 68% (12% +8% +29% +19%) of the respondents believed that deferred consent should be asked within 72 h after starting the study, while 32% (1% +26% +5%) felt that the time limit should be longer than 72 h (or even that consent was not at all required) [14].

Comparison with other countries in the European Union

The United Kingdom has recently introduced legislative and regulatory provision for emergency research. In principle, these provisions allow for proxy and deferred consent, and are included in the Mental Capacity Act 2005 (http://www.opsi.gov.uk/acts/acts2005/20050009.htm) and an amendment (http://www.opsi.gov.uk/si/si2006/20062984.htm) to the UK Clinical Trials regulations.

Italian implementation of the European Clinical Trial Directive 2001/20/EC enables enrolment of incapacitated patients in clinical trials, and deferred consent is required according to the ethics committee's approval [24].

In Austrian law, which allows proxy consent in the case of mental incapacity, there is a special provision regarding "emergency" situations in which inclusion of a patient can take place without proxy consent. The time period of the emergency is not considered as long as it takes to appoint a legal representative, but as long as the *specific* emergency is a medical emergency. If the patient regains the ability to consent, he/she is to inform without delay and to ask consent for further participation. Participation of such patients must be with the prospect of a potential direct benefit, "which exceeds the risks". Thus the prospect of any kind of group benefit is not enough. If the presumed patient's will is known and documented, this must be respected. Additionally, the public on the research site must be informed about the clinical trial (e. g. by notice on a notice-board at the hospital or on a web-site).

The issue of whether data from patients who have died can be used without formal authorization from patients or representatives is addressed in neither the Dutch, British, Italian and Austrian legislation. In the UK researchers have generally relied on interpretation of the provisions of the Data Protection Act 1998 (http://ico-cms.amaze.co.uk/documentUploads/use and disclosure of health data.pdf) to legitimize such data use. The UK also allows the use of an independent physician's consent in restricted circumstances, which would indeed be very useful when judging whether or not sufficient care has been taken to seek consent otherwise (i. e. prior to death), before using data without relatives' agreement.

Synthesis

Dutch regulatory bodies have ruled that if the patient dies shortly after randomization, and consent could not yet be obtained, this forms no reason to abandon the requirement to obtain deferred consent to use the data.

It is our conviction that the obligation to obtain consent should be respected as thoroughly as possible. However, (a) the validity of proxy consent obtained during emergency situations can be ethically questioned; (b) using data of patients who died and for whom deferred consent was not yet obtained will not harm the patient or relatives (pro-

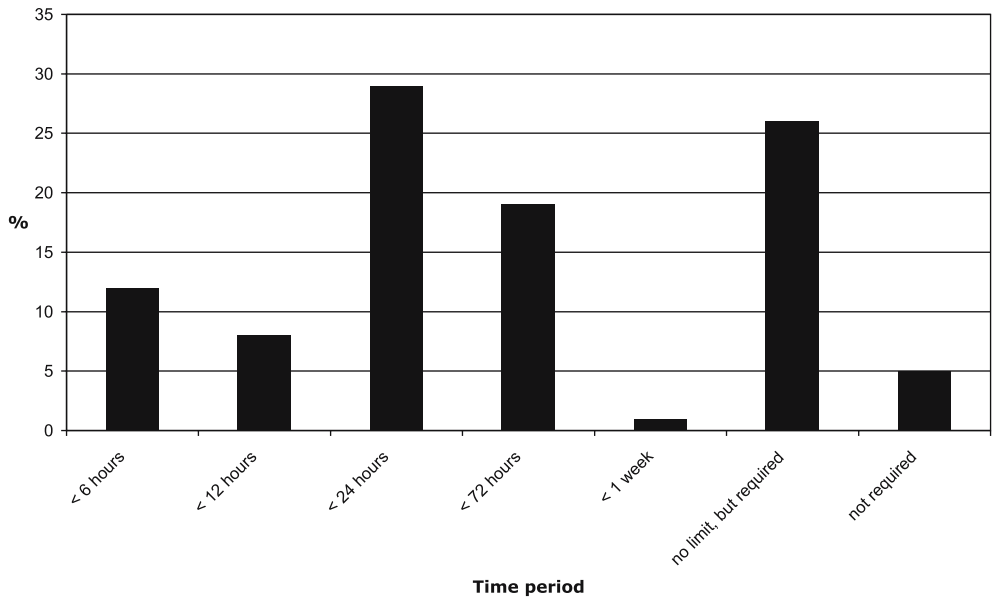

Fig. 2 Survey among investigators active in the field of traumatic brain injury. Within which time period should proxy deferred consent be obtained or information provided? ($n = 77$) [14]

vided that appropriate confidentiality and privacy measures have been applied); (c) not using data will probably introduce selection bias; (d) using data will benefit future patients and society; (e) confronting bereaved relatives to obtain consent is an additional burden; and (f) an individual's decision about the privacy of their medical information is not absolutely binding. We therefore think that it is inappropriate to enforce a strict rule that deferred consent must be obtained from bereaved relatives of deceased patients.

Recommendations

In studies that use deferred consent, data should be used if the patient dies before written (subject or proxy) consent can be sought. To prevent unauthorized use of this exception of the obligation to obtain consent, we do, however, recommend a time limit for the exception of 72 h (after start of study procedures). Only if a patient dies after this period and consent is not yet obtained, should data not be used. If national legislation (e. g. in the UK) allows the use of independent physician's consent, consent to use the data should be sought in this way. If not, as a sign of respect for patient autonomy, we plea for a written notification send to the patients' general practitioner and to relatives after the early mourning phase in cases where data are being used for study analyses despite the lack of deferred consent [17]. Reports on all non-survivors without obtained consent should, in addition, be sent to the local ethics committees.

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