

Legislation hampers medical research in acute situations

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ABSTRACT

INTRODUCTION: Informed consent in incapacitated adults is permitted in the form of proxy consent by both the patients' closest relative (next of kin, NOK) and general practitioner (GP). In research in acute situations not involving pharmaceuticals, Danish legislation allows for randomisation and subsequent proxy consent, as soon as possible. The aim of this study was to describe the delay associated with obtaining consent and to assess whether consent from NOK or GP/Danish Health and Medicines Authority is obtained with delays beyond the intervention.

METHODS: In a prospective study, 171 comatose out-of-hospital cardiac arrest (OHCA) patients were randomised to targeted temperature management. Patients were randomised before NOK could be informed, and proxy consent was obtained as soon as possible. Written consent from NOK and GP were our study data.

RESULTS: We obtained all legally required consent: 169 cases of consent were obtained from NOK, two patients gave consent before NOK, in no cases was consent denied by the proxy. Consent from NOK was obtained with a median delay of zero days (interquartile range (IQR): 0-1, max. 128 days). Delay from NOK consent to GP consent was a median nine days (IQR: 6-23, max. 527 days).

CONCLUSION: NOK fully accepted participation in a clinical trial after OHCA with short delays in consent. Consent from GPs was associated with long delays beyond the intervention, which make GPs less appropriate for proxy consent of incapacitated adults in acute situations. The Ethics Committees' approval of the trial justified by their competence and authority, combined with the NOK's insight into the patient's wishes may be a relevant and feasible alternative to the current consent procedure.

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Short-term survival after out-of-hospital cardiac arrest (OHCA) is approximately 10% [1, 2]. Guidelines on resuscitation in cardiac arrest are predominantly based on case series and expert opinion [3]. Very few randomised clinical trials have been performed, some of which have

questioned current treatment guidelines [1, 4]. Research in acute situations is challenging because of time constraints and the fact that acutely ill patients are often incapacitated and thus unable to provide informed consent for participation in research.

The Danish National (DNSEC) and Regional (RSEC) Scientific Ethical Committees [5, 6] comprise an independent system established through legislation by the Danish Parliament. By the Act on Research Ethics Review of Health Research Projects [6], regulated by the DNSEC and the RSEC, it is possible to include patients in trials in acute situations not involving pharmaceuticals prior to informed consent, as long as proxy consent is obtained as soon as possible. Proxy consent is defined as consent from the closest relative (next of kin, NOK) and by the patient's general practitioner (GP) or the Danish Health and Medicines Authority (DHMA) in Denmark [6]. We aimed to describe the delay associated with obtaining proxy consent in research in acute situations and to assess whether consent from NOK or GP/NBH is obtained with delays that extend beyond the intervention and whether the delays may introduce a risk of selection bias.

METHODS

The present study was based on the consent forms from 171 Danish participants in a multicentre clinical trial investigating the optimal treatment strategy for temperature management in postcardiac arrest care [7, 8]. In brief, the Target Temperature Management (TTM) trial was a randomised clinical trial in comatose patients resuscitated from OHCA, which showed no benefit with regards to mortality and neurological outcome, of targeting the traditional 33 °C versus 36 °C. The treatment intervention lasted for 24 hours. Patients eligible for the trial were comatose and therefore unable to provide informed consent.

The TTM-trial was classified as research in acute situations by the RSEC due to the urgent nature of TTM after OHCA; thus, randomisation and trial-intervention could be initiated before informed or proxy consent was obtained. The patient's NOK was informed of the patient's condition, treatment plan and given verbal and written information regarding the trial immediately after

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their arrival at the hospital. It was emphasised verbally and in writing that participation in the trial was voluntary, and if the NOK declined to provide consent the patient would receive treatment according to current guidelines outside the trial-protocol. If the NOK needed time and further information to consider consent, the investigator made it clear that the patient would continue treatment according to randomisation, unless the NOK decided not to consent to the inclusion.

Subsequently, consent from the patient's GP was requested: The consent form with the NOK's signature, a stamped self-addressed envelope, a summary of the trial and contact information of the investigator were sent to the GP. An initial telephone call was always attempted and consent forms could also be sent by fax. Reminders were sent by mail and telephone reminders were also used.

If the patient had no GP or the GP was unavailable, consent was requested from the DHMA. Patients were asked for informed consent when neurological function allowed written informed consent.

We used the standardised consent forms created by the DNSEC: S8 (incapacitated adults) and S4 (capacitated persons) [9].

Data used in the present study included: date of OHCA, date of consent from NOK, GP and from the DHMA, date of consent from the patient, age and gender of the patient, and NOK's relation to the patient.

Data are presented as means \pm standard deviation

or medians with interquartile range (IQR) and range if data were non-Gaussian distributed. Differences in time delay were tested between groups by log rank tests and illustrated by percentages of lacking and obtained consent 3, 7 and 14 days after OHCA to NOK consent and NOK consent to GP/NBH consent. A p-value < 0.05 was considered statistically significant. The primary outcome was delay from OHCA to NOK consent and delay from NOK to GP/DHMA consent.

Trial registrations: not relevant.

RESULTS

The study population included 149 males (87%) and 22 (13%) females with a mean age of 62 ± 11 years, (range: 24-94 years). OHCA occurred on weekdays in 125 cases (73%) (Table 1).

The continued inclusion and thereby verbal acceptance of the intervention allocated by randomisation was obtained by information of NOK in all patients. NOK provided written consent in 169 (99%) cases. The remaining two patients fully recovered, six and 17 days post OHCA, and gave informed consent prior to NOK, making proxy consent irrelevant. The relation between the patient and NOK can be seen in Table 1. The GP/DHMA gave consent in 141 cases (GP: 138 (81%), DHMA: 3 (2%)). The remaining 30 patients consented after neurological recovery before the GP had returned consent.

Delays in consent

The median delay from OHCA to written consent from NOK was zero days, IQR: 0-1, (range: 0-128) (Table 1). Seven (4%) cases of 169 NOK consent were obtained after day 3 (Figure 1). No significant difference in delay to NOK consent was found when the population was stratified by median age of the patients or when OHCA occurred during weekends. The median delay from consent by NOK to GP/DHMA consent was nine days, IQR: 6-23, (range: 1-527 days). The majority of cases of GP/DHMA consent (94%) were obtained more than three days after consent from NOK and only one signed consent form was received within the time period of the trial intervention. No GPs or NOK refused to consent, but the DHMA refused to take a stance in one case, in which consent was obtained from a GP who was well acquainted with the patient.

All legally required cases of consent for inclusion were obtained and no patients were excluded due to missing consent.

DISCUSSION

Obtaining consent from NOK as the first of the two parts of proxy consent seems feasible with 96% being obtained by day 3 after OHCA. The consent from the GP or

TABLE 1

Baseline characteristics and delays in proxy consent for the 171 patients included in the Target Temperature Management Trial.

<i>Included patients, n = 171</i>	
Age, yrs, median (IQR)	63 (54-69)
Males, n (%)	149 (87)
OHCA in weekdays, n (%)	125 (73 exp. 71)
<i>NOK consent (n = 169)</i>	
Delay, days, median (IQR), max.	0 (0-1), 128
<i>NOK relation, n (%) (n = 169)</i>	
Spouse/former spouse/cohabiter	118 (69)
Parent	6 (4)
Offspring	33 (19)
Sibling	7 (4)
Friend/acquainted/niece	4 (2)
Professional	1 (= 1)
<i>GP consent (n = 138)</i>	
Delay, days, median (IQR), max.	9 (6-23), 527
<i>DHMA consent (n = 3)</i>	
Delay, days, median (range)	114 (18-273)

DHMA = The Danish Health and Medicines Authority; GP = general practitioner; IQR = interquartile range; NOK = next of kin (i.e. nearest relative); OHCA = out-of-hospital cardiac arrest.

the DHMA is challenging and may take > 1 year to obtain, with 35% of all cases of requested consent still lacking 14 days after NOK consent. This suggests that the GP/DHMA may not be an ideal part of the proxy consent for research in acute situations in incapacitated patients.

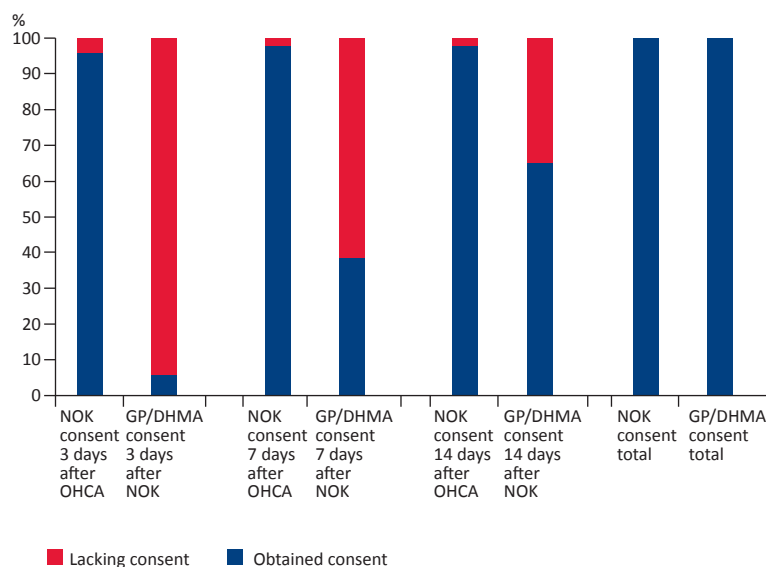
When including incapacitated patients in research studies and thereby being unable to respect the patient's autonomy, it is imperative that the interest of first the patient and next the general public is protected. This is addressed in the Declaration of Geneva [10] "The health of my patient will be my first consideration" and the Declaration of Helsinki [11] "Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation". This is in line with the first paragraph in the Danish Act on Research Ethics Review of Health Research Projects [6]: "Consideration for the rights, safety and well-being of trial subjects come before scientific and social interests in the possibilities of gaining new knowledge or investigating existing knowledge that may justify the undertaking of a research project". History has shown the purpose and scope of the act to be not only ethically correct, but also an essential part of the legislation to prevent unethical scientific studies [12]. With this in mind, the findings of the present study show some of the practical disadvantages associated with trying to meet the current legislative requirements.

These results challenge the relevance of the GP as part of the proxy consent. The legislation expects frequent reminders by mail or telephone, but it is unknown whether repeated reminders facilitate obtaining of the consent or will result in more GPs declining consent. Introducing a fee for the GP is not an option within the European Union (EU) as per the Directive 2001/20/EC of The European Parliament article 5d [13] regarding implementation of good clinical practice in the conduct of clinical trials.

The GP's role as part of the proxy consent is also challenged by the fact that GPs' perception of their patients' health beliefs seem to differ significantly from patients' actual beliefs [14], and the GP cannot be held legally responsible for giving their part of the consent, documented in Chapter 3, Section 4, Part 5 [6]. "Complaint against a general practitioner's proxy consent cannot be put to the National Agency for Patients' Rights and Complaints ...". Thus, the GP has the option to decline an inclusion while, on the other hand, has no legal responsibility consenting to the inclusion on behalf of the patient. The role of the DHMA in proxy consent may be limited since the strict interpretation of the accept-

FIGURE 1

Percentages of lacking and obtained consent three, seven and 14 days after out-of-hospital cardiac arrest from the nearest relative and from nearest relatives' consent to consent from the general practitioner or the Danish Health and Medicines Authority, respectively. All legally required cases of consent were obtained.



DHMA = The Danish Health and Medicines Authority; GP = general practitioner; NOK = next of kin (i.e. nearest relative); OHCA = out-of-hospital cardiac arrest.

able time delays in providing the proxy consent is difficult to meet if the GP is unavailable.

In practice, the GP/DHMA consent is obtained far later than the randomised treatment intervention. This is in contrast to the NOK consent; NOKs are informed within a reasonable time from randomisation, allowing for decline of consent to result in an actual change in treatment strategy. The ethical committees expressed purpose is as follows: "it is the responsibility of the committee system on health research ethics to ensure that from a research ethical point of view, health research projects are carried out in a responsible manner, and that the rights, safety and wellbeing of trial subjects participating in such biomedical research projects are protected, while at the same time possibilities are being created for the development of new, valuable knowledge" [5]. The combination of the professional and ethical competence and authority of the ethics committees, combined with NOK's personal insight into the patient's health wishes seems like a relevant, feasible and adequate alternative to the current proxy consent. Such a solution complies with the EU legislation, which requires the subject's legal representative (to be defined by the individual member country) to give consent [13].

Under the current legislation, patients who remain incapacitated in the acute phase of a trial will have a lower chance of being included in studies, which intro-

Evidence-based treatment is lacking in acute situations. When including incapacitated patients in acute research in Denmark, consent from the patient's general practitioner is required as an adjunct to consent from the nearest relative. This introduces a significant delay and may give rise to bias. We propose that the ethical committees approval of the trial combined with the nearest relatives personal insight of the patient's health wishes may be a more relevant, feasible and adequate alternative to the current consent process and this would be in line with EU legislation. Illustration: Claudi Clausen and Milos Fuglsang.



duces a significant source of bias, and may significantly affect the results of the trial. This is illustrated by Jansen et al, who demonstrated a beneficial effect on mortality of early intensive care guided by blood lactate levels, which became non-significant when excluding patients from whom proxy consent could not be obtained [15]. This example suggests that the validity of an entire trial is jeopardised when the likelihood of inclusion by proxy consent depends on the patients' survival. Such a source of bias should be minimised in the public's best interest.

Within the Danish legislation, other solutions apply for minors and persons under guardianship: "1: Proxy consent on behalf of trial subjects that are minors must be given by the holder of custody. 2: Proxy consent on behalf of trial subjects under guardianship that includes powers to give informed consent for participation in health research projects, cf. the Guardianship Act Section 5, must be given by the guardian" [6]. This means that no adjunct in the form of consent from GP/DHMA is required. It seems illogic that the legislation distinguishes between acutely incapacitated patients and more chronically "incapacitated" persons under guardianship, since the ethical considerations are virtually identical.

Norway and Sweden allow for inclusion of incapacitated patients, under certain circumstances, without any adjunct to consent from the closest relative as long as the trial is accepted by their respective ethical committee [16, 17]. Informed consent may be waived in the USA, although efforts to contact the legal representative should be made [18].

Limitations

While the presented data demonstrate that the GP/DHMA part of the consent process provides no additional protection of the trial subjects' integrity, the author group is not completely unbiased as they are all involved in research in acute situations. And the legislation did not cause selection bias in the present study, as a persistent effort to obtain the delayed consent was provided. Consent by trial guardians involving doctors with no relation to the trial, in addition to NOK and GP/DHMA, is required in acute research involving pharmaceuticals [6]. This solution is, however, not without challenges, as one could doubt that a well-considered decision can be made to consent on behalf of an unknown subject in a trial investigating, e.g., epinephrine administration during a cardiac arrest setting, and the doctors would often have a professional relation to the trial investigators, which invites possible bias. A 24-hour telephone consent duty by the DHMA could be a solution, though it is the authors' opinion that this provides no additional protection to a thorough approval process of the trial by the ethical committees.

CONCLUSION

When including incapacitated patients in clinical trials, proxy consent is needed and the current legislation requires GP/DHMA consent as an adjunct to the consent from NOK. We have demonstrated that GP/DHMA consent introduces a significant delay in the consent process and a potential source of bias. The legislation regarding studies on incapacitated patients must respect the patient's rights; however, the combination of the ethical committees' approval of the trial, justified by their professional and ethical competence and authority, combined with the NOK's personal insight into the patient's health wishes may be a more relevant, feasible and adequate alternative to the current proxy consent process and would be in line with EU legislation.

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