RESEARCH ETHICS

What determines whether patients are willing to participate in resuscitation studies requiring exception from informed consent?

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Objectives: To examine the willingness of patients to participate in a resuscitation study that requires exception from informed consent and to determine if willingness to participate is associated with demographic and other characteristics.
Methods: Adult patients in an emergency department and in a geriatric outpatient clinic were surveyed. Patients were asked to imagine that they presented to an emergency department with cardiac arrest and asked about their willingness to (1) receive a new drug outside of a study, (2) receive a new drug as part of a study and (3) participate in a randomised controlled trial (RCT) for a new drug. Patients were also asked about participation in studies of invasive procedures.
Results: 213 patients from a geriatric clinic and 207 from an emergency department were surveyed. Two thirds of patients from the geriatric clinic and 83% from the emergency department were willing to receive an experimental drug outside of a study. Patients were less willing to participate in a study of the new drug and even less likely to participate in an RCT for the new drug (χ^2 test for trend, $p<0.001$ for both settings). Patients were less likely to participate in a study of thoracotomy than in a study that required placement of a femoral catheter ($p=0.008$ for the geriatric clinic, $p=0.01$ for the emergency department). Willingness to participate was not associated with trust in the doctors.
Conclusions: Study design and invasiveness of the intervention were associated with the willingness of patients to participate in resuscitation studies that require exception from informed consent.

Research on new treatments for cardiopulmonary arrest (CPA) is challenging, controversial and necessary. The critical nature of the illness requires immediate treatment. Yet, the patients are unconscious and cannot provide informed consent, one of the major protections required for ethical human research outlined in the *Belmont Report*. This leads to a dilemma: although protecting human subjects is of vital importance, there is a compelling need for research on treatments for CPA. Despite some public misperceptions, most available treatments for CPA are either ineffective or unproved. Survival after CPA is no higher than 25%, except in specialised circumstances.[1]

In 1996, the US Food and Drug Administration (FDA) issued a regulation known as the Final Rule. The purpose of the Final Rule was to permit CPA research while protecting human subjects.[2] The rule allows CPA research to be conducted without consent in limited circumstances. According to the rule, the research must occur in a life-threatening disease state, when available treatments are unproved or unsatisfactory. In addition, the investigator must show that consent is not feasible because of the patient's condition and the short therapeutic window of the intervention. A potential for benefit to the patient must exist, with a reasonable level of risk. Additional requirements prevail for community consultation and public notification.[3 4] These provisions outline the emergency exception to the requirement for informed consent.

The Final Rule was based on the proceedings of a consensus conference, with input from scientists, lawyers, ethicists and federal regulators. There was, however, little input from the general public or, even more importantly, from patients who may one day be candidates for enrolment in resuscitation trials.[3 5 6] Two relevant published surveys[5 6] of patients in the emergency department suggested that patients vary considerably in their support for waivers of informed consent, their willingness to forgo consent to advance the cause of science and their desire to participate in a clinical trial in the event of CPA.[5 6] More information about the attitudes and values of patients regarding participation in research on resuscitation is necessary to inform and guide physician-scientists, institutional review boards and federal regulators.[7]

Although much has been written about the ethical and scientific framework of emergency waivers of informed consent, little information is available about values of patients. Patients may vary in their willingness to be enrolled in a research trial. They will differ in their perceptions of the potential risks and benefits, their trust in medical professionals, their altruism and their attitudes towards human experimentation.[8] To learn more about patients' attitudes towards informed consent and enrolment in resuscitation research trials, we surveyed patients in an urban emergency department and in a geriatric clinic. The purpose of the study was twofold: firstly, to measure the willingness of patients to participate in a hypothetical resuscitation trial without informed consent and, secondly, to determine whether willingness to participate without consent was associated with demographic characteristics, health status, religious beliefs, experimental study design or trust in doctors.

METHODS

Study design and setting

This survey was carried out in an urban, university-associated emergency department and a geriatric clinic. The emergency department has approximately 40 000 visits a year. The

Abbreviations: CPA, cardiopulmonary arrest; FDA, Food and Drug Administration; RCT, randomised controlled trial

geriatric clinic is a primary care site for patients aged ⩾75 years, and those aged ⩾65 years who have complex medical conditions. In both clinical sites, a convenience sample of patients was surveyed. In the emergency department, patients with critical illnesses, intoxication, dementia or language barriers were excluded. Verbal consent was obtained from all patients, and this study was deemed exempt from ongoing review by our local institutional review committee.

Survey development and administration

Survey questions were written, reviewed and reworded to improve clarity and face validity. The questions were pilot tested in the geriatric clinic and refined to improve clarity for this subpopulation. Research assistants who had undergone an orientation and training programme carried out the surveys. Each research assistant had carried out at least two surveys under the supervision of one of the authors. The research assistants were provided with scripts for each question. They were instructed to provide no additional information and were given explicit instructions on the wording used to clarify questions raised by the respondents.

Survey questions

To define and explain the prognosis of cardiac arrest, the research assistant read the following statement to all patients during a face-to-face interview:

> I'd like you to imagine you've been brought to the emergency room with a severe heart attack. You are in cardiac arrest, which means that your heart and breathing have stopped. The usual treatments, like CPR, electric shocks and medications, have not worked. You now have a less than 1% chance of surviving.

To measure the effect of study design, research assistants then read three scenarios. For each scenario, the experimental design of a hypothetical research study was changed. Patients were asked to express their willingness to receive the treatment or participate in the study. The first statement measured the willingness of patients to receive an unproved experimental drug, without giving consent, if the doctor ''thought it might help you''. The second statement asked whether patients would participate in a research study in which they would get a new drug, again without providing informed consent. The third statement measured the willingness of patients to participate in a randomised, placebo-controlled study (RCT), comparing a standard drug with a new drug without providing informed consent. The box shows the wording of each statement.

After completing the questions that measured the effect of study design, we asked two additional questions to measure the effect of the invasiveness of the intervention. Each patient was told, ''Doctors may also want to test the effectiveness of surgical procedures to treat cardiac arrest.'' Patients were then re-read a scenario describing that they were brought to an emergency department in cardiac arrest and had a less than 1% chance of survival. After the scenario, they were asked to rate their agreement with the following statements: (1) ''The doctor should be allowed to test a less invasive operation, without getting my permission, like putting a large IV [intravenous] line into a vein in my thigh, in order to put me on heart bypass or hook up special monitors'' and (2) ''The doctor should be allowed to test a more invasive operation, without getting my permission, like cutting my chest open to directly pump my heart with his hand.''

The following demographic data were recorded: age, race, sex, education, marital status and religion. Patients were asked to rate their health status (poor, fair, good, very good or excellent), whether they lived alone, their religion, how often they attend church services, whether they had prepared an advance directive and whether they make their own medical decisions. In addition, patients were asked if they would support a programme that would allow patients' wishes for participation in research studies to be designated on a card or bracelet, similar to the system for organ donation. Finally, to measure their trust in doctors, patients were asked to rate their agreement with the following statement: ''If I came to the emergency room unconscious, I would trust the doctors there to do what is best for me.''

Study questions used to measure the effect of study design on the willingness of patients to participate

- Statement 1: The doctor in the emergency room wants to use a new, experimental medicine, because he hopes it might help you. But no one knows if the new medicine will actually work for you. Please tell me how much you agree or disagree with the following statement: ''I would want to receive the new, experimental medicine.''
- Statement 2: Currently, when doctors want to test a new medicine on a patient, they have to explain the study, describe the possible risks and benefits, and ask for their patient's permission. Doctors are not allowed to enter patients into the study without the patient's permission. But in this case, you are so sick that you can't even speak, none of your family or friends is with you, and the doctor has no time to contact them. The doctor in the emergency room wants to give you a new, experimental medicine as part of a study, because he hopes it might help you. The hospital research committee has approved the study of this new medicine. But no one knows if it will actually help you survive. Please tell me how much you agree or disagree with the following statement: ''The doctor should be allowed to give me the new, experimental medicine to me as part of a research study, without getting my permission.''
- Statement 3: Now, I'll ask what you think about what is called a randomised study. This study is done to compare new treatments to standard treatments. In this kind of study, there is a 50–50 chance that you will get the new, experimental medicine, and a 50–50 chance that you will get the usual medicine. The doctor has no say in which one you will get. It's just up to chance, like tossing a coin. Again, please imagine that you have been brought to the emergency room and your heart and breathing have stopped. You are unconscious, and have a less than 1% chance of surviving. The doctor wants to enter you into a randomised study of a new, experimental medicine. This means you may or may not get the new, experimental medicine. Please tell me how much you agree or disagree with this next statement: ''The doctor should be allowed to enter me into a randomised study of the new medicine, without getting my permission.''

Measurements

Agreement was measured using a 4-point Likert scale (1, strongly agree; 2, agree; 3, disagree; 4, strongly disagree). To

facilitate data presentation and analysis, the responses were collapsed into two categories (agree or disagree). Education was categorised as ''did not complete high school'', ''high-school graduate'' or ''college graduate''. Self-reported health status was categorised as ''less than good'' (rated fair or poor) or ''good'' (good, very good or excellent). Patients reported themselves as Protestant, Catholic, Jewish, other or atheist, or as having no preference; and their church attendance as weekly or greater, monthly or less than monthly.

Data collection and analysis

We estimated that 80% of patients would agree to participate in a research trial dealing with exception from consent. To achieve adequate precision around this estimate (95% confidence interval (CI) +5% to −5%), we calculated that 200 respondents would be needed.

Data from the emergency department and geriatric clinic were analysed separately. Mean, range and SD were calculated for age of the patient. Categorical data and all survey responses were summarised using proportions and 95% CI. Proportions were compared using the χ^2 test and trends were measured using the χ^2 test for trend. Relative rates (with 95% CI) were calculated to compare willingness to participate in an RCT across demographic groups. When more than two groups were compared, the largest group was used as the referent.

RESULTS

Respondents

In all, 213 patients were interviewed in the geriatric clinic and 207 in the ED. Twenty five patients in the geriatric clinic did not make their own medical decisions and were excluded from the analysis. All 207 patients surveyed in the emergency department made their own medical decisions. Geriatric surveys were carried out between January and June 2002, and emergency department surveys between June and August 2004.

Table 1 shows the characteristics of the patient population. Most patients in the emergency department and geriatric clinic were women and non-Hispanic white people. Most had at least a high-school education, although patients surveyed from the emergency department were four times as likely to not have graduated from high school. In both groups, more than 90% of patients trusted doctors to ''do what's best for me'' in case of CPA.

Table 1 Characteristics of survey respondents in each setting

	Geriatric clinic	Emergency department
Mean age, years (SD)	74 (8)	41 (16)
Sex, male	62/175 (35)	98/206 (46)
Ethnicity		
White	146/172 (85)	136/207 (66)
Black	15/172 (9)	38/207 (18)
Hispanic	5/172 (3)	18/207 (9)
Other	6/172 (3)	15/207 (7)
Health status good	124/174 (71)	146/207 (71)
Marital status		
Married	71/147 (48)	69/207 (33)
Single/divorced	49/147 (33)	125/207 (60)
Widowed	27/147 (16)	13/207 (6)
Education		
Not completed high school	8/147 (5)	41/207 (20)
High school graduate	75/147 (51)	101/207 (48)
College graduate	64/147 (44)	58/207 (28)
Religion		
Protestant	83/143 (60)	83/207 (40)
Catholic	34/143 (24	37/207 (18)
Jewish	10/143 (7)	3/207 (2)
None	10/143 (7)	63/207 (30)
Other	6/143 (4)	21/207 (10)
Church attendance		
Weekly or more	73/152 (48)	46/207 (22)
Monthly	47/152 (31)	57/207 (28)
Less than monthly	32/152 (21)	104/207 (50)
Lives alone	58/148 (40)	64/206 (31)
Trust doctor to do what's best for me	128/141 (91)	188/193 (97)
Has an advance directive	104/147 (71)	42/207 (20)

Values in parentheses are percentages unless otherwise stated.

Effect of study design and invasiveness of intervention

Two thirds of patients surveyed in the geriatric clinic wanted a new experimental drug if they came to the emergency department with CPA and could not provide informed consent. An even higher fraction (83%) of patients in the emergency department wanted a new drug in the same circumstances (table 2). In both settings, the proportion of patients willing to participate in research without consent decreased as the study design became more rigorous. Fewer patients were willing to participate in a non-randomised, non-placebo-controlled research investigation on a new drug, and still fewer were willing to participate in an RCT in which, according to chance alone, they received either a standard treatment or the new treatment. Thus, the design of the study had a strong effect on willingness of patients to participate without consent in both settings ($\chi^2 = 11.6$, $p<0.001$ for the geriatric clinic; $\chi^2 = 10.6$, $p<0.001$ for the emergency department).

The invasiveness of the intervention was also strongly associated with willingness to participate in a study when informed consent was not possible. Patients in both settings were much less willing to participate in a study that involved a thoracotomy than in a study that involved placing a femoral catheter ($\chi^2 = 6.9$, $p = 0.008$ for the geriatric clinic; $\chi^2 = 6.4$, $p = 0.01$ for the emergency department).

Effect of patient characteristics and trust in the doctors

We tested for associations between the demographic and other characteristics of the patients (table 1) and willingness of patients to enrol in an RCT without consent. Patients in the geriatric clinic were less willing to participate in a trial than those in the emergency department (relative risk (RR) 0.7; 95% CI 0.6 to 0.8). In the emergency department, however, older patients (>65 years, which is the same age group surveyed in the geriatric clinic) were as willing as the younger ones to participate in an RCT (RR 1.1; 95% CI 0.8 to 1.5). In the geriatric clinic, men were more likely than women to agree to participate in an RCT (RR 1.4; 95% CI 1.0 to 1.9) and patients reporting good or excellent health were more willing to participate than those with fair or poor health (RR 1.7; 95% CI 1.0 to 2.9). Willingness to participate in RCTs was not associated with race, marital status, living situation, religion, church attendance, education, having an advance directive or trust in doctors. The relative risks were similar when these groups were compared for willingness to receive a new experimental drug ''that the doctor thought might help'' and for willingness to participate in a non-randomised, non-placebo-controlled trial for a new drug.

Finally, we found that most of the patients (82% in the geriatric clinic and 93% in the emergency department) would accept a system (eg, an identity card or bracelet) for identifying those who would be willing to participate in clinical studies on CPA.

DISCUSSION

Informed consent, which protects a patient's right to self-determination, is a fundamental tenet of clinical research.[8 3] Informed consent, however, cannot be obtained in case of CPA. We found that most respondents wanted to receive an

Table 2 Proportion of respondents who agreed to participate, by study design and study invasiveness

	Geriatric clinic	95% CI (%)	Emergency department	95% CI (%)
Receive a new drug	107/159 (67)	59 to 75	161/193 (83)	77 to 88
Study of new drug	90/153 (59)	51 to 67	156/193 (81)	76 to 86
Randomised controlled trial of drug	73/152 (48)	40 to 56	135/193 (70)	63 to 76
Place catheter	100/158 (63)	55 to 71	169/193 (88)	82 to 92
Thoracotomy	70/147 (48)	39 to 56	149/193 (77)	71 to 82

Values in parentheses are percentages.

experimental drug ''that might help [them]'' when their treatment was outside of a research protocol. They were less willing to be part of an organised research study, and even less interested in participating in an RCT. Patients' reluctance to forgo informed consent and to enrol in an RCT was not expected. It may reflect an aversion to being guinea pigs in an experiment, a mistrust of placebos or a reluctance to trust their fate to the flip of a coin. A patient involved in a research protocol that has been reviewed for scientific and ethical quality is more protected than the one who receives an unproved treatment at the discretion of a provider who believes that it may help. As most patients trusted their providers, our findings may reflect a distrust of the research process.

Many participants in this survey responded that they would enrol in an RCT without giving consent. They may have been motivated by a careful assessment of their risk of dying, a hope for cure, trust in the medical profession or an altruistic desire to advance science and improve medical care for others. Our study was not designed to measure all of these factors. All patients in this study, however, were told that their chance of survival was less than 1%. Furthermore, trust in doctors was more than 90% in both clinical settings. Despite a high level of trust and an awareness of their prognosis with current treatment, 30–52% of patients would not waive consent to participate in an organised RCT. In a thoughtful analysis of the US FDA's Final Rule, Adams wrote, ''In the final analysis, participation as a research subject must be considered an essentially altruistic act. The subject allows one's being to be used as a data source, contributing to the larger body of medical knowledge.''[8] Our study suggests that a consistently high level of altruism cannot be assumed.

Our study provides new data on the general wishes of patients in a hypothetical cardiac arrest situation. The study, however, does not change the underlying principles of ethics or law. Although the courts generally support the medical profession's research enterprise as both legitimate and necessary for medical progress, such experimentation cannot proceed unless informed consent is obtained. The overriding objectives of the doctrine of informed consent are to encourage rational decision making by patients and to protect their rights to autonomy and self-determination.[9] There is, of course, an inherent conflict between a patient's right to self-determination and the legitimate interests of physician-researchers. The results of the current study are disquieting, because they indicate that a large proportion of patients will opt out of a scientific study, even at the cost of medical progress. Patient autonomy, however, cannot be disregarded in the name of advancing medicine.[9]

The common tenets of biomedical ethics, which balance respect for autonomy, non-maleficence, beneficence and justice, provide little additional guidance. In the situation of refractory cardiac arrest, where survival approaches zero, experimentation may not help or harm the patient. Neither beneficence nor non-maleficence seems dominant. The principle of distributive justice, which requires that medical benefits be dispensed fairly, is also not directly applicable. Perhaps, in the dire scenario of cardiac arrest, healthcare professionals are given a greater right to conduct research, in the hope of helping others some day. Indeed, the goals of beneficence are often applied not only to a single patient but also to the good of society. It is, however, difficult to know whether that right to conduct scientific research can ever override the principle of patient autonomy, especially knowing that 45–70% of patients would choose not to participate in a clinical trial.

Two previous studies have considered willingness of patients to enter into research studies without consent in the case of CPA. Smithline and Gerstle[6] found that 73% of a sample of patients from the emergency department would waive consent if the risks of the intervention were minimal (eg, an extra blood draw), but the willingness to participate without consent dropped to 50% if the study involved a new drug. McClure *et al*[5] surveyed 530 patients and visitors in an urban emergency department waiting room and found that only 45% of respondents agreed it was acceptable to enrol critically ill patients without informed consent; yet, a much higher proportion (75%) personally agreed to enrol.

Despite more than 50 years of scientific study, resuscitation research is still in its infancy. Even today, it is a topic that is most distinguished by its promise. The slow pace, at least partly, is due to the practical, ethical and regulatory challenges that investigators face in designing and conducting randomised trials. Recent studies on hypothermia after cardiac arrest and several medical interventions for cardiac arrest have been conducted in Europe, Australia and Canada, and research in the US has decreased over the past decade, coincident after implementation of the FDA's Final Rule.[10] Recent developments in Europe may also complicate or limit future studies on resuscitation.[11] These guidelines are intended to fulfil the principle of respect for people by protecting vulnerable patients. The widespread implementation of more restrictive requirements, however, will further slow the implementation of useful treatments, a threat to the principle of beneficence, by denying these critically ill patients access to useful treatments.

If the results of the current study are replicated in other investigations, ethicists, regulators and physician-scientists may ask whether patient attitudes and preferences should dictate research design. For example, patients may be more accepting of clinical trials comparing new treatments with historic controls than of studies using concurrent controls and randomised treatment allocation. Such a paradigm shift would require patients to understand that non-randomised, historically controlled studies can produce biased results and actually slow the progress of research. In any case, as pointed out by Smithline and Gerstel,[6] ''…while referendum cannot be used as a substitute for appropriate ethical decision-making, concordance is eventually necessary.'' Ultimately, the objective is to allow scientific studies of new treatments for CPA to proceed, while protecting each patient's right to self-determination.

LIMITATIONS

Our study has several important limitations.

1. More than 10% of the patients in our geriatric sample did not respond to one or more of the questions. The attitudes of patients who refused to answer may differ from those of patients who did respond.
2. The survey was limited to a convenience sample of patients visiting a single emergency department and geriatric outpatient clinic. Our findings may not be applicable to other clinical settings, where demographic characteristics and health status are different.
3. The scenarios presented to our patients were hypothetical and the explanations offered to respondents were necessarily brief. The willingness of patients to participate in a research study without informed consent may be higher or lower after a longer, more detailed two-way conversation with a doctor.
4. The results may be biased by the face-to-face nature of the interviews. To please the interviewer, patients may overstate their willingness to waive consent or their trust in doctors.
5. We also did not ask patients whether their views would be different if the provisions of the FDA's emergency exception (including community consultation and notification) were implemented.

CONCLUSIONS

Our study found that study design and invasiveness of the intervention were both associated with the willingness of patients to participate in resuscitation research trials. Although most patients in the emergency department and geriatric clinic would want to receive an unproved, potentially helpful drug if they were in cardiac arrest, a much smaller proportion would participate in a randomised trial comparing a new drug with a placebo. Patients were also less willing to participate in studies that evaluated highly invasive interventions. Whereas patients in the geriatric clinic were less willing to participate in resuscitation studies that required exception from informed consent than those in the emergency department, we did not find a clear relationship between age or other characteristics of the patients and willingness to participate.

The results of this study suggest that patients are often not willing to participate in studies on new treatments for cardiac arrest that require exception from informed consent. Future studies need to determine why patients are reluctant. Patients may not understand that the current treatments for cardiac arrest offer very little chance of survival. If this is true, better education may increase the proportion of patients willing to participate. If other studies also, however, find a general reluctance in patients to being a ''guinea pig'', the principles of patient autonomy will require reconsideration of exception from informed consent for randomised controlled trials.

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