Attitudes of relatives of patients in intensive care and emergency departments to surrogate consent to research on incapacitated participants

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ABSTRACT

Background: When potential research participants are incapable of providing consent, it is common for clinicians and researchers to approach family members, attempting to ascertain that person's wishes. Where legally recognised, surrogate consent may also then be provided by relatives for therapy or research involvement. This practice is widely accepted as acknowledging and maintaining patient autonomy, yet there are few data on acceptability of this to the community, or on the accuracy of surrogate decisions.

Methods: We conducted a questionnaire-based survey of 283 people in the waiting rooms of the emergency and intensive care departments of a tertiary hospital in September 2006 to evaluate attitudes to critical care research, willingness to participate if incapacitated, and acceptability of surrogate consent in these circumstances.

Results: 283 people were approached with the questionnaire, with 185 people fully completing and returning them: 17% strongly indicated agreement to research participation if they were critically ill, with 25% indicating they would refuse. Only 26% of respondents thought it acceptable that a relative provide consent to research participation on their behalf. Demographic factors did not influence responses, but views of respondents that participation in research was beneficial to participants correlated with an increased willingness to participate themselves.

Conclusions: From our questionnaire, it appears that willingness to participate in research is less than we expected. Surrogate decision-making and the provision of surrogate consent to research was acceptable to only 26% of respondents.

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In Australia, the conduct of biomedical research involving humans is subject to guidelines issued by the National Health and Medical Research Council (NHMRC),[1] with proposed studies being prospectively reviewed by institutional human research ethics committees. Central to requirements for research approval is that voluntary informed consent is obtained from participants before their involvement. This requirement for consent is emphasised in ethical guidelines and regulations, acknowledging autonomy and voluntary participation. All persons have the right to be fully informed of their medical condition, to make decisions regarding courses of treatment or enrolment in research, so retaining some control over their own fate. Until proven otherwise all adults of sound mind are presumed competent to make such decisions, and no act may then be performed on a competent adult without their prior knowledge and agreement.

When patients or research participants are unconscious or otherwise unable to make decisions, efforts are made to establish what their wishes would be regarding treatment or research participation. This also respects individual autonomy, reflecting a desire not to perform acts against the will of the person, and complies with legal and ethical requirements. These efforts commonly involve discussion of medical information and options with the relatives or other close associates of the individual. From their knowledge of the incapacitated person's values, beliefs and personality, these "surrogates" then provide information or guidance by "substituted judgement", indicating the patient's wishes, and guiding treatment decisions and research participation.

Despite extensive discussion and published guidelines, areas of uncertainty remain as to correct conduct of human research, particularly when participants are incapable of decision-making. The agreement or consent of a "legally authorised" surrogate is recognised in many jurisdictions as an alternative to direct consent. Which persons are recognised as legally valid surrogate decision-makers, and what decisions are recognised, varies between jurisdictions. In Western Australia (WA), the *Guardianship and Administration Act 1990*[2] allows legal recognition of treatment decisions by a surrogate identified in a hierarchy provided within the Act. Guardianship legislation provides for surrogate consent on the premise that acts and decisions are made in the interests of the incapacitated person. There is no clear guidance on the provision of consent to research where participants may derive benefit but this benefit is not the direct motive for participation. The absence of law does not necessarily render research participation or surrogate

Box 1. Information provided to survey participants

Sir Charles Gairdner Hospital

Patient Information Sheet

A survey on attitudes to including unconscious people in research

The object of this questionnaire is to assess community opinion regarding people being enrolled in medical trials, when they are unable to consent due to being very unwell.

Patients often present to our hospital with severe illness, in either an unconscious or confused state. These patients are treated to the best of our abilities with therapies that have been proven to be of benefit.

From time to time new or alternative therapies appear that have been trialled in laboratories and show a potential to improve outcome. The only way to find out if these therapies do actually improve outcomes in humans is through clinical trials on humans.

While patients who participate in trials still receive the current best therapy we know is available — as do all our patients, in addition they may or may not receive a new treatment in a random manner. We do not know whether the patients will derive any benefit from the new treatment or they may suffer any as yet unknown side effect from this treatment under investigation. However, future patients will benefit from the knowledge we gain.

There is a problem with gaining consent to enrol people in these trials, as they are unconscious or confused and thus unable to provide consent. Time limits also often require the study to be started before being able to obtain consent from relatives of the patients.

(Completion of this questionnaire is totally voluntary, and your responses are entirely anonymous. Please answer all questions if willing to do so. It should take 5–10 minutes to complete.)

(The Sir Charles Gairdner Hospital Human Research Ethics Committee has given ethics approval for the conduct of this questionnaire. If you have any ethical concerns regarding the questionnaire you can contact the secretary of the Sir Charles Gairdner Hospital Human Research Ethics Committee on telephone no. (08) 93463528.) ◆

consent "unlawful", but indicates that the matter remains undecided.

Many conditions seen in emergency and intensive care medicine are associated with impaired cognition and decreased ability to make decisions. Increasing severity of disease has been observed to correlate with decreasing decision-making ability.[3] Capacity in critical illness may be further compromised by neurological disorders, sedation or analgesia. In addition, patients who are critically ill or in emergency situations are vulnerable — they may be in pain or distress from which they wish to be relieved; they may be frightened and facing mortality or disability; and they are in a dependent relationship with caregivers. In these circumstances, a person could be considered unable to carefully and rationally evaluate the risks and benefits of treatment alternatives, or to make an unbiased choice. It is questionable then whether even conscious critically ill patients have sufficient capacity to provide consent. Understanding the necessary distinction between research and therapy, and concepts such as randomisation and placebo administration may require even greater decision-making capacity when providing consent to research than in making treatment decisions.

Decision-making capacity can be impaired in other common conditions where research may be necessary. These include neuropsychiatric disorders and dementia,[4] ischaemic heart disease,[5] malignancy,[6] AIDS,[7] cerebrovascular disease, diabetes,[8,9] and alcohol and other substance abuse.[10] Progress in the understanding, diagnosis and treatment of disorders associated with impaired decision-making capacity necessitates clinical research involving human participants who have the studied disorder.

To accept substituted judgement and surrogate consent as means to respect and maintain participant autonomy, these must be validated as an alternative to direct participant consent. Firstly, it must be ascertained whether patients, relatives and the broader community consider the practice of substituted judgement acceptable — ie, the making of decisions on one's behalf when no longer able. Those making decisions on behalf of others must also be agreeable and have enough knowledge of a patient to make an accurate choice. Lastly, the accuracy of surrogate decisions should be evaluated. If decisions made by patients and their surrogates differ, then understanding these differences and the factors that contribute may allow development of mechanisms to more reliably elucidate the wishes of incapacitated patients and to respect their autonomy.

There are few published data on attitudes to surrogate consent to clinical research. To our knowledge, there have been none from Australia. We conducted a survey of the relatives of patients in our hospital to outline general attitudes to human clinical research, research participation, and surrogate consent to participation of incapacitated patients.

Methods

Setting and participants

The survey was conducted at Sir Charles Gairdner Hospital, Perth, WA, after review and approval by the institutional human research ethics committee. Visitors in the waiting rooms of the emergency department (ED) and intensive care unit (ICU) of this tertiary hospital were approached at random times (24 hours a day) over a 6-week period around September 2006, and were asked to complete a

Box 2. Questionnaire on attitudes to including unconscious people in research

Please answer all questions. Give your own viewpoint here. There is no right or wrong answer.
The questionnaire should take about 5–10 minutes to complete.
Personal details: please delete/circle as appropriate

Year of birth
Gender
Male / Female
Nationality (as stated on passport)
Employment status
Full-time employment
Part-time employment
Self-employed
Student full-time
Unemployed, looking for a job
Permanent long-term sickness or disability
Looking after home or family
Retired
Marital status
Single
Married
Widowed
Divorced
Do you have children?
Yes / No
What is your relationship to the patient?
Husband/wife
Father/mother
Son/daughter
Sister/brother
Uncle/aunt
Cousin
Friend
Other (please define)
How important are religious or spiritual beliefs to you?
Not very important
Moderately unimportant
Average
Moderately important
Very important
Which of the following best describes the highest level of education you have completed?
Primary school
Certificate or trade
Certificate secondary school or equivalent
Postgraduate qualification
University degree
Other
Have you ever been hospitalised yourself?
Yes / No
Is this the first time you have had a relative/friend in hospital?
Yes / No
Have you ever been a patient in Intensive Care or had a family member in Intensive Care that you have personally seen?
Yes / No

The following questions are based on you being a PATIENT in the hospital

(Please circle your response on the 1 to 10 scale)

You are brought into hospital in a very sick condition and unable to make decisions for yourself.

How do you feel about the following? Please mark your answer clearly.

1) Being enrolled in a clinical trial

1 2 3 4 5 6 7 8 9 10

Strongly against Strongly in favour

2) A relative giving consent on your behalf to be enrolled in a clinical trial

1 2 3 4 5 6 7 8 9 10

Strongly against Strongly in favour

3) That this type of research is likely to be in your best interest?

1 2 3 4 5 6 7 8 9 10

Strongly against Strongly in favour

The following questions are based on you being the RELATIVE of a patient in the hospital

Your relative is brought into hospital in a very sick condition and unable to make decisions for themself.

How do you feel about the following? Please mark your answer clearly.

1) Their being enrolled in a clinical trial

1 2 3 4 5 6 7 8 9 10

Strongly against Strongly in favour

2) Your giving consent on their behalf to be enrolled in a clinical trial

1 2 3 4 5 6 7 8 9 10

Strongly against Strongly in favour

3) That this type of research is likely to be in their best interest?

1 2 3 4 5 6 7 8 9 10

Strongly against Strongly in favour

Do you have any comments you would like to make about research in general?

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Table 1. Response rates to survey

	Number (% of total)	
	Emergency department	Intensive care unit
Questionnaires distributed	175	108
Completed surveys returned	122 (70%)	63 (58%)
Non-English speaking	4 (2%)	8 (7%)
Declined participation	21 (12%)	5 (5%)
Form incorrectly completed or not returned	28 (16%)	32 (30%)

Table 2. Respondent attitudes to research participation of incapacitated patients (*n* = 185)

	Self-participation			Relative's participation		
	Q1	Q2	Q3	Q1	Q2	Q3
Mean score (SD)*	5.4 (3.0)	6.0 (3.0)	6.7 (2.6)	5.3 (2.9)	5.7 (3.0)	6.5 (2.7)
No. of respondents (%)						
Strongly disagree (score 1–2)	42 (23%)	35 (19%)	16 (9%)	42 (23%)	37 (20%)	21 (11%)
Neutral (score 3–8)	112 (60%)	103 (55%)	119 (64%)	117 (63%)	113 (61%)	115 (63%)
Strongly agree (score 9–10)	32 (17%)	48 (26%)	51 (27%)	27 (15%)	36 (19%)	47 (26%)

* Respondents were asked to score their attitude on a visual analogue scale of 1–10, where 1 = strongly against, and 10 = strongly in favour.◆

questionnaire. Participants were excluded if they were younger than 16 years, did not speak English, or had previously completed the questionnaire.

Questionnaire

Design of the questionnaire considered factors that may bias responses, aiming to maximise validity of the data collected. The questionnaire was written in plain English and could be completed in less than 5 minutes according to a pilot staff survey. Participants were not identifiable from the survey forms. Participation was voluntary and anonymous, and replies were placed in a sealed box in the relevant waiting area.

The questionnaire provided a brief explanation of critical illness and associated decisional impairment, along with the need to conduct studies involving critically ill patients and regulatory requirements for consent. Participants were told the purpose of the survey and that their participation was entirely voluntary (Box 1).

Those surveyed were asked whether, if placed in a situation where they were critically ill and unable to make decisions, they would agree to research participation. We also asked whether they considered it appropriate for another person to make decisions on their behalf in such circumstances, as well as the reverse situation — whether they considered it appropriate that they may make similar decisions on behalf of a close relative or associate. To establish attitudes or perceptions of human clinical research, respondents were also asked whether they considered participation directly beneficial to participants. Demographic data collected included age, sex, employment status, marital status, ethnicity, educational level and relationship to the admitted patient, along with the importance placed on religious or spiritual beliefs, and previous experience with critical illness or clinical research. Space was also provided for comments from respondents (Box 2).

Data analysis

Demographic details were recorded along with measures of the person's attitude to participation in research, either for themselves or for a relative. Measurements were recorded on a visual analogue scale from "strongly against" (score 1) to "strongly in favour" (score 10). Responses were categorised into three groups: strong disagreement (responses 1–2), neutral (3–8), and strong agreement (9–10). For statistical analysis, raw measurements were used from questionnaires, with responses treated as continuous variables, in addition to secondary analysis of categorised responses.

Results

A total of 283 candidates were approached, 175 in the ED and 108 in the ICU waiting rooms. Completed questionnaires were returned by 122 candidates from the ED and 63 from the ICU, a total of 185 complete responses. Of responses not returned or not used, 38 candidates declined to participate in the survey (25 in the ED and 13 in the ICU), 12 because of language difficulties. Response rates are summarised in Table 1.

From responses, 42 (23%) would not agree to participate in clinical research if critically ill and incapacitated, 112 (60%) were neutral or undecided, and 32 (17%) felt strongly that they would agree to participate. No difference was seen in attitudes of those surveyed in the ED and those in the ICU. Asked whether they would agree to a relative providing consent to research participation on their behalf, 48 of the 185 (26%) agreed with this concept, 103 (55%) were neutral, and 35 (19%) felt strongly against the suggestion. Responses to questions relating to attitude of all respondents are summarised in Table 2.

Table 3. *P* values for associations between demographic variables and attitude responses*

Variable, response analysis*	Self-participation in research			Relative's participation in research		
	Q1	Q2	Q3	Q1	Q2	Q3
ICU or ED						
Continuous	0.03	0.78	0.42	0.37	0.64	0.31
Categorical	0.02	0.58	0.69	0.66	0.79	0.38
Age group						
Continuous	0.27	0.17	0.09	0.65	0.83	0.10
Categorical	0.37	0.18	0.004	0.86	0.68	0.19
Sex						
Continuous	0.90	0.72	0.06	0.38	0.75	0.046
Categorical	1.00	0.30	0.06	0.41	0.42	0.21
Nationality						
Continuous	0.79	0.23	0.80	0.46	0.52	0.78
Categorical	0.67	0.70	0.62	0.23	0.83	0.95
Employment						
Continuous	0.22	0.69	0.08	0.11	0.71	0.13
Categorical	0.05	0.41	0.21	0.18	0.53	0.32
Marital status						
Continuous	0.88	0.43	0.65	0.46	0.63	0.72
Categorical	0.67	0.81	0.64	0.41	0.53	0.50
Children						
Continuous	0.42	0.47	0.68	0.83	0.72	0.46
Categorical	0.51	0.63	0.18	0.23	0.14	0.17
Relationship						
Continuous	0.55	0.17	0.50	0.27	0.08	0.07
Categorical	0.88	0.40	0.10	0.85	0.27	0.06
Religion						
Continuous	0.61	0.33	0.10	0.70	0.56	0.61
Categorical	0.56	0.25	0.02	0.65	0.30	0.008
Education						
Continuous	0.83	0.91	0.27	0.70	0.82	0.16
Categorical	0.99	0.93	0.82	0.63	0.92	0.39
Self hospital†						
Continuous	0.83	0.79	0.74	0.20	0.85	0.46
Categorical	0.87	0.84	1.00	0.54	0.82	0.92
First‡						
Continuous	0.84	0.47	0.38	0.73	0.74	0.36
Categorical	0.96	0.54	0.62	0.81	0.69	0.57
ICU contact§						
Continuous	0.36	0.03	0.66	0.89	0.46	0.49
Categorical	0.07	0.008	0.15	0.55	0.34	0.28

* *P* values were calculated analysing data both as continuous (ANOVA) data, and after categorising responses (χ^2 statistic).
† Self hospital = respondent had been previously hospitalised themselves.
‡ First = first time that respondent had a relative/friend in hospital.
§ ICU contact = respondent had previously either been a patient in intensive care or had a family member in intensive care that they had personally seen.
ICU = intensive care unit. ED = emergency department. ◆

Of the 185 respondents, 41% were male and 59% female, with no observed effect of sex detected on attitudes to research or consent. Age distribution was: 35% aged 16–35 years, 52% aged 36–60 years, and 13% aged over 60 years. Completion of primary or secondary school, or trade certification were reported by 55%, while 36% had a university degree or postgraduate qualification, and 9% marked "other" as their main occupation. The importance of religion was "less than average" to 37%, "averagely important" to 24%, and "more than averagely important" to 39%, with no correlation between this and attitudes to research.

To identify any significant associations between demographic data and attitude responses, *P* values were calculated for the comparison of each independent demographic variable with each attitude outcome variable using ANOVA (continuous data) or χ^2 test (categorical data) (Table 3). Univariate *P* values are shown, calculated without adjustment for other variables.

Multivariate analyses were also performed using ANOVA with backward elimination, initially including all demographic variables, followed by stepwise removal of factors until only those with significant correlation remained (Table 4). Multivariate extension to the categorical analyses was performed by grouping categories into responses strongly in favour against all others, with multivariate logistic regression applied to identify variables associated with strong agreement (Table 5). No conclusive correlation was shown between recorded demographic variables and attitude, although some trends appeared and are shown in Table 5. Respondents who were disabled, sick or unemployed generally were more likely to record strong agreement to research participation compared with most others. Those recording home or family duties as an occupation were likely to object.

Responses to questions about self-participation and participation of a relative were combined in examining whether respondents considered participation in research directly of benefit. From this, research was not considered directly beneficial to participants by 10% of respondents, while 63% were unsure. Participation was thought likely to directly benefit research subjects by 27%. These beliefs tended to influence attitudes to participation, with 90% of respondents who saw no direct benefit from research stating they would not agree to enrolment. Of those who believed research to be directly beneficial, 70% stated they would agree to enrolment (24% stating they would refuse).

Comments given in the space provided included: "Move to a third world country if you don't think that this research is beneficial", and "Have concerns over side effects of drugs as occurred in recent study in the UK".

Discussion

This survey was conducted in response to the observed lack of data available on community attitudes to research involving critically ill patients, and to surrogate consent in incapacitated subjects. Attitudes to research were sought, along with whether respondents would agree themselves to participate in studies. We also asked whether respondents agreed with the notion of another person providing consent on their behalf if they were rendered unable by illness. Around half of those surveyed indicated that they would agree to participate in clinical research, but only 17% indicated strong agreement and a quarter of respondents objected to participation. Regarding provision of consent, 19% indicated that they did not agree with decisions on research participation being made by others on their behalf. If research participation was considered beneficial, responses were more likely to be favourable. Demographic factors such as age, sex, and level of education did not affect responses to the survey, nor did spiritual beliefs or previous experience of intensive care, emergency medicine or research.

The survey was conducted over two departments of a single centre, and so was subject to some bias. As the sample comprised relatives, it was not truly representative of the broader community. Attempts were made to construct questionnaires so that responses produced objective and measurable indicators of respondents' beliefs, but the possibility remained for misunderstandings and inaccurate replies.

Our findings highlight the need for acceptable and effective alternatives to direct consent from incapacitated subjects in clinical research. Approaches considered should be acceptable to prospective participants in research, to their surrogates and to the community in general. They

Table 4. Factors contributing to question response (results of ANOVA multivariate regression on continuous values)

Attitude response	R^2	Variable	*P*	Mean score*
Self				
Q1	4.4%	Employment status	0.02	
		Disabled/sick/unemployed		7.8
		Home/family		4.1
		Other		5.5
Q2	2.5%	Previous ICU contact	0.03	
		Yes		5.6
		No		6.6
Q3	5.0%	Employment status	0.009	
		Disabled/sick/unemployed		9.2
		Home/family		5.5
		Other		6.7
Relative				
Q1	5.0%	Employment status	0.009	
		Disabled/sick/unemployed		8.0
		Home/family		4.0
		Other		5.4
Q2		None significant		
Q3	5.2%	Employment status	0.008	
		Disabled/sick/unemployed		9.2
		Home/family		5.3
		Other		6.6

* On visual analogue scale with range 1–10. ◆

Table 5. Contributors to favourable response to questions (results of multivariate logistic regression models on categorical outcomes: strong agreement v other response)

Attitude response	Variables	*n*	*P*	Odds ratio	95% CI
Self					
Q1	Employment status				
	Disabled/sick/unemployed	6	0.13	5.0	0.95–25.9
	Home/family	19	0.06	0.6	0.13–2.68
	Other	161	0.49	1.00*	
Q2	No significant correlation				
Q3	Age group (years)				
	61+	23	0.02	3.40	1.2–9.5
	36–60	98	0.99	0.99	0.5–2.1
	18–35	65		1.00*	
	Sex				
	Female	110	0.04	0.48	0.2–0.97
	Male	76		1.00*	
	Employment status				
	Disabled/sick/unemployed	6	0.03	7.60	1.3–44.6
	Home/family	19	0.81	0.84	0.2–3.2
	Other	161		1.00*	
Relative					
Q1	No significant correlation				
Q2	No significant correlation				
Q3	No significant correlation				

* Reference variables. ◆

must also aim to accurately reflect participant wishes as far as possible. Correlation between patient and surrogate choices is vital if substituted judgement is to be considered a valid extension of individual autonomy. From our responses, willingness to participate in studies was associated with belief in direct benefits to participants from involvement. To encourage research participation, there is therefore a need to positively reinforce the image of medical research. The influence of publicity and the media is shown in the comment from one respondent expressing concern at drug side effects in healthy volunteers in a recent drug trial in the United Kingdom.

Consent may be defined as the voluntary "autonomous authorisation of a medical intervention by individual patients",[11] where competent adults are entitled to make treatment decisions and so retain some control over what happens to them and their bodies. The competent adult is entitled to be provided with any available information relevant to making these decisions, enabling "informed" decision-making. This principle of patient autonomy was articulated in a 1914 New York court ruling stating "every human being of adult years and sound mind has a right to determine what shall be done with his own body".[12]

Over the past century, the idea of consent has been debated and spoken of in judicial decisions, along with the rights of patients and duties of practitioners in the course of obtaining consent to medical treatment.[13-17] The doctrine of consent was developed and became an intrinsic component of legal and ethical requirements for both treatment and research. Consent advances patient rights to personal medical information necessary to appropriately decide which course of therapy to take, or not to take. Valid consent must relate specifically to the action proposed and performed, it must represent a voluntary choice made in the absence of coercion, and in the knowledge of available relevant information. Consent must also be provided prospectively. A patient not fully informed of information relevant to a decision may be deprived of the opportunity to choose another course of action, with information interpreted in the context of their own circumstances and desired outcome. Poorly informing patients may also impede effectiveness of the "therapeutic alliance" formed between patient and clinician, seeking to define and work towards commonly understood therapeutic goals based on equally shared information.

Patients with diminished capacity may have increased vulnerability to unethical, harmful or inappropriate research practices or exploitation. This is seen as necessitating greater measures of protection. In human biomedical research, formal ethical codes of conduct were introduced after the 1947 Nuremberg trial of doctors from Nazi Germany who conducted research on concentration camp inmates, and were charged and convicted for their torture and murder. The resulting Nuremberg Code[18] focused on the rights of human subjects of medical research, and the protection of subjects from harm or exploitation. These ideas were later endorsed by the World Medical Association in the 1964 Declaration of Helsinki,[19] which outlined the ethical obligations of investigators, rather than listing the rights of participants. The Declaration of Helsinki also first distinguished "therapeutic" research, where there was a reasonable possibility of direct benefit to subjects, from "non-therapeutic" research conducted for scientific purposes only. That in research "[t]he voluntary consent of the human subject is absolutely essential"[18] is the first stated principle of the Nuremberg Code. The Declaration of Helsinki also states that "subjects must be volunteers and informed participants in the research project".[19]

Traditional descriptions of consent in the fully competent subject are simplistic and outline discrete observable events. Within the clinician–patient relationship, diagnoses are communicated and interpreted by the individual patient, leading to an individual and unique understanding of the problem in their own context. Treatment options, and the potential risks and anticipated benefits of these options are considered. Decision-making then balances potential risks and benefits of therapeutic options, the ultimate question becoming what degree and form of risk the patient accepts in the hope of achieving the outcome he desires. Clinically, consent is not a set of discrete events culminating in the signing of a form absolving a clinician from responsibility. Consent is more complex, and probably represents an ongoing process of communication. Existing knowledge, information provided, and positive or negative responses to interventions contribute to continuing evaluation and adjustment of therapy. Patient expectations of effects and outcomes from interventions may also change with time, necessitating ongoing communication and clarification of a commonly understood goal from treatment.

A patient or participant in research is not the cool, rational individual found in textbooks. As a member of a community, a patient possesses all the beliefs, expectations and doubts present throughout that community, and is also influenced by past experiences and associations. Knowledge, faith or trust in medicine or clinicians may be influenced by social, economic and educational factors, and patients are increasingly informed by the media and community about medical science and research. Historical aspects of racial or ethnic oppression may influence trust or mistrust placed in institutions or professions, along with varying gender roles which leave some assertive and questioning, and others submissive or accepting. The patient or participant then commences the consent process holding

conscious or subconscious knowledge, beliefs, expectations, trusts and mistrusts, as does the clinician or investigator.

Failure to understand verbal, written or other information provided in the course of consent is common. In research, this often produces the "therapeutic misconception" that study participation is of direct therapeutic benefit to subjects. While benefit may occur, perception of research as a form of treatment, rather than aiming to improve knowledge and to evaluate therapies, is an incorrect belief on which decisions may be based. In a survey of participants in a phase I clinical study in cancer patients, only 33% were able to state the purpose of the study, and 85% stated they agreed to participate because of expected direct personal benefit.[20] Provision of information in an understandable manner is important to comprehension and valid consent. Despite guidelines advocating use of simple plain language and format, information provided in consent forms is increasingly excessive and often too complex for many patients to fully understand.[21] Conveying information in a simple and understandable way may be more important in a research setting compared with a treatment setting, with the additional information required to be understood.

In research, the idealised model of consent is further confused by dual roles of clinician-investigators and patient-participants. It has been suggested that many who enrol in clinical research do so based on feelings of trust in their clinician or hope that new treatments are better than older or standard therapy — another incorrect belief. Patients who become participants place trust in their clinician, whose role has shifted to that of investigator. The therapeutic misconception and trust within the patient–clinician relationship may alter interpretation of provided information and evaluation of risk, so bypassing the described model of unbiased rational decision-making.[22]

The influence of trust on decision-making may undermine increasing regulatory requirements in research. On one side, institutional arrangements and regulatory requirements foster a potential view of clinician-investigators as not to be trusted, so necessitating these regulations. Alternatively, patient-participant trust in the same clinician-investigator may predispose to agreement to participate in clinical studies regardless of these regulatory safeguards.

Models of informed consent poorly suit the circumstances of critical illness. Informed consent presumes that a patient is rational and competent, and that information is fully disclosed despite circumstances of emergency and limitations on time. It presumes the unbiased formation of a decision in the face of pain, distress, fear and prospects of further suffering or death. Consent from patients in these circumstances remains the best means we have to assess patient wishes and respect their autonomy, and should not be dismissed. However, the limitations of consent in these circumstances should be recognised.

Capacity to provide consent refers to cognitive, situational and other factors contributing to the individual producing a rational decision based on provided information. Full capacity equates with legal competence.

Capacity involves abilities to receive and understand information, to distinguish between therapeutic and non-therapeutic intent, to recognise and compare risks and benefits of different options, and then to rationally consider these in making an individual choice. All adults are considered competent until proven otherwise, capacity technically being a legal decision based on a current specific decision that is to be made, with authority to decide on capacity deriving from guardianship legislation. Judicial advice on capacity in a medical setting is impractical, and reasonable informal assessment of capacity by treating clinicians is generally accepted, being a prerequisite for valid informed consent. While clinicians have a responsibility to estimate capacity in providing information and determining validity of decision-making, capacity is not easily assessed. Simple assessments such as the Mini Mental State examination predict capacity poorly,[23,24] but may identify patients in whom more formal assessment of capacity is warranted.

An unconscious patient obviously lacks the ability to receive, understand and consider information to make decisions, and so lacks capacity. Even when conscious, the capacity of a critically ill and apparently lucid adult remains questionable.[5,25] Even where a rational choice could be made, bias may be introduced by the simple desire for relief from pain or suffering, or to recover or even survive, added to by the trust placed in clinicians in pursuit of these. The ability of a conscious, critically ill patient to decide on research participation may then be questionable, doubt increasing with increasing importance and complexity of information and decisions to be made.

Decision-making capacity depends on the decision to be made. Complex decisions, and decisions with significant consequences require greater understanding and consideration, and so higher degrees of capacity. Decision-making capacity required to consent to research participation is considered greater than that required to consent to equivalent therapeutic interventions. In addition to understanding and comparing risks and benefits, agreement necessitates understanding the distinction between the therapeutic or scientific intent of treatment compared with research, and comprehension of concepts such as randomisation and placebos.[26,27] Intent is a fundamental difference between research and therapy. Treatment is provided with the intent of direct benefit to the patient, and risks are weighed against actual expected benefits to that patient. Although patients enrolled in research are known to have more

favourable outcomes from disease than non-participants, this is not the intent of enrolment. Decision-making in research does not then necessarily involve acceptance of risks in expectation of known direct or intended benefit.

Ethical guidelines specifically address the issue of patients lacking capacity to provide voluntary consent to research participation. They suggest participation in research only when absolutely necessary, when there is no alternative means of discovering the desired information, and the research is directly relevant to the disease causing incapacity. Guidelines advocate research involvement only where this represents minimal risk and where the value of knowledge gained may reasonably justify risk and the threat to participant autonomy. Exceptions to restricted participation occur where there is the reasonable expectation of some direct benefit to participants which may justify attendant risks, or where risks do not exceed those of non-participation. Enrolment of incapacitated persons into dangerous, unnecessary or poorly designed research without consent may be seen as unethical, exploitative or, at worst, assault.

While literal reading of law and research guidelines would indicate that all persons incapable of providing prospective voluntary informed consent should be excluded from "all but the most minimally invasive observational research",[1] this complete exclusion may itself also be viewed as unethical. Exclusion denies participation of patients most likely to derive benefit from improvements in knowledge and care.

Protection may be provided to incapacitated subjects either through complete exclusion from involvement, or by enhancing other safeguards where capacity is questionable and impedes participant self-protection. Safeguards may include more rigid review of proposed studies, ensuring scientific validity and adequate preclinical evaluation, relevance to the studied population, and inability to gain the knowledge by alternative means. Oversight of research is by independent bodies focusing on participant welfare and proper safe and ethical conduct of research. Efforts to accurately ascertain participant wishes and encourage ongoing autonomy are promoted. It has been observed that increasing regulatory requirements have led to a *decrease* in, rather than facilitation of, research into acute cardiac disorders,[28] raising concerns that improvements in patient care and public health may be threatened. In the United States, attempts were made in 1996 to address any impediment to clinical research arising from consent requirements. Criteria were provided by which studies could be exempted from consent requirements with fulfilment of strict safety criteria.

In Australia, there are no reports of litigation relating to consent to research, but several events in the US have increased awareness of ethical conduct in medical research. These include the deaths of two volunteer participants,[29] and cessation of research in prominent institutions resulting from lapses in ethical research practices.[30,31] Awareness of the practice of surrogate consent has also been raised by incidents in the US. A large study sponsored by the National Institute of Mental Health[32] aimed to assess control of behavioural disturbance in Alzheimer's disease with antipsychotic medications. Approval of the study was denied at one of 30 centres, the Institutional Review Board (IRB) refusing inclusion of incapacitated participants. A 2001 review by Californian IRB members found that State law allowed only a legally appointed guardian to act as surrogate in consent to research, leading to the cessation of research involving surrogate consent at the University of California. California State law was amended to address this. In Maryland, legal action was pursued on behalf of children enrolled in research on lead toxicity.[33] The court stated in its findings that "[i]n Maryland, a parent, appropriate relative, or other applicable surrogate cannot consent to the participation of a child or other person under legal disability in non-therapeutic research or other studies in which there is any risk of injury or damage to the health of the subject".

Current understanding of many disorders associated with decreased cognition is incomplete, and improvements in management and outcomes cannot progress without research involving incapacitated subjects. Treatments may be developed in laboratories and tested on healthy competent volunteers, but all interventions must at some time be applied to a patient with the relevant disease. Clinical research into these disorders is becoming more frequent, also increasing awareness of unanswered legal and ethical questions and obligations. Progressively increasing the ethical and legal requirements with the valid intent of participant protection may have adverse impacts on research and clinical care. Future ability to perform research may be restricted, and investigators discouraged along with formerly willing participants.[34] Restrictions on the conduct of research may also encourage "alternative" solutions and practices which may be less palatable than those currently discouraged. There is an apparent divide between the valid intent of regulators in the pursuit of patient-participant rights, and the reality of a patient who only wishes for recovery or relief from suffering[22] who then exercises a form of "second order autonomy" in entrusting decisions to others. Research participants seem to rarely make use of regulatory policies in self-protection.

Exercise of true autonomy via informed consent may simply be impossible in some circumstances where research remains necessary. Policies are required to enable safe and ethical conduct of research in critical illness, recognising participant rights and autonomy, alongside their vulnerabil-

ity, while not denying participation in studies that could contribute to their own or a future patient's benefit. Several alternative approaches have been proposed to consent from an incapable person.

Deferred or delayed consent: Enrolment in studies representing minimal risk may occur, with consent then obtained from subjects retrospectively on recovery. As this approach advocates seeking consent for an act that has already occurred, it is an illogical means to maintain autonomy. Uncertainty also arises in dealing with participants who die or fail to recover capacity. Where survival or recovery is an outcome measure, the exclusion of these participants could invalidate results of research conducted.

Consent waivers: This has been advocated where valuable knowledge gained justifies research participation and threats to autonomy alone, or where participation is reasonably expected to directly benefit subjects.

Prospective consent: In groups at risk of future incapacity, such as those with neurological disorders, prospective consent to research participation may be possible before loss of capacity.

Surrogate consent: When potential participants lack capacity to provide direct informed consent, a surrogate decision-maker is approached. This is most commonly a close relative, such as a spouse or parent, who is asked to make a substituted judgement or choice based on what they believe the participant's wishes would be.

Substituted judgement and surrogate consent are common in critical care research, but issues of moral and legal validity must be addressed. Public acceptability of the practice, reliable assessment of capacity, identification of surrogate decision-makers, and the accuracy of surrogate decisions require investigation. Our survey showed that even in a potentially biased sample of relatives already exposed to critical illness, only 26% agreed with someone providing consent on their behalf. We did not compare study protocols of varying risk, but other investigators have found a greater likelihood of agreement to participate in trials where there is minimal participant risk. One survey of ED patients found that 73% would support a waiver of consent if the risks of research involvement were minimal.[35] Another survey of patients and visitors in an ED[36] considered a waiver of consent to resuscitation research, with 49% finding this acceptable, and 70% responding that they would not object to enrolment in the absence of consent. Enrolment into emergency research prior to obtaining consent was acceptable to 84% of respondents to a Glasgow survey.[37] Respondents considered that direct or surrogate consent should be obtained as soon as possible after enrolment under this arrangement.

Our results agree with the limited available data. If incapacitated, some people would not agree to participate in clinical research in the absence of consent. Rather than contradict the wishes of a group of potential study participants, this uncertainty highlights the importance of obtaining accurate predictions of patient wishes from surrogate decision-makers.

Despite the common use of surrogate decision-making, its accuracy is poorly understood. Observations have been made that substituted judgement is an imperfect means to establish the wishes of those unable to make or express decisions.[38-40] In a study that presented research scenarios of varying risk to 250 patients with differing terminal illnesses and their surrogates, surrogates accurately predicted patient responses 66% of the time.[38] Improved correlation was associated with having discussed end-of-life issues with the patient previously, and with increased level of education. Others have also found the accuracy of substituted judgements to correlate with previous discussions between the patient and the surrogate on health care.[39,41] Another study interviewed patients in a cardiac surgical service and their surrogates regarding two proposed studies with differing associated risks, finding the prediction of consent by surrogates to be inaccurate.[42] Patient and surrogate decisions matched in 84% of cases for a low-risk study and in 80% for a higher risk study. Incorrect consent from surrogates may then have occurred in 16%–20% of cases, with no reliable predictors of accuracy identified. Others have made similar observations.[43] Investigation of factors leading to inaccurate substituted judgement may alert clinicians and researchers to potentially incorrect surrogate decisions, and allow the development of mechanisms to optimise accuracy in decision-making.

Conclusions

The importance of consent to research interventions is recognised, but obtaining prospective consent from critically ill patients may often be either impossible or questionable. Our survey demonstrated that 26% of the competent adults asked considered it appropriate for another person to provide consent to research participation on their behalf if they were incapacitated. Of concern, around a quarter stated they would refuse participation in clinical research if critically ill.

Reliance on the advice and substituted judgement of surrogates for incapacitated patients is a less acceptable practice to the public than we expected in this single centre survey. Additionally, the accuracy of surrogate decisions may be poor in circumstances where the implications of decisions are great. Investigation is needed to evaluate public perceptions of biomedical research, and to promote

potential participation in safe and ethically conducted clinical research. There is also a need for closer examination of the accuracy of surrogate decision-making and factors contributing to this if substituted judgement is to be accepted as an alternative to direct informed consent.

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