Special Article

Informed consent for clinical anaesthesia research

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Most surgical patients are first seen by an anaesthetist after admission to hospital, either the evening before or on the day of surgery. Some medical ethicists believe that an approach by an anaesthesia researcher made after admission is unethical because the hospital itself is a coercive environment, and patients have insufficient time for reflection or consultation. Others believe that an approach prior to admission may be an invasion of the patient's privacy and confidentiality. The implications of these views for anaesthesia researchers may not be apparent to research ethics boards (REBs). To determine current practice, a questionnaire concerning the membership and function of REBs and the time of obtaining informed consent was sent to each research representative of the 16 Canadian university departments of anaesthesia. Membership of REBS was similar, but not identical, in all centres. Most representation was from medical disciplines. Consent was generally obtained following the patient's admission to hospital. In one centre, the REB always requested informed consent to be obtained before the patient's admission to the hospital. Surgeons had no involvement with consent for anaesthesia research in 14 centres while in the other two they gave permission for their patients to be studied and informed patients of the potential approach by anaesthesia researchers. We conclude that it is ethically acceptable to obtain informed consent for most low-risk clinical anaesthesia research after the patient's admission to hospital.

La plupart des malades programmés pour une chirurgie sont visités par une anesthésiste après leur admission, soit la veille, soit le matin de l'intervention. Certains éthiciens médicaux croient que la rencontre post-admission par un chercheur-anesthésiste ne respecte pas l'éthique parce que l'environnement hospitalier est coercitif et que les patients n'ont pas le temps voulu pour réfléchir et consulter. D'autres croient que la rencontre avant l'admission constitute une invasion de la vie privée et une brèche à la confidentialité. Le conséquences de ces opinions sur la recherche anesthésique ne sont pas évidentes pour les comités d'éthique. Pour déterminer les pratiques usuelles au regard de la composition et du fonctionnement de ces comités, un questionnaire sur le moment de l'obtention du consentement éclairé pour un projet de recherche a été expédié à chacun des responsables pour la recherche des 16 départements universitaires d'anesthésie du Canada. La composition des comités d'éthique se ressemble sans être identique dans tous ces centres. La grande partie de la représentation vient des disciplines médicales. Le consentement est généralement obtenu après l'admission. Dans un centre, le comité demande que le consentement éclairé soit obtenu avant l'admission. Les chirurgiens n'ont aucune part dans la demande du consentement anesthésique dans 14 centres alors que dans les autres, le chirurgien accorde la permission au chercheur-anesthésiste afin que leurs patients soient évalués et informés. Nous concluons qu'il ne va pas contre l'éthique d'obtenir après l'admission hospitalière un consentement éclairé pour la recherche clinique anesthésique présentant peu de risque.

Key words
ANAESTHESIA: clinical research;
ETHICS.

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For several years, the Conjoint Medical Ethics Committee of the University of Calgary has taken the view that written informed consent for clinical research protocols must be obtained before the patient is admitted to hospital. This is because the hospital itself is perceived as a coercive environment and consent on the day of admission will generally be inadequately reflective. Patients may also incorrectly assume that the research is linked to their therapeutic procedure. This created a dilemma for anaesthetists for several reasons. First, the suitability of patients for inclusion in research protocols should be determined by the anaesthetist or principal investigator. These individuals do not normally meet healthy, elective patients until after their admission. For some protocols

it would be difficult to determine suitability from surgeons' notes or even by telephone contact with the patient. Second, the Medical Research Council (MRC) of Canada's *Guidelines*[1] state that confidentiality cannot be breached without the subject's consent, reinforced by the principle that patients should not be approached by strangers. Who are "strangers"? If clinical investigators who will not be providing clinical care to the patient are regarded as strangers, they should not have access to patients' medical records nor contact them as potential research subjects at home or at work.[2-4] Third, referral of suitable patients by surgeons to anaesthetists, for example at a preoperative assessment clinic, ostensibly for clinical reasons but actually to facilitate recruitment for research, may be interpreted as "insider trading" and therefore unethical.

Decisions in medical ethics depend on striking a balance between competing ethical claims and particular factors may weight differently at different times and in different circumstances.[1] The primary responsibility for decisions on the ethics of clinical research protocols is delegated by institutions to Research Ethics Boards (REBs). Each REB should include lay members who can reflect community values, and relevant specialists including at least one permanent or *ad hoc* specialist in the relevant discipline of the research proposal. Their purpose is not to prevent experimentation and research, but rather to ensure that these are performed in an ethically acceptable fashion.[5]

Research Ethics Boards base their deliberations on respect for autonomy, confidentiality and privacy of the subject, absence of coercion, time for reflection and informed consent. Local requirements may add further conditions such as the ability to seek counsel.* Confidentiality requires that information concerning a potential subject's medical condition should not be available to "strangers," nor should subjects be approached by "strangers" who have knowledge of their medical circumstances. There must be no coercion to participate; the potential subject should understand that participation is voluntary, appropriate medical care is not dependent on participation, withdrawal from the study will have no adverse consequences on clinical care, and alternative forms of therapy have been explained. The amount of time required for reflection has no absolute definition.

Serious practical problems for clinical anaesthesia research are created if terms such as "adequate time for reflection" and "coercive environment" are rigidly defined by an REB whose members are unfamiliar with anaesthesia practice. Anaesthesia investigators at the University of Calgary made unsuccessful attempts to reach a mutually acceptable agreement with the REB about the time and place for obtaining informed consent. Approval of anaesthesia research protocols was often delayed, irrespective of their complexity, degree of risk, and time involvement of the patients. Investigators explained that the condition of pre-admission consent was impractical for most anaesthesia studies and all protocols were eventually approved. The chairman of the REB, in an attempt to resolve this impasse, sought the opinion of the Panel on Consent of the National Council on Bioethics in Human Research in 1991. The Panel's response favoured the approach of the REB over that of the investigator anaesthetists, although it commented that the time required for decision-making could not be stated in the abstract. Subsequently, a memorandum was sent by the outgoing chairman of the REB to the incoming chairman, the head of anaesthesia, the chairman of the hospital's Research and Development Committee, and the associate dean for research to inform them that "we should now ensure that no confusion persists locally concerning recruitment and informed consent procedures for anaesthetic research. There should be no concern that our revised local position [pre-admission consent for all investigations on elective patients] would set us apart from national anaesthetic research standards. I am reasonably confident that MRC and PMAC [Pharmaceutical Manufacturers Association of Canada] will accept NCHBR's opinion as the basis for national policy in this area."*

Informal discussions with anaesthesia researchers in university centres in Canada and the United States suggested that the University of Calgary position was the exception rather than the rule. Because of the implications of universal application of this rigid policy throughout Canada and its potential impact on Royal College residency programmes,[6] a survey of all Canadian university departments of anaesthesia was conducted to determine the range of the structure and functions of REBs, with particular reference to guidelines for obtaining informed consent.

Methods

A survey in the form of a questionnaire was prepared by the authors in consultation with the chairman of the Research Committee of the Association of Canadian University Departments of Anaesthesia (ACUDA). The questionnaire was mailed to the ACUDA research representative at each of the 16 Canadian university departments of anaesthesia. A covering letter explained that a national ethics body might require informed consent for all anaesthesia research to be obtained before patients' admission to hospital, and that information on this issue from across

*University of Calgary, Ethical Guidelines

*Personal communication. Dr. T.D. Kinsella.

ACUDA Anaesthesia Research Ethics Questionnaire

Biomedical Ethics Committee for Human Research

A. Is under the jurisdiction of
- ☐ university
- ☐ hospital
- ☐ department
- ☐ other (specify) _____

B. Is responsible to
- ☐ dean of faculty of medicine
- ☐ hospital board
- ☐ department director
- ☐ other (specify) _____

C. reviews human research proposals with reference to
- ☐ ethical considerations
- ☐ scientific merit
- ☐ consent form
- ☐ time when written informed consent must be obtained
- ☐ place where written informed consent must be obtained
- ☐ persons qualified to obtain written informed consent

Comments: _____

D. Invites the principal investigator to attend meetings at which his/her protocol is discussed
- ☐ always ☐ sometimes ☐ never

E. has the following representatives (please attach a list similar to example)

Example
UNIVERSITY OF CALGARY - FACULTY OF MEDICINE
Conjoint Medical Ethics Committee Membership

Chairman
Medical Ethicist
Social Scientist
Representative of Law (2)
Public Representative
Basic Medical Scientist
Clinical Investigator
Community Physician
Institutional Affiliates
- Foothills Hospital
- Calgary General Hospital
- Tom Baker Cancer Centre
- Alberta Children's Hospital

Health Sciences Centre Representative
Medical Student Representative
Postgraduate Medical Student Representative
Graduate Medical Sciences Representative
ex officio - Assistant Dean, Medical Bioethics
ex officio - Associate Dean, Research
ex officio - Dean, Faculty of Medicine

FIGURE 1 Jurisdiction and membership of ethics committee.

ACUDA Anaesthesia Research Ethics Questionnaire

Hospital Research and Development Comittee

If your Ethics Committee and Research and Development Committee are one and the same, please state this under "A. Comments" and proceed to Section 3.

A. Is under the jurisdiction of
- ☐ individual hospital
- ☐ department within each hospital
- ☐ university
- ☐ other (specify) _____

Comments: _____

B. Is responsible for informing the following concerning proposed or ongoing research activities
- ☐ Hospital Board
- ☐ Medical Advisory Committee
- ☐ Nursing Advisory Committee
- ☐ other (specify) _____

C. reviews human research protocols with reference to
- ☐ strategic goals of the hospital
- ☐ scientific merit
- ☐ ethical considerations
- ☐ availability of funds
- ☐ impact on human resources (nursing time, etc)

Comments: _____

D. Invites the principal investigator to attend meetings at which his/her protocol is discussed
- ☐ always ☐ sometimes ☐ never

E. has the following representatives (please attach a list similar to example)

Example
FOOTHILLS HOSPITAL
Research and Development Committee Membership

Chair A Clinical Dept. Head appointed by the Board on the recommendation of the Medical Advisory Committee of Foothills Hospital (FH) (3 years)

Secretary Vice-president, Clinical Development and Research (FH)

Members

President, Foothills Hospital (FH)
Vice-president, Management Services (FH)
Representative, Dept. of Nursing (FH)
Representative, Medical Staff Executive (FH)
Associate Dean, Research, U of C
Representative, Tom Baker Cancer Centre
Director, Ctr. for Advancement of Health (FH)
Representatives (4), Clinical Depts (FH) (2 years)
Chair, Conjoint Medical Ethics Comm., U of C
Representative, Finance Dept. (FH) (non-voting)

Quorum Half of the members

FIGURE 2 Jurisdiction and membership of research and development committee.

the country would be useful if attempts to implement such a policy were pursued. Section 1 concerned the jurisdiction, responsibility, functions, and membership of the REBs (Figure 1). Section 2 covered similar areas for individual hospital Research & Development committees (Figure 2). Questions in Section 3 were related to time and place for obtaining informed consent. These were based on three examples of clinical research protocols which are simple to understand, carry minimal risk, and do not require patients' time involvement beyond that necessary for clinical care (Figure 3). This section also contained questions regarding the surgeon's contribution, if any, to the informed consent process, whether research anaesthetists considered it appropriate for surgeons to be involved, whether the REBs specified when and where consent must be obtained, and whether release of confidential patient information in order to contact patients at home or at work specifically for research purposes caused ethical concern.

No independent confirmation of the accuracy of the reported data was undertaken.

Results

Responses were received from all 16 centres. The REB was under the jurisdiction of the university in ten centres, the hospital in four, and both in two. All REBs reviewed ethical considerations and the consent form, and all except one reviewed scientific merit. Three specified the time, and two the place, for written informed consent to be

ACUDA Anaesthesia Research Ethics Questionnaire

Informed Consent for Clinical Research

The Medical Research Council of Canada's "Guidelines in Research Involving Human Subjects" (1987) state that:

"The invitation to a prospective research subject must be made in a way that allows the individual freedom of choice. Sufficient time to refuse is important. It need scarcely be said that undue influence must not be employed."

For clinical research protocols similiar to those listed below:

i. Incidence of gastroesophageal reflux using pH probe
ii. Randomized double blind epidural vs. intravenous PCA for postoperative pain
iii. Phase IV clinical evaluation of keterolac

A. Does your Ethics Committee specify when informed consent must be obtained? Yes ☐₁ No ☐₂

B. If yes, must it be obtained before the patient enters hospital? (because the hospital is considered a "coercive environment") Yes ☐₁ No ☐₂

C. Is the patient's surgeon involved in obtaining written informed consent for clinical anaesthesia research?

☐₁ yes, for all studies (GO TO QUESTION D.)
☐₂ no (GO TO QUESTION E.)
☐₃ only for joint anaesthesia/surgery studies (GO TO QUESTION F.)

D. If "yes, for all studies", what is the extent of the surgeon's contribution?

☐₁ explanation of anaesthesia research protocol and obtaining signed consent
☐₂ explanation of anaesthesia research protocol but not obtaining signed consent
☐₃ giving protocols to patients to take home and read
☐₄ telling patients they may be invited to participate in anaesthesia research
☐₅ permission for their patients to be studied
☐₆ no involvement

E. If "no" (Q. 'C' above) would you consider it appropriate for the Ethics Committee to request that surgeons be involved in the informed consent process for anaesthesia studies? Yes ☐₁ No ☐₂

F. If anaesthesia investigators in your hospital have to obtain informed consent before the patient's admission, who provides the following information?

☐₁ OR booking details (name and age of patient, surgical procedure) ☐₁ surgeon's office ☐₂ hospital
☐₂ relevant medical details of the patient ☐₁ surgeon's office ☐₂ hospital
☐₃ patient's home and work telephone numbers ☐₁ surgeon's office ☐₂ hospital

Comments: _____

G. Does the release of such confidential information in order to contact patients at home or at work specifically for research purposes cause ethical concern to

i	ethics committee	☐₁	yes	☐₂	no	☐₃ don't know
ii	you personally	☐₄	yes	☐₅	no	☐₆ don't know
iii	OR booking / admission office	☐₇	yes	☐₈	no	☐₉ don't know

FIGURE 3 Time, place and involvement of surgeon in process of informed consent.

obtained. The principal investigator was always invited to attend REB meetings in four centres, sometimes in six and never in the remaining six.

A separate Research and Development committee under the jurisdiction of individual hospitals existed in nine centres. This committee reviewed protocols with reference to strategic goals of the hospital, availability of funds, and impact on human resources as well as scientific merit and ethical considerations. It was responsible for informing the hospital board, medical advisory committee, and nursing advisory committee of proposed or ongoing research activities. Two of these committees always, and three sometimes, invited the principal investigator to attend meetings.

Research Ethics Boards showed minor variation in membership from one centre to another. They all included several physicians, although not all specialties were represented. In each centre, at least one lay person, one lawyer, and one representative each from nursing and pastoral care were included. Some also included one or more of the following: medical ethicist, medical student representative, psychologist, social service representative, and the dean of the faculty of medicine.

Informed consent before admission to hospital was routinely requested by one REB. Four others specified that informed consent must be obtained before the patient leaves the ward or ambulatory centre to go to the operating room suite. In ten centres, the surgeon played no part in the consent process for anaesthesia-only protocols, and in five others only for joint anaesthesia-surgery studies. Surgeons in two centres gave permission for their patients to be studied and informed patients that they might be invited to participate in anaesthesia research. Fourteen respondents considered it inappropriate for the REBs to request that surgeons be involved in the informed consent process for anaesthesia studies. Release of confidential information in order to contact patients at home or at work specifically for research purposes was known to cause concern to the REB in two centres, to the clinical investigator in six, and to the hospital administration office in three; the opinion of the REB in ten centres was not known.

Discussion

The survey showed that the REBs are constituted in a similar manner across the country and are responsible to the affiliated university in the majority of centres. In most cases, informed patient consent to participate in clinical research projects is obtained after admission to hospital. Members of REBs may consider that, for most studies, an in-hospital approach provides adequate time for reflection and ensures protection of confidentiality and privacy. To emphasize the importance of completing the questionnaire, the introductory letter alerted respondents to a potential obstacle for anaesthesia research, which raises the possibility of bias in the results.

Respect of the autonomy of patients and subjects was defined in 1948 by the Nuremberg Code: "The person involved should have the legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision."[7] More recently, the MRC has recognized and addressed a number of

unusual ethical problems, including research on the mentally disabled, children, and embryos. However, it does not appear to have addressed issues related to informed consent in medical specialities such as anaesthesia and radiology whose patterns of practice and patient contact are different from those of internal medicine, surgery, psychiatry and oncology. The lack of understanding of anaesthesia practice by other specialists may unduly influence the decision of REBs.[8] The MRC's Standing Committee on ethics and experimentation includes neither an anaesthetist nor a radiologist. Unlike internists and surgeons, anaesthetists do not routinely meet healthy elective patients before their admission to hospital. The response to our questionnaire suggests that most REBs in Canada do not see this as an issue or they recognize the peculiar nature of anaesthetic practice and permit informed consent to be obtained following the patient's admission to hospital.

There appears to be no definitive answer concerning the time and place for obtaining informed consent. Various authorities use ill-defined terms such as "adequate time for reflection," "sufficient time to refuse is important." The Nuremberg Code,[7] The Helsinki Agreement,[9] and other authorities do not specifically address this issue.[5,10,11] Rather they emphasize full disclosure, absence of coercion on the part of the person seeking to obtain consent, and freedom of the subject to withdraw at any time. The MRC *Guidelines* state that, "Ideally, subjects should be fully informed, and should make the decision on whether to participate at leisure and in complete freedom from any pressure" but add the qualifying statement, "Practically speaking, this is rarely, if ever, possible."[1]

According to the Chief of Bioethics Program at the National Institutes of Health in the United States, the local REB's responsibility is to interpret the general guidelines and it can exercise considerable discretion regarding local practices, provided these are compatible with general national standards. In general, high standards of informed consent must allow the patient adequate time to reflect in a setting that is non-coercive and that provides an opportunity to consult with friends and advisors. In many cases, however, these standards may not be entirely practicable. The NIH tries to match the standards to the risk and experimental aspects of the research.* For example, when a non-standard anaesthetic drug or procedure is being studied and not all risks have been fully evaluated, a higher standard of informed consent is required than when the research involves comparison of two standard procedures or drugs. In the latter case there is no added risk and the investigator is simply requesting permission from the patient to gather data and informed consent does not require a large amount of time for reflection in a non-hospital setting.

The practical problems for anaesthetists in obtaining informed written consent from patients for clinical research prior to admission vary with the type of research and the patient population. For studies related to a particular surgical procedure, or a medical condition in the surgical population, it may be practical for the anaesthetist to be informed in advance and for the patient to be contacted prior to admission. However, unless the patient has given his or her consent, the transfer of such information from one physician to another for research purposes may be unethical.[2] Thus the surgeon who provides information without the patient's permission could be accused of not respecting the patient's confidentiality, while the anaesthetist who contacts the patient could be accused of invasion of privacy. Whether a telephone call at home or work 24–48 hr before admission from an unknown anaesthesia investigator, when the patient has many other concerns, is more or less upsetting than an interview after admission is unknown but would appear to be worthy of study. When the authors suggested that such a study be undertaken, representatives of the local ethical review board took the view that the results would not influence their deliberations. Furthermore, even if verbal consent is given by the patient to the surgeon at the time of consultation in the surgeon's office for a research anaesthetist to make contact at an unspecified later date, this may easily be forgotten in the intervening period.[12] In Calgary, the REB recommended that written consent be obtained from the patient for pre-admission review of medical records and contact by the researcher. This assumed that suitable subjects could and would be identified by the surgeon who would also be knowledgeable of current anaesthesia research protocols. This is practical in cooperative studies confined to a single area of practice, for example, cardiac surgeons cooperating with cardiac anaesthetists. On the other hand, it would be impractical for the many studies which are not controlled by speciality and whose inclusion criteria are not of surgical interest, for example, cardiovascular response to intubation of patients whose trachea may be difficult to intubate. Such patients are rarely identified by surgeons and would therefore be excluded from participation in clinical research if the practice of pre-admission consent were mandatory.

In summary, decisions in medical ethics depend on striking a balance between competing ethical claims.[1] We have drawn attention to those claims that are pertinent to obtaining informed consent for clinical anaesthesia research. It could be argued that neither REBs nor investigators are without bias although both groups may sincerely believe that they are working for the benefit of

*Personal communication. Dr. F. Bonkovsky to Dr. J. Remmers.

patients. Potential for conflict arises when certain ethical principles are challenged by the practical constraints faced by clinical investigators. Anticipation and understanding of these concerns and constraints should allow investigators and REBs to work constructively.

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