Original Article

INFORMED CONSENT AND RESEARCH WITH STORED BIOLOGICAL SAMPLES

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Study conducted at the Brazilian National Cancer Institute - INCA - MS/HC1, Rio de Janeiro, RJ, Brazil

ABSTRACT

Objective. To report practical experience in obtaining consent for a retrospective study conducted at the Brazilian National Cancer Institute (INCA). The study involved review of medical records and analysis of paraffin blocks of patients surgically treated for colon cancer between 2000 and 2004. Attempts to obtain informed consent were made in compliance with the resolution 196/96 of the Brazilian National Health Council and determination of INCA Research Ethics Committee.

Methods. At scheduled appointments, we could approach only four patients for consent during three months. After attempting contact by phone, an information sheet summarizing the content of informed consent, two copies of the consent form and a prepaid return envelope were then mailed to the patients.

Results. Of the 155 consent forms mailed, 115 were returned (74%). Of these, 111 patients gave consent to participate in the study, one refused consent, and we were informed that three patients had died. The time course of return of these forms ranged from 2 to 89 days (median: 10 days). Attempts to contact patients by phone were successful in 60 out of 160 cases (37.5%). The Research Ethics Committee waived the requirement of consent for those who had died or not responded. Overall mailing cost was R$ 1,004.40.

Conclusion. Obtaining consent from patients by phone and mail for a retrospective clinical study is feasible. Most patients responded to contact and gave consent to participate. However, the process entails costs and risks that cannot be overlooked.

Key words: Informed consent. Consent form. Bioethics. Biomedical research.

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Introduction

Clinical trials are now considered essential to scientific and technological development in health, ensuring that decisions on prevention and treatment are based on well-founded evidence. Medical research involving human beings is an essential tool for this progress. However, the conduct of clinical trials by health professionals has many ethical implications.

In order to standardize the principles of research ethics, some documents were prepared, becoming a global reference on the subject: the Nuremberg Code, in 1947, after the Second World War[1]; the Declaration of Helsinki in 1964 by the World Medical Association[2-7] and the Universal Declaration on Bioethics and Human Rights, UNESCO[8].

In Brazil, the approval of the resolution 196/96 by the Brazilian National Health Council[9] represented a milestone in the regulation of ethical aspects of clinical research. This resolution established guidelines and standards to be considered when designing the content of informed consent. For example, the information must always be communicated to participants in terms they are likely to understand.

Thus, informed consent is an integral part of medical research involving human beings in Brazil. However, there are few publications on the procedures for obtaining consent, especially in studies involving the analysis of archival tissue samples.

Objective

The objective of the present study was to report practical experience in obtaining consent for a retrospective study carried out at the Brazilian National Cancer Institute (INCA). The study involved molecular analysis of specimens stored in paraffin blocks from patients surgically treated for colon cancer between 2000 and 2004. In addition, medical records of these patients were reviewed. This study and the specific consent form were approved by INCA Research Ethics Committee (registration no. 022/07). Attempts to obtain informed consent from the patients involved were made in compliance with the resolution 196/96

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of the Brazilian National Health Council and determination of INCA Research Ethics Committee.

Methods

To make a survey of patients to be included in the study, data were retrieved from the hospital information service (INCA Hospital Registry). After reviewing the medical records, 185 were considered eligible. Of these, 21 patients had already died (Figure 1).

Our search for informed consent started in September 2008. Using INCA information system, Absolute, we investigated the appointments scheduled at the Division of Abdominal Surgery, where, as a rule, these patients are followed. From October to December 2008, four patients were approached for consent during their scheduled appointments.

A list containing name, hospital registration, address and telephone number of the patients was then organized. Patients were first contacted by phone in order to confirm mailing address and update their data on family history of cancer. An information sheet summarizing the content of informed consent was then drawn up. The information sheet, two copies of the consent form and a prepaid return envelope were then mailed to the patients. In the summary, patients were requested to return the letters even if they refused consent to participate in the study, marking this decision in the appropriate field.

At each stage the number of patients contacted and their responses to give or refuse consent to participate were recorded. A specific field for inclusion of such information was created in the database (MS Access® v2003). Written comments sent spontaneously were filed. All statistical analyses were performed using R software (v2.9.0).

Results

Attempts to contact patients by phone were successful in 60 out of 160 cases (37.5%). Thus, we were informed that four patients had died and one was living abroad, information not contained in the medical records (Figure 1).

Of the 155 consent forms mailed, 115 were returned (74%). Of these, 111 patients gave consent to participate in the study and one refused consent. By return mail and phone calls from family members, we were informed that three more patients had died. The time course of return of the forms ranged from 2 to 89 days [median: 10 days; mean: 18 days; 95% confidence interval (CI) 14-22], considering a median follow-up of 331 days (mean: 323 days, 95%CI 314-331).

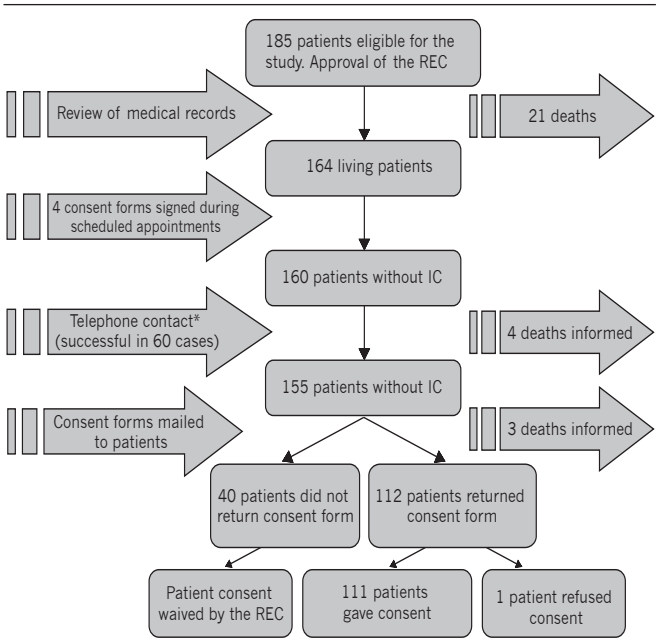
Two patients sought the return address (INCA Clinical Research Center) to deliver the consent form in person instead of mailing it. The researchers answered three phone calls after the forms were mailed: two to answer questions and one from family members informing that the patient had died. Along with the consent form, we received six written messages from patients or relatives who had given consent to participate in the study. The contents reported appreciation for the treatment received at the Institution (4), religious references (1), information about death of patient (2), and request for information on the research results and heritability of the tumor (1). There were no negative comments about the research, even in the one form that refused consent.

Overall mailing cost was R$ 1,004.40 (R$ 6.20 per patient). This expense was due to the purchase of envelopes and stamps and making photocopies. For telephone contact, we used the structure of the Institution; therefore, we could not estimate these costs.

INCA Research Ethics Committee waived the requirement of consent for those patients who had died or not responded. During the stage of telephone contact, the researchers were provided with the electronic address (e-mail) of the patient living abroad so that the consent form could be sent in electronic format. A few days later, a scanned signed copy of the form, giving consent to participate in the study, was returned via internet. This consent form was submitted to INCA Research Ethics Committee, which validated its use in the study.

Figure 1 shows the sequence in which the study was developed. Tables 1 and 2 summarize the final situation of the study. These tables describe the total number of patients included, deaths, and consent forms needed and obtained, in addition to the method used to obtain consent and response of patients.

Figure 1 - This flowchart represents the sequence in which each stage of the study was performed.



*During telephone contact, we were informed that one patient was living abroad. The patient was e-mailed the consent form, which was then signed, scanned and returned via internet.

IC: informed consent.

Table 1 – Total of living patients and deaths

Patients included	185
Living patients	157 (85%)
Deaths	28 (15%)
Information on deaths	
- Medical records	21
- Search for IC	7

This sum refers to the total number of patients included in the study and the total number of deaths identified after reviewing medical records and our search for IC.

IC: informed consent

Table 2 – Total IC needed and obtained

IC needed	157
IC obtained	117 (74.5%)
Method to obtain consent	
- in person	4
- by mail	112
- internet response	1
Participation in the study	
- consent	116
- refusal	1

Total de TCLE necessários: definido como o número de pacientes dados como vivos ao final do estudo

A única recusa em participar foi manifestada mediante retorno da correspondência, assinalando tal decisão no sumário enviado junto ao termo

TCLE: termo de consentimento livre e esclarecido

Discussion

Once approved by the Research Ethics Committee, the first stage of this research was the selection of patients, conducted by reviewing medical records. At this stage, it was possible to exclude patients with tumors of characteristics different from those established in the inclusion criteria as well as to discover which patients had already died. During this review, we also obtained the patients' mailing address and telephone number in order to start our search for informed consent. Although this stage may seem trivial, it is worth noting that the medical record is a document that should be handled with the utmost care, in accordance with the determinations of the Criminal Code[10], Civil Code[11], the Code of Consumer Protection[12] and the Code of Medical Ethics[13], in addition to the Brazilian Constitution[14].

To carry out this research, it was necessary to seek consent from patients who had already, in most cases, completed their treatments. Therefore, only four consent forms were obtained in person, over a three-month period, during appointments already scheduled at the hospital. The follow-up of these patients at INCA is performed as follows: control examination is made once a year from the second or third year of surgery. After the fifth year, patients without recurrence are discharged. Thus, most patients were no longer being followed, since our search for informed consent from patients treated between 2000 and 2004 started only in October 2008.

Therefore, it was necessary to find another method to obtain consent from these patients. We chose to contact patients by phone and mail.

The practice of sending forms by mail to obtain consent has already been reported by other authors. Vermeulen et al[15]described its use in a study conducted in the Netherlands that analyzed biological samples archived for 10 years. Of the 132 consent forms mailed, 90% were returned; the forms were mailed more than once, if necessary. Patients who did not respond to the postal request were also contacted by phone. Furness et al.[16] mailed consent forms to 495 patients who underwent renal transplant followed by biopsy in the United Kingdom, and 68% of the forms were returned. The present study conducted at INCA, which involved patients with colon cancer for at least four years, after attempting contact by phone and mail, had a return rate of 112 out of 152 living patients without signed informed consent (73.6%). After a review of the literature, Brazilian data that could serve as a comparison were not found. Likewise, there are no references as to the time course of return of the forms, which ranged from 2 to 89 days, with a median of 10 days, in our study. The time course observed, as well as mailing costs, may serve as a parameter for other studies attempting to obtain consent by mail.

However, in addition to the return rate, other aspects with respect to obtaining consent by mail are worth analyzing. Its use virtually eliminated personal contact between researchers and the research subjects. One may then speculate whether, for this reason, some patients would have failed to express their doubts. According to Concone[17] this step is essential to ensure that consent is considered actually free and informed. Not infrequently the degree of difficulty to understand informed consent is incompatible with the educational level of our population[18]. Unfortunately, this study did not aim to assess the degree of understanding of informed consent. On the other hand, the lack of face-to-face interaction may have minimized the chance of coercion, which can sometimes occur, albeit unintentionally.[19,20] Nevertheless, some patients contacted the researchers by visiting the Institution, calling them or sending written messages.

Sending consent forms by mail may present other risks. Some patients would probably not like to receive a letter at home telling about their medical treatment. Even if we chose not to mail the consent form, a simple telephone contact, telegram or call from the Brazilian National Cancer Institute would be sufficient to refer to the type of illness treated.

Thus, it is worth noting one more consideration: the so-called research subjects of the present study are people who received a diagnosis of malignant neoplasm and survived a major surgery, which was often supplemented by chemotherapy. Subsequently, these patients have to live with the risk of cancer recurrence. Some psychological disorders can markedly occur in this group of patients, such as anxiety, depression, and posttraumatic stress disorder[21]. Whatever the

method chosen for these people to indicate whether or not they would give consent to participate in the study, it would be impossible to prevent the patients from reporting to their disease and treatment. In addition, it would not be possible to predict whether or not these memories could bring some degree of emotional maladjustment.

Some authors suggest that, considering these potential risks and the high rates of consent obtained, it would be worth giving up informed consent in certain situations.[16,22] Furthermore, those authors argue that the conduct of these investigations is likely to lead to advances that will benefit the society as a whole and that the risks are minimal, if the biological samples are used for the purposes previously specified.

The responsibility of judging each case and defining the potential risks resulting from the use of biological samples and obtaining or failing to obtain consent from patients rests, without a doubt, with the Research Ethics Committees. For this, the Committees should, always trying to defend the interests of patients, refer to the resolution 196/96 of the Brazilian National Health Council and to international documents on which this resolution was based. Among their principles, we highlight the right of autonomy of research subjects. Moreover, one cannot forget that the indiscriminate use of biological samples may have frightening consequences, such as, in extreme cases, the marketing of human body parts.[23]

It is therefore of paramount importance that we seek ways to minimize possible psychological damage resulting from attempts to obtain consent from patients. Mailing consent forms, even without prior success in telephone contact, as performed with some patients in this study, does not seem appropriate, since this procedure may inadvertently expose personal information.

Regarding the attitude of INCA Research Ethics Committee, obtaining consent was required based on the resolution 196/96 of the Brazilian National Health Council. This resolution states that "in cases where it is impossible to record the informed consent, this must be properly documented, with an explanation of the causes of failure and opinion of the Research Ethics Committee." [our translation]. This was the argument used by the researchers to request the waiver of consent for patients who had died and those who failed to respond either by phone or mail.

Finally, it should be noted that, through our search for consent, important information was obtained on the outcome of patients. Seven deaths that were not recorded in the medical records were discovered, that is, 25% of the total. Moreover, the loss of sample due to refusal of consent was negligible.

Conclusion

Obtaining consent from patients by phone and mail for a retrospective clinical study using archival tissue samples is feasible. Most patients responded to contact and gave consent to participate. However, the process entails costs and risks that cannot be overlooked. Thus, when demanding consent for archival tissue use, the Research Ethics Committees should be particularly concerned with the methods to be employed in the search for patients. It is recommended to avoid sending mail without prior authorization of research subjects.

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