

RESEARCH ETHICS

Obtaining explicit consent for the use of archival tissue samples: practical issues

P N Furness, M L Nicholson

J Med Ethics 2004;30:561–564. doi: 10.1136/jme.2003.003368

See end of article for authors' affiliations

Correspondence to: Professor P N Furness, Departments of Pathology, Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW, UK; pnf1@le.ac.uk

Received 29 January 2003
In revised form 15 May 2003
Accepted for publication 2 June 2003

Background: Over the past few years, research ethics committees have increasingly demanded explicit consent before archival tissue samples can be used in research projects. Current UK guidance in this area requires an assessment of whether it is "practical" to obtain explicit consent. Ethics committees have little experience or evidence to help them to judge what is "practical" in this context.

Methods: We attempted to obtain general consent for research use of surplus tissue from renal transplant biopsies from the entire patient population of the renal transplant unit in Leicester. The nature of this patient population would be expected to facilitate this task.

Results: A total of 495 letters were sent. Attempts were made to contact non-responders when they attended the outpatient clinic. One year after the initiation of the project, the opinions of 26% of the patients had still not been ascertained.

Conclusions: The results confirm that the vast majority of patients are happy for "surplus" biopsy material to be used for research; the situation does not parallel the use of autopsy tissue. A requirement to obtain explicit consent for the study of archival tissue is likely, however, to block or at least seriously delay research, which is contrary to the public interest and specifically may harm the interests of the patients concerned. In the UK, the problem of tissue being used against the wishes of the donor has now been largely replaced by the problem of *prohibition* of tissue use against the wishes of the donor.

Publicity surrounding the retention of organs removed at postmortem,¹ especially at Alder Hey Hospital in Liverpool, UK,² has led to a widespread reappraisal of the circumstances under which it is ethical to use human tissues for a variety of socially laudable purposes such as teaching, laboratory quality assurance, and biomedical research.

The stimulus to change came from organ retention after postmortem examination, but the effect has not been limited to the use of postmortem tissue. Changes have also occurred in relation to the use of tissue excised from living patients, by surgeons and physicians, for therapeutic or diagnostic purposes. Such specimens are first examined in pathology laboratories for the direct benefit of the patient concerned. Almost always, however, some tissue remains after this examination is complete. This may be an extremely small amount of tissue in the case of small biopsies, but with major surgical resection the amount of "surplus" tissue may be substantial.

There is evidence from surveys of public opinion that the majority of the public regard most "surplus" therapeutically excised tissue as having little or no emotional value.^{3,4} This clearly differs from the situation in respect of autopsy tissue. The use of such tissue was subjected to detailed ethical scrutiny by the Nuffield Council on Bioethics as recently as 1995.⁵ The Nuffield report recommended that patients should be informed of how surgically resected tissue might be used for the benefit of others and emphasised that patients had a right to object to such use. The Nuffield Council concluded that the consent of the patient determines the legitimacy of any future use. If appropriate information is given, then unless specific instructions were issued to the contrary by the patient, the initial consent to removal of the tissue could be assumed to indicate consent to any future ethically acceptable use of the tissue. This does not resolve the problem with using existing archives, but laboratory workers could reasonably assume that "surplus" tissue resected from *living*

patients had been "abandoned". Such abandoned tissue could then legitimately be used for any ethically acceptable purpose without further consent from the patient. Similarly, in 1999 a report from the College of American Pathologists recommended that patients should be asked to indicate if they wished to *opt out* of such use of resected tissue as part of the process of obtaining consent to any surgical procedure.⁶ Positive, explicit consent was not required.

Hence, unlike the retention of whole organs at autopsy, there have been recent ethical reviews of procedures in this area. Nevertheless, under the influence of the postmortem organ retention scandals, a number of authoritative sources in the UK have rejected the concept of "abandonment" and concluded that appropriately informed consent, and usually specific explicit consent, is necessary before surplus surgical tissue can be used for purposes other than the direct benefit of the patient.^{7–9}

These sources recognised that this creates a potential problem in relation to existing collections and archives of tissue. Histopathology departments, for example, collect large archives of tissue fragments, initially processed for diagnosis, for the direct benefit of patients. These are stored primarily as part of the medical record, but in the past it has been considered acceptable for thin sections to be removed from such tissue blocks for research and other ethically acceptable purposes. This practice meant that even when studying a rare disease it was possible to search an enormous archive and thus find a statistically valid number of cases for study. If, however, such cases are only available on the basis of appropriately informed consent, the problem arises of how to obtain such consent years after the sample was excised.

To avoid making such collections unavailable for future medical research the Medical Research Council⁷ recommended that in the case of archival samples it may be

Abbreviations: GPs, general medical practitioners; NHS, National Health Service; RECs, research ethics committees.

appropriate for research to proceed without consent if it is impractical (or unethical) to trace patients and ask them for such consent. The UK Department of Health has followed broadly the same line.⁹

Unfortunately there is so far no guidance on what constitutes "impractical". Clinical research ethics committees (RECs) have in the past principally been concerned with research projects which require the presence of the patient. If the patient is present there is no problem in contacting them to ask for consent. Perhaps as a result, some RECs have invariably instructed researchers to use archival tissues only after obtaining explicit consent, including a signed consent form. The result, in many cases, has been that research projects have been blocked, potentially against the wishes of patients, simply because the researchers were unable to contact the patients. Evidence that obtaining consent was "impractical" came too late.

The present study was therefore undertaken to assess not only what proportion of patients would give explicit consent to the use of surplus tissue when asked, but also to ascertain the practical difficulties involved and the significance of a failure to respond to a postal request for consent.

The population studied was one which is arguably as easy to study in this way as is possible: the entire cohort of living renal transplant recipients at a single renal transplant centre. By the nature of their illness, such patients are never discharged from hospital based care until death. In Leicester this population contains about 50% non-white patients, mainly of Asian origin. The population is relatively static geographically, so the patients are in most cases not difficult to contact.

MATERIALS AND METHODS

Patients who had renal transplants and who had biopsies taken from the graft were identified by a search of the disease codes on the hospital pathology department computer system. This unit takes "protocol" biopsies at engraftment and from stable transplants, so this list should include all transplant recipients. Patients who had subsequently died were excluded by searching against two clinical databases held in the departments of nephrology and transplant surgery and by a manual check by a transplant coordinator.

A combined patient information sheet and consent form was drafted, under the supervision of the Leicestershire Research Ethics Committee (REC), asking for explicit consent to the use of archival transplant biopsy material for any future research project which was approved by the REC. It was explained that such approval would not be forthcoming for controversial research or research with potential to harm the tissue donors. Safeguards to preserve confidentiality were explained. The information sheet, consent form, a personalised covering letter, and a prepaid return envelope were posted to all living renal transplant patients registered at the transplant unit. Patients were asked to return the form in every case, irrespective of whether consent or objection was recorded.

Initially the REC argued that as the patients were all attending follow up clinics, it should be possible to obtain consent by face to face interview, and they said they would prefer this approach to sending a letter. (Using interviews rather than letters provides a closer parallel to standard procedures in clinical trials, with which RECs are more familiar). Agreement to send letters was achieved after discussion pointing out that: approaching large numbers of patients in busy clinics was difficult; patients who took the trouble to take a letter to the post were, if anything, demonstrating greater commitment to assist research than those seen in the clinic, and minimising the use of a face to face interview would reduce the risk of unintended coercion.

The letters would come from clinicians whom the patients already knew were responsible for their ongoing clinical care.

A purpose built database was designed and written using Microsoft Access to import patient details from the pathology department computer, to generate the personalised letters, and also to record responses as they were returned, in a manner designed to facilitate subsequent authorisation or rejection of samples for use in research projects. (A data free copy of this database, with a "user's manual", is available free on email request to peter.furness@le.ac.uk).

Two months after the letters had been posted, patients who had not responded were identified from this database. After this time point, any non-responder who attended a transplant outpatient follow up clinic was presented with another copy of the information sheet and consent form, with a verbal request that they record their wishes. The time course of return of these forms, and the proportion of patients giving consent or objection, were recorded. In this way we obtained a measure of the proportion who were willing to give consent among the group of patients who did not respond to the initial postal request.

TIME COURSE OF THE STUDY

The start of the project was regarded as the date of submission of the proposal to the REC (19 November 2001). The proposal was initially approved by the REC, but only subject to several amendments to the patient information sheet. One of these would have led patients to believe that a failure to reply would indicate adequate consent for research to proceed (though this would have been merely implied consent rather than explicit consent). This would have greatly decreased the motivation to respond from all except patients who objected, thus seriously reducing the value of the project. Subsequent discussions about the precise wording delayed final confirmation of approval, and letters were not posted to patients until May 2002, over six months after the project was initiated. Two months were allowed for patients to return the prepaid envelopes, after which time follow up in outpatients started. Data for this report were compiled one year after the start of the project, on 19 November 2002, allowing four months of tracing patients as they attended the outpatient clinics.

RESULTS

Postal questionnaire

In the first phase of the study 495 letters were posted. Of these, 328 were returned (68%). Of these, 316 (96.3%) gave consent to use of surplus biopsy tissue in research and 12 (3.6%) objected.

Letters sent in error

In 13 cases we found that we had inadvertently sent a letter to a patient who had died. In one case, this was as a result of the death occurring in the few days between the list being prepared and the letters being posted. Members of the family sent an anonymous reply expressing considerable anger and distress and issued a specific instruction that they should not be contacted again, thereby preventing us from apologising. The other cases where we inadvertently wrote to individuals who had died resulted from an error in our method of compiling the list of patients. This was initially generated from a list of patients known to have had biopsies taken from renal transplants. It was subsequently checked to identify transplant patients who had died. Unfortunately, it transpired that a small number of transplant biopsies had been erroneously submitted to the pathology laboratory bearing the name of the donor rather than that of the recipient. Such individuals were not identified in our search for transplant patients who had died, because they were not transplant

patients. This led to inappropriate letters being posted. In six cases this resulted in a letter from a relative, or a comment on the consent form, giving consent on behalf of the deceased person and merely pointing out the error without expressing any serious upset. One person, however, whose spouse had died several years earlier in particularly distressing circumstances, responded with considerable anger and grief. We subsequently rescreened our database and identified five more cases where letters had been inadvertently sent to cadaveric donors, but which had elicited no response. These cases have been eliminated from all the results described here.

Outpatient follow up

One hundred and fifty nine patients (32%) failed to respond to the initial postal questionnaire. One year after the study was initiated only 33 of these patients had been traced through the outpatient clinics. Of these, 32 gave consent and one objected. Thus, the proportion of patients objecting to the use of tissue in research was 3.6% in those who responded to the initial postal questionnaire and 3.0% in those who failed to respond but were subsequently traced in outpatients. This is not statistically significantly different.

At the end of one year, the wishes of 126 patients (26%) had still not been ascertained.

DISCUSSION

It is now widely accepted that patients should be empowered to control the uses to which their tissues are put after those tissues are removed from the body. From this it follows that it is wrong to use tissues against the wishes of the tissue donor, and this conclusion has led to a widespread requirement for explicit informed consent before tissues can be used in any form of research, however simple.

A second conclusion can be drawn, however, from this initial premise, namely that if the tissue donor is content for excised tissue to be used for the good of society, it is immoral to prohibit that use. Recent events in the UK have demonstrated that many RECs either ignore this second conclusion, or assume it can be simply dissolved by asking the tissue donor for consent. This is a valid assumption only if asking for consent is not a difficult matter. Communications received through the Royal College of Pathologists indicate that demands for explicit consent have led to the abandonment of many research projects in the UK. These include the abandonment of the UK limb of at least two international studies, both of which subsequently went ahead in other developed countries without a requirement for explicit consent for the use of archival tissue samples in research (Dr I Ellis, personal communication, 2001; PNF, personal experience, 2003).

When RECs are considering whether to demand consent for archival tissue use, and if so whether explicit consent is needed, we hope these results will help to illuminate debate about whether such a requirement is indeed "practical" or not. Research ethics committees exist to protect the interests of the patients. Those interests include facilitating the development of improved medical care through research, so prohibiting research merely because the views of the patient are not known is contrary to the aims of the RECs.

The present results confirm that when tissue samples have been stored without recording the views of patients on their subsequent use, it can be very difficult to ascertain those views, even under the favourable conditions which we studied. We took a stable population of patients, all with a condition which precludes discharge from medical care. One year after the start of the project we had still not ascertained the wishes of 26% of the patients. Those non-responders whom we had traced in outpatients may be assumed to be a

random sample of the non-responders, from which we may deduce that 97% of the 26% we have not yet traced will eventually give consent. Hence in this population, if an REC had demanded explicit consent before a research project could proceed, then 25% of the patient population would have been wrongly prohibited from contributing to the research project—and this after we had spent a year working to request consent.

In most studies using archival tissue samples the situation is likely to be even less favourable. In one recent study which needed to use archival tissue, the patient population had received treatment for colorectal cancer. These patients are often discharged from follow up if they are regarded as cured and therefore can only be contacted through their general medical practitioners (GPs). The REC initially demanded explicit consent from all living patients before archival samples of colorectal cancers could be studied, despite the protestations of the investigators that this would cause distress to some patients and might make the study impossible to conduct. It was subsequently demonstrated that the majority of GPs were unwilling to collaborate with efforts to obtain consent, or would expect a fee. Furthermore the majority of patients regarded requests for consent to be unnecessary. Some patients also regarded such requests as a distressing reminder of a disease they would rather forget (Professor P Quirke, personal communication, 2003). After a considerable delay that study was allowed to proceed without patient consent, but this is currently unusual in the UK. In the present study, even though chronic renal failure is not a disease the patients could possibly forget, we found that unexpected factors could still result in letters requesting consent causing considerable distress to a few recipients. In some circumstances, apparently innocuous requests for consent can have unpredictably damaging consequences.

The proportion of patients who objected to research use of their biopsy samples is low. Even lower rates of objection, around 1.0%, have been recorded by others.¹⁰ In a study of the more controversial area of genetic testing, only 2.6% of respondents registered an objection.¹¹ Our slightly higher rate of objection might be a consequence of the high proportion of patients from ethnic minorities in Leicester. One patient who refused consent cited his Muslim religion as the reason, though this did not appear to be a problem for the vast majority of Muslims we contacted. The number of patients who objected in this study is too small to permit statistical testing, and as the patients in question have objected to involvement in research we believe that to attempt that analysis may be unethical.

The low objection rate supports the results from surveys of public opinion indicating that surgically resected tissue has very different emotional importance from postmortem tissue;^{3,4} the former is usually regarded as waste to be disposed of, whereas postmortem tissue represents the precious remains of a loved relative. It is therefore not appropriate to assume that guidance for the control of postmortem tissue will necessarily be appropriate to the use of all human tissue. Indeed, the UK Department of Health appears to share this view. Postmortem tissue has received such extensive press coverage that it is easy to forget that, in numeric terms, samples removed from living patients are far more important in teaching, laboratory quality control, and research than are autopsy specimens.

Hence we may conclude that since the introduction of new guidance in the UK, the problem of tissue use against the wishes of the donor has been largely eliminated, but it has been replaced by the problem of *prohibition* of tissue use against the wishes of the donor. We do not wish to enter into

debate about which of these is the more heinous crime, but it would appear that the latter is now the more frequent.

Of course, we should strive to eliminate both. This can only be done by knowing the opinions of all patients, as proposed by the Royal College of Pathologists.¹² Until measures to solicit, record *and make such opinions available to researchers* are implemented (and paid for), we still have a problem. If we accept that the problem exists, that 97–99% of patients are willing for surplus tissue to be used in research, and that the vast majority want to benefit from medical research, then it becomes legitimate to ask how the wishes of the majority can be facilitated. At present, UK guidance is that research using archival tissue can usually proceed only if consent is available.^{7–9} This is being interpreted in most cases as meaning explicit consent, with a signature on a consent form. In contrast, use in teaching and laboratory quality control can proceed on the basis of the absence of any objection, that is, with implied consent.⁸ It is notable that, in relation to consent for the use of data by the health service, the UK information commissioner has recently said: “It is a mistake to assume that implied consent is a less valid form of consent than express. Both must be equally informed and both reflect the wishes of the patient”.¹³

If a research project is in a non-controversial area and can be shown to have no risk of adversely affecting the interests of the tissue donors, is it acceptable to use implied consent to permit research use? This move would put the onus on the 1–3% who object; they would have to respond to information provided and register their objections. Is this an unreasonable expectation if it avoids blocking medical research, which is conducted for the good of all, when 97–99% are willing for their tissues to be used in research? In a recent debate published in the *BMJ*, both protagonists seemed to think that suitably robust forms of implied consent would in most cases be acceptable.^{14–15} This is not the present position taken by most UK research ethics committees or the UK Department of Health.

AUTHORS' NOTE

Since this manuscript was accepted for publication the UK Government has published the text of a new Human Tissue Bill, which is currently progressing through Parliament. The current text of that Bill is available at <http://www.publications.parliament.uk/pa/pabills.htm>.

ACKNOWLEDGEMENTS

We are grateful to Ms Karen Iliffe, who provided secretarial assistance, undertook data entry, and was responsible for tracing patients in the transplant outpatient clinics. Mr N Dean provided helpful informal advice on the position of the UK Department of Health, and pointed out that this is under active review at present. We are also grateful for the assistance of the staff of the renal

transplant unit at Leicester General Hospital, and for the advice of the Leicestershire local research ethics committee.

Authors' affiliations

P N Furness, Department of Pathology, Leicester General Hospital, Leicester, UK

M L Nicholson, Department of Transplant Surgery, Leicester General Hospital, Leicester, UK

Disclaimers/declaration of interest: The authors are involved in non-commercial biomedical research using archival tissue samples.

Sources of support: National Health Service (NHS) Research and Development.

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