Get patients' consent to enter clinical trials

Elizabeth Wager, Peter J H Tooley, Michael B Emanuel, Stuart F Wood

Gaining patients' consent to enter clinical trials is essential, but not easy. Giving careful thought to the design of the study itself, information which patients receive, and the use of a signed consent form may all help. To be properly informed, patients need to know something about their condition, the proposed study, and alternative options. The type and amount of information will vary and investigators need to judge the level appropriate for each person. Patients should understand that taking part in a clinical trial is voluntary and that their decision will not affect the quality of care they receive. The process of obtaining consent requires time and good communication. Working with young, elderly, or mentally impaired patients, or those particularly vulnerable to coercion, requires special sensitivity to the potential dangers.

Although about 3000 papers on informed consent have been written since 1989, little practical guidance is available for doctors recruiting patients to clinical trials. Many view the process as a legal safeguard,¹ though there is no doctrine of informed consent in English law.² The process should therefore be seen as enabling patients "to make a choice or state a preference about the treatment on offer" rather than a prudent form of defensive medicine.³

Outside a trial, doctors can decide how much patients participate in decisions about treatment. Some have argued that this discretion should extend to trials with a complex range of options. Otherwise, confronting the fact that there is no agreed optimum treatment may do the patient more harm than good.^{4,5} Our aim in this article is not to debate whether it is ever morally justifiable to include patients in trials without obtaining their consent, but to offer some practical help when patients explicitly give their consent.

Study design

Before starting to recruit patients you should be satisfied that the study itself is ethical. Anyone designing a study should consider the issue of patient consent at the outset. You must obtain approval from your research ethics committee for any clinical trial involving patients, and the committee should review any information and consent forms given to patients.

As consent is about asking patients to make a choice, patients should perhaps be consulted about trial design. Consent can be regarded as a reasonable choice only if the patient's aspirations match those of the study.⁶ This is particularly important for patients with life threatening illnesses, when choices between quantity and quality of life may be more affected by personal circumstances than medical considerations. In the United States organisations such as the National Breast Cancer Coalition campaign for patients to participate more in research. In Britain such advocacy movements are less common, but some well established self help groups for patients could be consulted about clinical trials.

To explain a trial clearly the investigator must understand the aims of the trial and exactly how it will

be conducted. One study of the quality of informed consent found that patients attending centres that had not participated in designing the study considered that they received poorer information than those recruited by investigators who had been active in the study from the start.⁷

What information should patients receive?

Before considering entering a trial, patients will need some information about their diagnosis, the nature of their condition, and the treatments available. Written information about conditions may be useful. To be properly informed a patient needs to know not only about the proposed trial but also about the other options.

INFORMATION ABOUT THE TRIAL

Explaining the concepts of randomisation and the placebo effect to patients is not easy. The difficulties may partly be due to fear of losing patients' confidence in admitting to not being aware of what treatment they will receive or to not knowing which treatment would be best for them. Randomisation may sound less threatening if you explain that it ensures that the hoped for benefits and unknown risks are spread fairly between groups of patients. You might also explain how randomisation reduces bias. For example, in an unrandomised study comparing a new drug with an established treatment, patients who had not responded to available treatments might be more likely to choose the new drug, causing this group to include more cases of treatment resistant disease.

Most patients can appreciate the need for double blind procedures if you explain that results could be affected by either the patients' or the doctors' expectations. The placebo effect can be explained by saying that patients who know they are not receiving treatment often do less well than those who think that they are being treated. It may also be helpful to explain that a placebo is frequently used in trials of new drugs, when less is known about the new treatment's possible risks. Placebos are also common when no comparator treatment is available. In this case, patients receiving placebo are no worse off than those who are not in the trial. Therefore, you must explain the treatments available outside the trial.

How much detail about potential risks do patients require? Legal criteria state that the doctor should disclose any material risks—that is, those to which a reasonable patient would attach significance in that particular situation.² Patients might reasonably be expected to attach significance to events that are either severe—for example, paralysis or blindness—or are fairly likely to occur—for example, a 30% likelihood of nausea. In other words, consider telling patients about serious risks that are rare and about less serious events which are expected to happen more often.⁸ Patients should be told what to do if they experience an adverse event and whether compensation is available for serious injury. You must also be prepared to answer any questions patients might have about the trial.

You should tell patients about the implications of the

Janssen-Cilag, PO Box 79,
High Wycombe,
Buckinghamshire
HP14 4HJ

Elizabeth Wager, medical
writer

Peter J H Tooley, head of
medical affairs

Michael B Emanuel,
research and development
director

Department of General
Practice, University of
Glasgow, Woodside Health
Centre, Glasgow G20 7LR
Stuart F Wood, senior lecturer

Correspondence to:
Mrs Wager.

BMJ 1995;311:734-7

Writing clearly for patients

- Use short sentences
- Avoid jargon, or explain it when necessary
- Pay attention to layout:
 - Lists are clearer than paragraphs of text
 - A question and answer format can be useful
 - Headings are helpful
- Use a clear, legible typeface and design:
 - Everything in capital letters is less legible than upper and lower case
 - Serif typefaces—for example, Times or Courier—are easier to read than sans serif—for example, Univers
 - Black text on a white background is usually clearest; avoid white on black or strong coloured backgrounds
 - Use at least a 12 point (or 10 characters per inch) font size

trial—for example, if it entails extra visits to the surgery or travel to another centre. Patients need to know how long the trial will last and what will happen when it ends (especially in terms of the provision of unlicensed treatments). They should be told about any discomfort or inconvenience associated with any assessments.

Patients vary in the amount of information they expect to receive, but this should not be used as an excuse to gloss over potential risks. Dawes and Davison studied patients' information requirements before surgery and concluded that "just because somebody is anxious it does not mean that they do not want any information."⁹ Another surgical study found that providing a detailed account of what might go wrong did not significantly increase patients' anxiety.¹⁰ The same probably applies to clinical trials, but this has rarely been tested.

Patients with serious illnesses may seem to want reassurance from their doctor rather than the uncertainty of a trial. Fallowfield *et al* found, however, that 94% of patients with cancer wanted as much information as possible.¹¹ Simes *et al* found that patients given full information about a cancer trial were more anxious than those who received a shorter explanation, although this anxiety did not affect their relationship with the doctor.¹²

In all cases, doctors should develop the skills necessary to identify how much information each patient requires, but they should remember that for clinical trials there is probably a bare minimum that all patients should receive. Byrne *et al* describe patients "who simply want to be treated . . . so that they can leave the hospital, forget their illness, and resume growing prize marrows as far from the medical confraternity as possible,"^{11 13} while Brewin and Bradley describe patients who "thrive on a diet rich in detailed information about their illness."¹⁴ Doctors must decide where each patient fits on this continuum.

What do patients need to know about a trial?

Always explain that taking part in a trial is voluntary and that patients will get the best treatment available and the full attention of the doctor even if they do not want to participate. Patients also need to understand that they are free to withdraw from a trial at any point, and again, that this will not prejudice their treatment. Using a written consent form may make patients feel that they have signed an agreement to complete the trial.⁷ You may have to explain that the consent form aims to ensure exactly the opposite.

Practical considerations

In designing a trial, careful consideration should be given to:

- The ways in which information is given to the patient
- The use of written consent forms
- The setting in which consent is obtained
- The timing of obtaining consent.

PATIENT INFORMATION

Consider providing both oral and written information to patients, as recommended in the code of European good clinical practice.¹⁵ Preparing written information for patients is not easy, and guidelines for writing clear English should always be followed.¹⁶⁻¹⁸ A few essential points are shown in the box. Always test your written material on colleagues who are not part of the trial, and also on some lay people, to check for ambiguities, missing information, or sections that are difficult to understand. Keep the needs of the patients in mind—for example, translations for non-native English speakers or large print for elderly patients.

If written information is insufficient or inappropriate, audio or video tapes may be helpful. Tape recordings of consultations improve patients' understanding about their condition and reduce their degree of anxiety.^{19 20} They might be useful if large amounts of information need to be given to the patient.

Patients recall more about the practical aspects of a study than the potential risks⁷ and tend to forget risks more quickly than benefits.²¹ It may therefore be helpful to repeat information to help understanding and retention.

CONSENT FORMS

Using a consent form to register the patient's decision may help to reinforce information about the voluntary nature of trials or their implications. Forms also provide a useful procedural checklist. Several model consent forms are available (figure).²² Although models are useful, a consent form should relate specifically to the trial or procedure in question. Legal cases have established that consent is limited to a specific trial or treatment, and the patient cannot be considered to have given consent for anything else.

The consent form should be a separate document, not torn off the bottom of the patient information leaflet.²³ Forms using NCR (no carbon required) paper provide an instant copy for the patient to retain. The ethics committee will usually request to see the consent form before approving the study.

Study title	
Have you read the information provided?	Yes/No
Have you had an opportunity to ask questions and discuss the study?	Yes/No
Have all your questions been answered satisfactorily?	Yes/No
Have you received enough information about the study?	Yes/No
Who have you spoken to about the study?	
Do you understand that you are free to withdraw from the study	
—at any time?	
—without having to give a reason?	
—without affecting your future medical care?	
Do you agree to take part in this study?	Yes/No
Signed (patient)_____ (date)_____	
Signed (doctor)_____ (date)_____	

Model consent form²²

SCIENCE PHOTO LIBRARY

Always tailor the consent process to the individual patient

WITNESSED CONSENT

The role of a witness is to confirm that the patient was reasonably informed about the trial and consented freely to take part. Witnesses may also provide information for patients, answer their questions, and test their understanding of the trial.²⁴ However, these roles conflict to a certain extent, since a witness designed to prevent coercion should be as independent of the trial as possible, whereas one expected to discuss the trial with the patient needs to be well informed and therefore part of the research team. The names and addresses of independent witnesses should be recorded so that they could be traced to give their opinion on how consent was obtained if this was subsequently challenged. Nurses often have an important role in explaining the trial to the patient and may also act as advocates or go between if patients have concerns about a trial but feel daunted about approaching the doctor.

The fact that patients' signatures are witnessed may reinforce patients' belief that they are entering into a binding contract in signing the consent form. This misapprehension should be overcome by explaining that the witness is there to protect the patient from being forced to sign a form by the investigator. Witnessed consent may be particularly helpful if patients are infirm or have difficulty in speaking. In this case the witness should probably be someone who knows the patient, is familiar with his or her likely wishes, and can interpret for him or her.²³

The presence of a witness or the second opportunity to ask questions in a different setting may also help to allay patients' anxiety. This may not only make patients feel better but also improve communication as anxious patients may not be able to communicate clearly and may believe that they cannot withhold or withdraw consent.

SETTING AND TIMING

Patients should not feel rushed into giving consent, which may be difficult to achieve in a busy surgery or clinic. A separate appointment may therefore be needed. Patients also need to feel that they cannot be overheard and are treated in privacy.²⁵ Patients experiencing serious uncontrolled pain or acute emotional distress may be unable to give valid consent. Gravely ill patients may, however, have times when they are more lucid and alert than others, and investigators should try to approach patients during these times and simply withdraw if they have picked a bad moment. People's ability to make decisions will also be affected by their emotional state; patients who have just been told that they have cancer may not be competent to give consent

at that moment, but they may have been so before and may become so later.

Ideally, patients should be given a cooling off period before making a final decision. This may also enable them to discuss the decision with friends and family. Guidelines from the Association for the British Pharmaceutical Industry (ABPI) recommend at least 30 minutes of thinking time for non-emergency situations, and 24 hours whenever possible.¹⁵

Patients in some circumstances may be particularly vulnerable to unintentional coercion, as described by Fitten, who suggests that: "Chronic care institutions tend to breed a loss of self-esteem, learned helplessness and dependence in residents that may lead to fears, real or imagined, about the consequences of not pleasing their caregivers."²⁶ Extra care is also needed when considering patients in the armed services and those who are compulsorily detained in hospital. An independent witness may be helpful in these circumstances.²⁷ Research on prisoners is not permitted because of these problems.

The setting may also materially affect the patient's ability to give consent, since patients with impaired cognitive function perform better in their own homes than in unfamiliar surroundings such as hospital wards.²⁸

TESTING UNDERSTANDING

Even providing the best designed patient information sheet and a well planned interview cannot ensure understanding.¹ To make matters harder, patients may have perfect comprehension of the information but fail to appreciate its consequences.²⁹ You should therefore try to test patients' understanding—for example, by asking them to put the information into their own words.

Remember that the ability to repeat information is not the same as understanding its consequences. For example, you should tell patients that after an operation they will not be able to drive rather than state that their foot will be stiff or in plaster.

WHO SHOULD OBTAIN THE PATIENT'S CONSENT?

European guidelines on good clinical practice state that the investigator is responsible for obtaining consent, but they do not specify that such responsibility cannot be delegated. Other members of the team, such as research nurses, often explain the trial to patients and answer their questions, but consent should be obtained by a medically qualified person with responsibility for treating the patient. Lavelle-Jones *et al* found that patients thought that house officers were "the most effective in imparting information relating to surgical treatment,"²⁸ but Kerrigan *et al* suggested that standards of obtaining consent are low "because the task . . . is left to more junior staff."¹⁰ We suggest that seniority or age are probably poor criteria for deciding who should obtain the patient's consent, but essential qualifications are:

- Familiarity with the study
- Knowledge of optional treatments
- Appreciation of the need for informed consent
- Having time for a full discussion with the patient
- Recognition that people are not logical and that patients have a right to make apparently illogical decisions
- An understanding that a patient's personal circumstances, experience, and personality may affect the decision as much as medical considerations.

Difficult situations

Much has been written on the ethics of research on young, old, and mentally impaired people. It is outside the scope of this article to rehearse these arguments,

but sometimes research in such populations is justified, and therefore guidance on gaining consent is needed.

Under English law consent may be given on behalf of a child by the parent or, if the child is a ward of court, by the court authority.³⁰ The child's views must, however, be respected, and even if the child is too young to be considered legally competent to consent, every effort must be made to explain the procedures and potential outcomes.^{30,31} When parents are asked to give consent all the usual considerations, such as providing information, will apply.

In legal terms as soon as people reach their legal majority, whatever their mental capacity, no other person has authority to grant consent on their behalf.³² In clinical trials, however, it may often be good practice to seek consent from a carer or relative. Blanket definitions of categories of patients unable to give consent are probably unhelpful. Patients may be competent to consent to some trials but not to others according to the complexity of the information and the consequences of treatment.

Patients with fluctuating or deteriorating conditions may be able to give informed consent during a remission or in the early stages of the disease. In these cases a patient advocate may be appointed with power of attorney to act on the patient's behalf if he or she becomes incompetent.³³ Warren *et al* have, however, graphically described the problems of informed consent by proxy. They found that nearly a third of proxies would give consent on behalf of elderly relatives even if they believed the relative would have refused. Similarly, 21% were prepared to give consent for elderly relatives to take part in studies which they (the proxy) would not have entered themselves.³⁴ This suggests that special consideration should be given to explaining the risks and discomforts of a trial if consent is being given on another person's behalf.

For patients living in residential homes the American College of Physicians suggests that, in addition to obtaining the approval of an ethics committee, a committee of residents might also be consulted.³⁵ The Law Commission recommends that "the consent of a medical treatment proxy or attorney appointed with authority to give such consent" should always be obtained for research involving incapacitated adults.³⁶

As a general rule, you should be satisfied that the patient has not expressed an objection to taking part in a trial and should also try to obtain consent from someone close to the patient. Pay particular attention to explaining the trial to anyone giving consent by proxy and avoid making patients feel obliged to cooperate because they live in an institution.

Conclusions

The process of obtaining a patient's properly informed consent to take part in a clinical trial should not be seen as an exercise in bureaucratic form filling but as an essential part of the trial requiring time, insight, and communication skills. Remember that patients refusing to give their consent is not a sign that you have failed but may indicate that you are conscientious enough to ensure that they are properly informed and make a free decision. Large proportions of patients refusing to enter a study may, however, signal a problem with the study design.

Some doctors argue that informing patients only worries them, but a little anxiety is a price worth paying to protect patients' rights, and patients may in fact be reassured by more information. Similarly, fears have been expressed that obtaining consent will damage the doctor-patient relationship. We suggest that, on the contrary, developing the skills needed to obtain consent for clinical trials will enhance relations, improve communication, and encourage increased patient participation in all decisions about their treatment.

- 1 Kessel A. On failing to understand informed consent. *Br J Hosp Med* 1994;52:235-8.
- 2 Heneghan C. Consent to medical treatment: what should the patient be told? *Br J Anaesth* 1994;73:25-8.
- 3 Silverman W. The myth of informed consent: in daily practice and in clinical trials. *J Med Ethics* 1989;15:6-11.
- 4 Tobias J, Souhami R. Fully informed consent can be needlessly cruel. *BMJ* 1993;307:1199-201.
- 5 Barer D. Patients' preferences and randomised trials. *Lancet* 1994;344:688.
- 6 Thornton H. Patients' preferences and randomised trials. *Lancet* 1994;344:689.
- 7 Lynøe N, Sandlund M, Dahlqvist G, Jacobsson L. Informed consent: study of quality of information given to participants in a clinical trial. *BMJ* 1991;303:610-3.
- 8 Samuels A. Informed consent: the law. *Med Sci Law* 1992;32:35-42.
- 9 Dawes P, Davison P. Informed consent: what do patients want to know? *J R Soc Med* 1994;87:149-52.
- 10 Kerrigan DD, Thevasayagam RS, Woods TO, McWelch I, Thomas WEG, Shorthouse AJ, *et al*. Who's afraid of informed consent? *BMJ* 1993;306:298-300.
- 11 Fallowfield L, Ford S, Lewis S. Information preferences of patients with cancer. *Lancet* 1994;344:1576.
- 12 Simes R, Tattersall M, Coates A, Raghavan D, Solomon H, Smartt H. Randomised comparison of procedures for obtaining informed consent in clinical trials for cancer. *BMJ* 1986;293:1065-8.
- 13 Byrne D, Napier A, Cuschieri A. How informed is signed consent? *BMJ* 1988;296:839-40.
- 14 Brewin C, Bradley C. Patients' preferences and randomised clinical trials. *BMJ* 1989;299:313-5.
- 15 Brown L. GCP and informed consent: a UK perspective. *Good Clinical Practice Journal* 1994;1(3):20-3.
- 16 Alberts T, Chadwick S. How readable are practice leaflets? *BMJ* 1992;305:1266-8.
- 17 Smith T. Information for patients: writing simple English is difficult, even for doctors. *BMJ* 1992;305:1242.
- 18 Priestley K, Campbell C, Valentine C, Denison D, Buller N. Are patient consent forms for research protocols easy to read? *BMJ* 1992;305:1263-4.
- 19 Cornbleet M, Knowles G, North N, Leonard R. Recording of outpatient consultations. *Lancet* 1992;340:488.
- 20 Anonymous. Outpatients on tape [editorial]. *Lancet* 1992;340:23.
- 21 Saw K, Wood A, Murphy K, Parry J, Hartfell W. Informed consent: an evaluation of patients' understanding and opinion (with respect to the operation of transurethral resection of the prostate). *J R Soc Med* 1994;87:143-4.
- 22 Royal College of Physicians. *Research involving patients*. London: RCP, 1990.
- 23 Ranson P. Consent: the legal aspects. *Good Clinical Practice* 1994;1(3):24-5.
- 24 Goodman N, Cooper G, Malins A, Prys-Roberts C. The validity of informed consent in a clinical study. *Anaesthesia* 1984;39:911-6.
- 25 Chopra S, Conquest I, Hirst L, Marshall P, Rutherford A. *A pharmacy study comparing miconazole and clotrimazole for vaginal candidosis*. Grove, Oxfordshire: Janssen Research Foundation, 1994.
- 26 Fitten L. The ethics of conducting research with older psychiatric patients. *International Journal of Geriatric Psychiatry* 1993;8:33-9.
- 27 Fulford K, Howse K. Ethics of research with psychiatric patients: principles, problems and the primary responsibilities of researchers. *J Med Ethics* 1993;19:85-91.
- 28 Lavelle-Jones C, Byrne D, Rice P, Cuschieri A. Factors affecting quality of informed consent. *BMJ* 1993;306:885-90.
- 29 Appelbaum P, Grisso T. Assessing patients' capacities to consent to treatment. *N Engl J Med* 1988;319:1635-8.
- 30 Skegg P. English law relating to experimentation on children. *Lancet* 1977;ii:754-5.
- 31 Shield J, Baum J. Children's consent to treatment. *BMJ* 1994;308:1182-3.
- 32 Brahmans D. Incompetent adults and consent to treatment. *Lancet* 1989;ii:340.
- 33 Helmchen H. The problem of informed consent in dementia research. *Med Law* 1990;9:1206-13.
- 34 Warren JW, Sobal J, Tenney JH, Hoopes JM, Damron D, Levenson S, *et al*. Informed consent by proxy: an issue in research with elderly patients. *N Engl J Med* 1986;315:1124-8.
- 35 American College of Physicians. Cognitively impaired subjects. *Ann Intern Med* 1989;111:843-8.
- 36 Brahmans D. Consent to research in presence of incapacity. *Lancet* 1993;341:1143-4.

(Accepted 15 June 1995)