

Offering patients entry in clinical trials: preliminary study of the views of prospective participants

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Abstract

Objective—To ascertain attitudes to different methods of obtaining informed consent for randomised clinical trials (RCTs).

Design—Structured interviews with members of the public, medical secretaries and medical students.

Setting—The public were approached in a variety of public places. Medical secretaries and students were approached in their place of work.

Subjects—Fifty members of the public, 25 secretaries and 25 students.

Main outcome measures—Views on RCTs were elicited, with particular emphasis on how subjects thought the concept of randomisation should be explained. Each participant was presented with descriptions of proposed clinical trials and asked to select his or her preference from a range of options.

Results—Written information was preferred over verbal information in 91% of replies. Most respondents (86%) would prefer to sign a consent form. Of the seven statements explaining randomisation, a significant difference was found in favour of explanations that were less explicit about the play of chance (ANOVA; $p=0.0004$). Eighty-three per cent of participants thought that randomised trials were morally acceptable when there was no prior medical preference between treatments. However, over half (55%) thought they would find it upsetting to be offered entry in such a trial and a quarter thought the outcome of treatment might be adversely affected.

Conclusions—Our results offer some support for the idea that “economy with truth” is less unsettling than a frank description of the stark reality of what randomisation means. It is a matter of debate as to whether, if we are correct, autonomy should have precedence over beneficence.

The offer of entry in a clinical trial is likely to affect the experience of care for many people, especially if the process of randomisation is described explicitly. Potential participants should be given a detailed written explanation of the rationale for the trial and be asked to sign a consent form if they agree to take part.

Key words

Randomised trials; attitudes; clinical trials.

Introduction

Randomised Clinical Trials (RCTs) are being carried out at an increasing rate, involving ever greater numbers of participants. They are accepted as the most reliable form of clinical research for detecting moderate differential effects of alternative treatments.¹ It is also widely accepted that consent for randomisation should be obtained in the majority of instances – certainly, most Research Ethics Committees (RECs) demand this. The process of obtaining consent for randomisation may affect a patient’s experience of care, especially when treatment can be a matter of life and death. We were particularly concerned to find a form of words to describe the process of randomisation itself, since this has not previously been researched (see Discussion) and because it is a topic of great practical importance. Re-submissions to RECs are often required to improve on wording. The views of potential participants in trials should be taken into account. We were also concerned to find out how people think the offer of participating in a trial might affect them. The extra staff time and attention, and the deeper insight the patients might get into their care process, along with a feeling of altruism, might enhance experiences for patients. Against this, the feeling that the staff are not in control, resulting from the implied ignorance on a point of care, might be profoundly worrying. We therefore interviewed members of the public and people with medical knowledge (secretaries and students) to ascertain their views on how information should be presented to those considering participation in RCTs of different kinds and on the effect the offer to take part may have.

Method

Members of the general public (n=50) were interviewed in a variety of places in Leeds. They were approached in parks and outside shopping centres, in art galleries and libraries. Medical secretaries (n=25) were interviewed in their place of work and medical students (n=25) approached outside the entrance to the library of Leeds University Medical School.

Key words

Randomised trials; attitudes; clinical trials.

The interview was split into three sections, dealing with (i) methods for obtaining consent, (ii) explaining the concept of randomisation and (iii) the likely effect of being offered entry in a trial.

SECTION 1: VERBAL V WRITTEN CONSENT

Each person was asked to imagine himself first to be the sufferer from a non-life threatening but painful condition (migraine headaches – scenario 1) and then in a life-threatening situation (either parent of an unborn baby who is failing to grow properly – scenario 2; or a life-threatening form of cancer – scenario 3). In each case the respondent was invited to read a description of his condition (appendix) and then to imagine that the doctors were unable to decide between two different methods of treatment. *The rationale for the RCT* was explained and he was then asked to imagine that he was to be invited to participate in such a study. Whether scenario 2 or 3 was described was determined by choosing one of two unmarked and shuffled opaque envelopes.

We first enquired about the preferred format for the relevant information. Possible answers were:

- a – “Discussed in depth on a personal basis with your doctor, without any written information”.
- b – “Discussed in depth on a personal basis with your doctor, and *then* be given a written copy of the information about the trial”.
- c – “Given as a written copy to be read in your own time, and *then* discussed in depth on a personal basis with your doctor”.

If he indicated that he would prefer to have written information, then he was asked to choose between two levels of detail, and he was asked if he wanted to sign a consent form.

SECTION 2: WORDING TO EXPLAIN RANDOMISATION

Seven statements (figure 1) were presented in a random order, and interviewees were asked to place a cross along a 100 mm visual-analogue scale corresponding to how good an explanation they thought each was.

SECTION 3: EXPECTED EFFECTS OF BEING OFFERED ENTRY TRIAL

Respondents were asked whether they thought that clinical trials such as those described in section 1 were acceptable and whether they thought that being offered entry in a trial would be upsetting. In addition, they were asked whether they thought that being involved in a clinical trial would affect the outcome of their recovery and, if so, whether they thought that it would be for the better or for the worse.

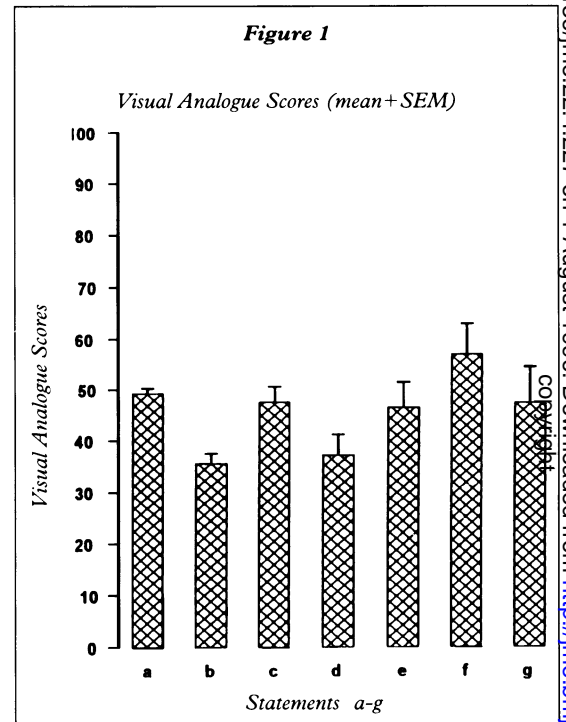
The questionnaire was checked for readability by the “Word for Windows” Microsoft package and scored 11.6 on the Gunning Fog Index – a figure considered acceptable for patient information

leaflets.² The data were then analysed using SPCC for Windows, version 6 on an Elonex 486.

Results

SECTION 1: WRITTEN V ORALLY GIVEN INFORMATION, PREFERRED LEVEL OF DETAIL AND SIGNING CONSENT FORM

The great majority of respondents preferred written information (90.8%) but opinion was nearly evenly



Different descriptions of the seven(a-g) statements explaining the concept of randomisation

A Once you have agreed to enter the trial, a computer will randomly allocate you to one of two possible methods of treatment.

B Once you have agreed to enter the trial, a computer will perform the equivalent of tossing a coin to allocate you to one of two methods of treatment.

C Once you have agreed to enter the trial, you will be randomly allocated to one of two possible methods of treatment by chance alone; that is, independent of who you are and who your doctor is.

D Once you have agreed to enter the trial, a computer will perform the equivalent of drawing names out of a hat to decide which of two methods of treatment to allocate you to.

E Once you have agreed to enter the trial, a computer and not a doctor will decide which of the two treatments to give you. Its decision will be random and due to chance alone, and not based upon the patient's or the doctor's decision.

F Once you have agreed to enter the trial, you will be allocated to one of two treatments with equal chances of each treatment being the one you will receive.

G Once you have agreed to enter the trial, one of two methods of treatment will be chosen by chance, and not by a decision made by the patient or the doctor.

Table 1 Preference for oral v written information in the non-life threatening and the two life-threatening situations

	Option chosen		
	Scenario 1	Scenario 2	Scenario 3
a	8 (8.2%)	7 (12.7%)	3 (7.1%)
b	36 (36%)	27 (49.1%)	19 (45.2%)
c	55 (55.6%)	21 (38.2%)	20 (47.6%)

Ninety-nine of the 100 respondents gave answers on scenario 1 and 97 on scenario 2 or 3

split between those favouring presentation of this material before or after the relevant consultation (49% v 42%). Students, in particular, would prefer the written information first (72%) but this difference was not statistically significant. These results did not vary by clinical scenario – table 1.

The overwhelming preference among those requesting written information, was for the more detailed option (89%) with no significant difference across scenarios 1 to 3 (92% v 98% v 95%).

Eighty-six per cent of interviewees favoured signing a consent form. All 25 secretaries preferred to sign, v 82% of the general public and 80% of medical students (χ^2 and Mantel-Haentzel; $P=0.06$).

SECTION 2: EXPLAINING THE CONCEPT OF RANDOMISATION

The mean visual-analogue scores allotted on the seven different statements explaining randomisation (“a” to “g”) in question 1 are shown in figure 1.

Overall statement “f” (“... you will be allocated to one of two treatments, with each treatment having equal chance of being the one you will receive”) was the most popular (mean score of 56.7 mm), while “b” (which involved the tossing of a coin) and “d” (which involved names pulled from a hat) were the least popular (mean scores 35.6 mm and 37.1 mm respectively (figure 1)).

Differences in responses between the different groups of participants were sought using ANOVA, with the exception of statements “b” and “e”, where the data were not normally distributed, and where the Kruskal Wallis test was used. The most striking difference (ANOVA; $P=0.0004$) applied to statement “g” (“... one of the two methods of treatment will be chosen by chance, and not by a decision made by the patient or doctor”), which was especially disliked by the public (Tukey – B test; $P<0.05$). The only other significant difference (Kruskal Wallis: $P=0.026$) was on statement “b” (“... a computer will perform the equivalent of tossing a coin to allocate you to one of two methods of treatment”), which was much less disliked by the medical students (Mann-Whitney; $P=0.0095$).

SECTION 3: EXPECTED EFFECTS OF BEING OFFERED ENTRY IN A TRIAL

Randomised clinical trials were considered ethically acceptable by 83% of respondents, given that there

was no medical preference between treatments (equipose).³ In the individual groups, this corresponded to 82% of the general public; 88% of the medical secretaries, and 80% of medical students ($p=0.7$).

Over half of those questioned thought that they would find being invited to enter a clinical trial upsetting (55%), with figures for the general public, medical secretaries and medical students of 50%, 64% and 56% respectively ($P=0.5$). However, a smaller proportion (one third) thought that participating in an RCT would affect their recovery. Of those who thought that it would affect their recovery, 63.6% thought it would be for the worse (for example, “make me more likely to give up”), and 36.4% thought it would affect them for the better (for example, “make me try harder”). There was no measured difference across groups for any of these comparisons.

Discussion

The sample in our study was not perfect. Since the respondents were approached in public places they are unlikely to be completely “representative” of all citizens. An opinion pollster, if using a sample similar to ours to predict the results of an election, would issue a disclaimer about the precise numerical interpretation of the data. Thus, our results, when extrapolated to the public at large, should be treated as indicating an order of magnitude, rather than an exact level. Furthermore, particular groups, for example, parents of sick children or people with chronic disabilities, may have different views from the public at large. Nevertheless, clinical trials are now so widely used that they are an issue of legitimate public interest and we think the views of our respondents are likely to be widely shared. Also, the use of three very different “constituencies” enhances confidence, at least where they concur.

The question of whether or not to supplement verbal information has been addressed by several studies. Simes *et al*⁴ demonstrated that the combination of verbal and written consent, in comparison with merely verbal consent, produced more anxiety and less willingness to agree to randomisation, yet gave a better understanding of the procedures involved. Their results reveal a trade-off between autonomy and beneficence. In a survey among members of 16 clinical trials committees and evaluation teams for the Spanish Ministry of Health, Dal-Re⁵ found that 96% of respondents thought that a document containing written information should be supplied to patients. Marsh⁶ explains that written information ensures that all patients receive the same minimal data-set and Dal-Re⁵ points out that when the patient may take the material home (if clinically appropriate) the benefits and risks may be considered at leisure, perhaps with the help of a third party. In our study, almost all the respondents

preferred to have some form of written information, irrespective of whether they were dealing with a life or death scenario. However, there was no consensus on whether written material should be presented before or after discussing the issue with a clinician.

The majority of respondents in this study would appreciate a consent form. White⁷ points out that too much emphasis may be placed on obtaining a witnessed signature without making sure that the patient is fully informed. In Dal-Re's⁵ study, 68% of clinical trials committee members thought that a patient's informed consent should always be obtained in writing, compared with only 23% who believed that this was required only in certain situations, for example, if a major intervention was involved.

It is important, at least from the scientific and utilitarian perspectives, that a large proportion of citizens are prepared to take part in trials. Information offered to the participants must be of sufficient quality and quantity to obtain as near to genuine informed consent as is possible, yet ethics committees lack general rules for the wording construction of consent forms.

The question of exactly how detailed the written information should be remains to be answered. White *et al*⁷ conducted a study of whether breast cancer patients preferred long, medium, or short information leaflets to explain a chemotherapy trial. Like us, they found that a majority (68%) of patients preferred the more detailed option. In contrast to Simes,⁴ they did not demonstrate higher stress levels when more detail was provided. No study has yet defined the upper ceiling for the amount of detail which should be included. Too little information may conceal material which could affect decisions,⁸ while too much may obscure the crucial points or discourage careful reading.⁹ Clearly, there is no "perfect solution" which will match everyone's preference,¹⁰ but it is interesting to note that when people are heavily involved in deciding on trial entry, non-participation rates are high.¹¹ We also note that it is impossible for a person to make a rational judgment on how much information he would like until he has seen the information. Detailed leaflets, in which the crucial points are highlighted, might be the best compromise.

Patients can only make an informed choice if they fully understand the concept of randomisation.¹² Even when patients are given an apparently explicit explanation of randomisation, many still fail to understand – in the study by Simes,⁴ over half the participants failed to grasp this concept. We believe we are the first authors specifically to explore the preferred wording to explain the concept of randomisation. The last author is carrying out a systematic review of the ethics literature relating to clinical trials and has ascertained that 83 articles contain empirical data. No other author has addressed this issue of the precise wording to be used to explain the concept of randomisation. Of seven statements in this study, two ("b" and "d") were clearly disliked by

most of the people interviewed. Both of them explain change in terms of either "drawing names out of a hat", or "tossing a coin". The clear favourite explanation was "f", which made no attempt to explain how chance would result in treatment allocation. Hence, it seems to us that the preferred wordings are less explicit and allow the mind not to dwell too long on the random nature of treatment assignment or the loss of medical control. Although terms such as "spinning a coin" may appear flippant, randomisation itself may be perceived in a similar light. This fits with our further observation that most people did *not* like the idea of having treatment chosen at random and a quarter even thought this might adversely affect treatment outcome.

If we are correct that explicit explanation of randomisation is unsettling to many people, then a trade-off between autonomy and beneficence exists, but we think that modern opinion would give more weight to the former – not to do so might create an element of deception.

The disclosure implicit in the offer of randomisation of medical ignorance on an important aspect of therapy might be upsetting to some people. In practice this may be cancelled out by the extra time and attention which the consent procedure involves. This "hunch" along with our formal finding that potential patients like *detailed* explanations, suggests that obtaining consent for clinical trials must be an unhurried process – the extra time and explanation may then more than offset any negative reactions to the offer of trial entry. The views of people who have been offered entry in trials irrespective of whether or not they decided to participate, would be fascinating, especially if contrasted with others randomised not to be offered trial entry. Consent for such follow-up studies should be sought when the original offer of trial entry is made.

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Appendix

SCENARIOS USED AS AN EXAMPLE OF CLINICAL SITUATIONS WHERE RANDOMISED TRIALS MAY BE USED
Scenario 1

Please try and imagine yourself in the following situation for a few minutes. You have been diagnosed by your doctors as suffering from attacks of migraine, causing you to feel sick, dizzy and have terrible headaches. As a consequence you have had to take time off work and feel too unwell to enjoy your leisure time.

There are two methods of treatment available and the doctors are unsure which method to choose in your case. One choice would be the use of a new technique, called biofeedback, which involves

learning how to relax. The other choice would be the more traditional drug therapy. Both have slight drawbacks, as biofeedback is time-consuming and needs to be learned, and drug therapy may cause stomach irritation.

Biofeedback involves learning relaxation techniques to decrease the size of muscle contractions in the forehead and seems to be effective. Recent research seems to suggest that it may work as well as, if not better than, drug treatment in decreasing the discomfort and number of migraine attacks.

Traditional drug therapy has been shown to decrease the symptoms of migraine, but does not prevent future attacks (which biofeedback may do).

Scenario 2

Please try and imagine yourself in the following situation for a few minutes. You are shortly to become a parent, but your unborn baby, which is not yet fully mature, is failing to grow properly.

There are two options to take in helping the baby, and the doctors are unsure in this case which option to take in the baby's best interest. They have invited you to enter into a trial.

In this trial, either the baby will be left in the womb and its progress monitored, or it will be delivered without delay, but both have possible problems.

Delivering the baby without delay means that it will be born prematurely and without fully developed breathing ability and will be at risk from infections. Leaving the baby inside the womb could also be dangerous, because the baby may not get enough blood supply to remain healthy.

Scenario 3

Please try and imagine yourself in the following situation for a few minutes. You have been diagnosed by your doctors as suffering from a life-threatening form of cancer.

In this trial, you will either receive drug treatment or surgery. If you are given drug treatment you will feel very sick for a few days and possibly lose some of your hair. Surgery to remove the cancerous tissue will leave a wound which will be sore, open to infection and leave a scar. In addition, surgery also runs a slight risk of death.

Because the doctors are uncertain about which method would be more effective in this case, they offer you entry into a trial.