Are we getting informed consent from patients with cancer?

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Keywords: informed consent; medical ethics; uncertainty; clinical trials

Summary

We developed a consent form for a hypothetical trial and asked patients to underline information that was pertinent to their decision to accept or refuse to participate in the proposed trial. We also investigated whether patients correctly interpreted statements describing the probability of certain events occurring. Of the 50 patients, 74% did not indicate that both risks and benefits were pertinent. Of the 20 patients who would not enter the trial, 70% focused on risks of therapy only. In contrast, of the 30 who agreed to enter, only 33% focused entirely on risks, while 10% did not note potential for either benefit or risk. For each of four probability statements, patients chose one of four possible interpretations, only one of which was correct. Depending on the statement, between 26 and 54% of the interpretations were incorrect. It appears that many decisions regarding trial entry may be based upon incomplete or incorrect information.

Introduction

There has been a long and slow evolution in medicine toward the doctrine of informed consent. The Hippocratic Oath, which has guided physicians' behaviour from ancient times until the present, makes no recommendations about informing and conversing with patients^{1,2}. It is only since the middle of this century that the idea of disclosing information and obtaining voluntary consent has been given serious consideration. The disclosures at the Nuremberg trials of the atrocities that took place with unwilling captives, in the name of research, served as the stimulus for the development of a code of ethics to guide human experimentation. The Nuremberg Code makes explicit the importance of the subject's autonomy³.

The essence of autonomy is self-determination. This means that the individual is free to make his/her own decision about what will or will not be done to his/her body, without coercion, and after some period of deliberation^{1,4,5}. In the case of research involving humans, the patient/subject must be informed about the risks, benefits, and alternatives in order to deliberate and choose whether or not to participate. Whether patients are being asked to take part in clinical trials or to make decisions about undergoing treatments, the same principles regarding information disclosure and decision-making apply.

The issues about informing and being informed have merited a great deal of attention and there have been many empirical studies of various aspects of informed consent⁶. Meisel and Roth reviewed the literature by examining studies concerning what patients were told, what patients know and their capacity for decision-making, pressures that come to

bear upon patients, and how these various aspects of informed consent relate to each other⁷. Their general conclusions were that there is very little knowledge about the mechanics of obtaining informed consent and that the validity of the information that is available is in question.

Clinical trials provide an interesting situation to study since 'informed' consent, documented by written agreement, is required for both legal and ethical purposes. A standard consent form usually includes a written summary of the reasons for the study, risks, benefits, and the nature of the procedures. It also guarantees the right to refuse or withdraw from the study and provides assurance that the subject's identity will be protected³. To examine some of the issues relating to the patient's perspective on providing consent, a consent form for a hypothetical trial was developed and patients were asked to consider the information and to indicate whether or not they would participate in the study if it were to be undertaken. The primary objective was to seek the patients' interpretation of information by: (i) recording the information that they described as being pertinent to their decision to accept or refuse trial entry, and (ii) eliciting their views about the meaning of statements that described either the likelihood of certain events occurring, or the meaning of randomization. As a secondary objective, patients were asked for their preferences for various ways of providing information about probabilistic events.

Methods

General plan

A consent form, analogous to those currently in use at our institution, was developed for a hypothetical trial of chemotherapy. Patients were asked to underline statements that were pertinent to making a decision about participating in the study and to indicate whether they would agree or refuse to enter the proposed clinical trial if it were to be undertaken. In addition, they answered questions regarding the meaning of four statements describing the probability of an event occurring and indicated their preference for verbal and/or numerical descriptors of probability.

Subjects

Of 52 outpatients approached, a convenience sample of 50 participated in this project. All patients had been admitted to the Princess Margaret Hospital Lodge, an ambulatory care facility for patients from various parts of the province of Ontario who require post-surgical treatment for cancer. All patients were aware that they were being treated for cancer. Inclusion criteria were: an established diagnosis of cancer, an understanding of written and spoken english, and

I have a particular type of cancer for which there is no known effective treatment. Approximately half the patients with this disease are alive and well twenty years after diagnosis. A new drug called Cyclo-uracil has been developed. It has potential for improving control of this type of cancer and perhaps for prolonging survival.

This trial is designed to determine if Cyclo-uracil is effective in treating my kind of tumour. In this trial, half the patients will receive the drug and half will not receive treatment. Whether an individual patient receives the drug or not will be determined by a process called randomization, whereby, each patient has an equal chance of either receiving or not receiving the treatment. Those who receive the drug will have it intravenously (ie. through a vein) on the first two Mondays of every month for a period of one year. The procedure takes about three hours on each occasion. Regardless of whether or not an individual patient receives the drug, all patients will have blood tests and x-rays done twice a year to monitor their health for a decade of follow-up.

There is a possibility of certain side effects occurring during treatment with Cyclo-uracil.

1. A fall in the level of white cells and/or platelets in the blood frequently occurs. This side effect, though short lived, increases the risk of serious infection or bleeding. Doses will be adjusted to counteract the risk of this side effect.
2. Nausea and vomiting may occur.
3. Mucositis (sore mouth) occasionally occurs.
4. Itchy, red skin rashes are unlikely to occur.
5. Congestive heart failure resulting in death rarely occurs.

Side effects will be treated symptomatically or by dose reduction if necessary.

If I decide not to participate in this study or if I decide to stop participating at any time, my future care will not be prejudiced in any way. My name will be known only to those people who are directly involved in my care in this study and will not be used in any publication that may result from this study.

I would AGREE to participate in this study _____
I would REFUSE to participate in this study _____

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Figure 1. Consent form for the hypothetical chemotherapy trial

written consent for participation. Since patients who had previously agreed or refused to enter a clinical trial or who had undergone chemotherapy might have a bias, we chose to exclude them. It should be noted that the participants in this study had the opportunity to be in contact with patients undergoing chemotherapy and could observe the effects of cytotoxic drugs as evidenced by hair loss, stomatitis, etc.

Consent form

The consent form is shown in Figure 1. It describes a hypothetical, randomized, controlled clinical trial of a fictional new drug 'Cyclo-uracil' intended for use in cancer chemotherapy. The disease and treatment options, the potential benefits and risks of therapy, the procedures, and the rights of the patient are described. The format is analogous to that of consent forms used in oncology and, as is customary, only verbal descriptors of probability are used.

We chose to use a hypothetical situation for a number of reasons. It allowed us to standardize the information patients received about the study. We were able to get a cross-section of patients by designing a 'generic' trial and we avoided any potential influence on the accrual rate of an actual trial.

Six-part questionnaire

Three statements about the likelihood of certain events occurring were given; (i) 'itchy, red skin rashes are unlikely to occur', (ii) 'a particular type of cancer responds to radiation treatment in 10% of cases', and (iii) 'nausea and vomiting occurs in 45% of patients'. A fourth statement about randomization was also presented: 'a process called randomization is used to select your treatment in this clinical trial'.

These statements were either taken directly from the consent form or adapted from it. For each of these four statements, four meanings were given, only one of which was correct. An open-ended 'other' category was also provided. The incorrect responses had been given in a previous pilot study in which patients were asked to state the meaning of these same statements in an open-ended format. The statements and possible responses are shown in Tables 3-6, with correct answers in bold text.

Two additional questions enquired about patients' preferences for the way potential benefits and risks or side effects of therapy are described; 'If you wished to know what chance you had to benefit from a treatment, would you prefer that chance to be described using words (ie 'may') or numbers (ie '45%') or both (ie 'may (45%)')?' and 'If you wished to know what chances there were for risks or side effects, would you prefer these chances to be described using words (ie 'rare') or numbers (ie '5%') or both (ie 'rare (5%)')?'. Each patient was asked whether s/he preferred verbal (word) or numerical descriptors or both.

Design

Patients were asked to read through the consent form once to obtain an overview of the study. They were then asked to reread the form and underline any phrases or sentences that caught their attention. Certain information might stand out as being positive, ie would encourage entering the study, or negative, ie would discourage trial entry. In addition, patients were asked to put a plus sign beside underlined statements they considered 'positive' and a minus sign beside those considered 'negative'. Patients were not given any additional information by the research assistant. All patients then indicated whether they would agree or refuse to take part in the hypothetical study if it were to be undertaken. The six-part questionnaire was then completed, with the two questions about preferences for verbal or numerical descriptors of probability being separated by the other 4 parts of the questionnaire. Information about age, gender, education and work status, diagnosis, and previous experience with cancer were recorded. Previous experience meant that the patient had a recurrence or a second primary malignancy.

Statistical analysis

To examine the associations between categorical variables (education, gender, work, previous experience with cancer) and participation in the hypothetical trial, chi-square tests were used. Mann-Whitney tests were used to compare median age in the two groups⁸.

Results

The characteristics of the patients are shown in Table 1. There were no statistically significant differences between patients who agreed or refused to participate in the hypothetical trial, except in their previous experience with cancer, ($\chi^2_1=4.678$, $P<.05$). More patients who refused to enter the trial had a recurrence or a second primary malignancy.

Underlined statements on the consent form

To assess the information that these patients considered pertinent to their decision about trial entry, the underlined statements in the consent form were examined in two ways. First, the benefits and risks

Table 1. Characteristics of the subjects

	All (n=50)	Agree (n=30)	Refuse (n=20)
Age: mean (standard deviation)	53.7 (12.0)	53.7 (12.8)	53.8 (10.9)
range	26-77	26-77	32-68
Gender: female	26	14	12
male	24	16	8
Education: less than high school	25	16	9
completed high school	5	2	3
some post secondary	8	4	4
post secondary diploma or certificate	8	6	2
BA or equivalent	2	2	0
graduate degree	2	0	2
Work: (outside the home)	29	18	11
Diagnosis: head & neck	7	3	4
breast	18	10	8
urological & male genital	7	4	3
gastrointestinal	9	7	2
lymphoma/Hodgkins	3	2	1
other	6	4	2
Previous experience with cancer	12	4	8*

*Chi square on 1 df=4.678 ($P<.05$)

of treatment were examined. The percent of patients who underlined benefits only, risks only, both benefits and risks, and neither are shown in Table 2(A). Of those refusing the trial, the majority noted only the potential for risk (70%). In contrast, of those who agreed to enter the proposed trial, a much smaller percentage (33%) saw only risks. Twenty-seven percent saw only benefits, 30% saw risks and benefits, while 10% did not note potential for either benefit or risk. Second, the statements that encouraged (marked with a positive sign) or discouraged (negative sign) patient participation were tabulated. Table 2(B) shows the same phenomenon as A, in a less dramatic way.

Six-part questionnaire

To assess the patients' views about the meaning of statements of the kind found in consent forms, their answers to the six-part questionnaire were tabulated. Depending on the statement, between 26 and 54% of the answers were incorrect for the group of 50 patients. Table 3 shows the percentage of patients responding to each statement describing the meaning of 'rashes unlikely to occur'. One-third misinterpreted this statement. Table 4 shows the variation in meaning

Table 3. Interpretation of a verbal descriptor of probability, 'unlikely'

'Itchy, red skin rashes are unlikely to occur'

Which statement best describes the meaning of this sentence?

No patient will experience itchy, red skin rashes	0%
Most patients will experience a few itchy, red skin rashes	20%
Within a group of patients, only a few will have an itchy, red skin rash	66%
Within a group of patients, each patient will have some degree of an itchy, red skin rash	14%
Other	0%

Table 4. Interpretation of '10% response rate'

'A particular type of cancer responds to radiation treatment in 10% of cases'

Which statement best describes the meaning of the sentence?

The radiation treatment is about 10% effective in an individual patient	22%
On average, for 10 out of every 100 patients, the tumour will decrease in size after radiation treatment	46%
There is a 10% chance of survival	10%
10% of patients are cured	22%
Other	0%

Table 2. Summary of the underlined statements

(A) Benefits and risks of treatment

	Benefits	Risks	Benefits & risks	Neither
Agree (n=30)	8 (27%)	10 (33%)	9 (30%)	3 (10%)
Refuse (n=20)	2 (10%)	14 (70%)	4 (20%)	0 (0%)

(B) Positive and negative aspects of the study

	Positive	Negative	Positive & negative	Neither
Agree (n=30)	7 (23%)	5 (17%)	16 (53%)	2 (7%)
Refuse (n=20)	0 (0%)	8 (40%)	12 (60%)	0 (0%)

of a '10% response rate'. Fifty-four per cent of patients gave an incorrect meaning. Table 5 indicates the interpretation of a '45% event rate'. In this case, 26% of patients were incorrect in their interpretation of the statement. Table 6 shows what patients thought 'randomization' meant. Thirty-two per cent of the patients gave an incorrect interpretation.

Each individual patient was given a score according to whether s/he had 0, 1, 2, 3, or 4 of the statements interpreted correctly. There was no difference between those who agreed and refused on this parameter and

Table 5. Interpretation of a numerical descriptor of probability, '45%'

<i>'Nausea and vomiting occurs in 45% of patients'</i> <i>Which statement best describes the meaning of the sentence?</i>	
On average 45 out of every 100 patients will experience nausea and vomiting	74%
Nausea and vomiting will happen to everyone, but it will not bother the majority of patients	8%
45 patients will experience nausea and vomiting, 100 patients will not	6%
All patients will experience some degree of nausea and vomiting	12%
Other	0%

Table 6. Interpretation of 'randomization'

<i>'A process called randomization is used to select your treatment in this clinical trial'</i> <i>Which statement best describes the meaning of this sentence?</i>	
The process will select the best treatment for me	14%
Each individual patient has exactly the same chance of receiving the drug, or not receiving the drug, as any other participating patient	68%
One treatment is given one time, another is given another time	0%
The doctor decides which treatment is the right one for me	18%
Other	0%

the results for the whole group were as follows: 30% had 4, 30% had 3, 18% had 2, 8% had 1, and 14% had 0 of the statements correct.

Preferences for verbal and/or numerical descriptors of probability

When patients were asked for their preferences for words and/or numbers when the chances for benefit from treatment were being described to them, 16% preferred words, 34% preferred numbers, 48% preferred both and 2% marked other. The one patient selecting 'other' thought information about benefits and risks should not be given to any patient. When describing the likelihood of risks or side effects, 16% of patients preferred words, 28% preferred numbers, 54% preferred both and 2% marked other. Only 4/50 patients did not give the same answer when asked first about benefits and then about risks.

Discussion

The doctrine of informed consent has been described by several authors^{7,9}. The conceptual framework of Meisel & Roth has several facets: (i) information or disclosure which involves the provision of certain information by the doctor, (ii) competency which presumes that the patient is considered able to comprehend the information disclosed by the physician, (iii) understanding which assumes that the patient is competent and has been given information, (iv) voluntariness which refers to freedom in arriving at a decision, and (v) actual decision making which refers to the patient accepting or refusing therapy⁷.

We have used this framework to examine some aspects of the patient's perspective about providing

consent to participate in clinical trials. We did not assess competency, and have used interpretation of the information as a surrogate for understanding. Patients' interpretation of the information provided in the consent form was sought in two ways. First, they were asked to underline the information that they considered to be pertinent to their decision to accept or refuse trial entry. Second, they were provided with statements analogous to ones included in the consent form, and asked questions about their meaning.

The underlying concept regarding informed consent presumes that each individual receives certain information, proceeds to 'weigh' that information in terms of potential benefit or good against potential risk or harm, and then arrives at an autonomous decision. Our first approach to an assessment of the way patients interpreted the information provided in the consent form permitted a test of this concept. Analysis of the underlined information considered by patients as pertinent to their decision about trial entry indicated that only 13/50 patients underlined both benefits and risks. When the scope of the analysis was broadened to include aspects of the information, in addition to benefits and risks, that patients would consider 'positive' (encourage trial entry) or 'negative' (discourage participation), only 28/50 underlined both positive and negative aspects. Thus, a substantial number of patients did not appear to approach the decision by consciously weighing both benefits and risks, nor by weighing both positive and negative aspects of the information that was provided to them.

The data about information considered pertinent to a decision about trial entry also indicated that patients assigned very different meanings to the same information. The following phrases were seen by some patients as promoting participation in the hypothetical trial, while others regarded them as discouraging participation: 'half the patients... alive and well twenty years after...', 'a new drug...', 'half the patients will receive the drug and half will not...' and '... receive the drug... every month for a period of one year'. Several patients indicated that the idea of intravenous therapy was negative. Many patients regarded the 10-year follow-up period, the assurance about the option of withdrawing from the study, and the protection of confidentiality as positive. In talking to patients following the tasks, several had interpreted the design of the study to include a placebo arm rather than the specified no treatment arm. Many patients stated that the side effects were not noteworthy and half the group did not indicate any special interest in the fact that congestive heart failure was said to occur 'rarely'. Several patients volunteered that they interpreted 'rarely' as 'never', therefore, this side effect was of no concern.

Our second approach to an assessment of patients' interpretation of information involved an analysis of their responses to statements analogous to those often included in consent forms. Examination of the meaning patients ascribed to four single-sentence statements revealed that within the group many of them misinterpreted the intended message. Twenty out of 50 patients were unable to correctly interpret more than two of the four statements and 14% indicated an incorrect meaning for all four statements. Patients had most difficulty with the statement that: 'A particular type of cancer responds to radiation

treatment in 10% of cases'. The incorrect answers may be confounded by a misinterpretation of the word 'responds'. This is of interest since it is common to discuss the probability of responding to therapy with oncology patients.

The statement with the most correct interpretations was: 'Nausea and vomiting occurs in 45% of patients'. However, this statement still posed a problem for 26% of the patients.

The statements based more directly on the consent form for the hypothetical trial had a 32% and 34% incorrect response rate. Although the consent form was explicit about the meaning of randomization, 32% of the patients did not select the correct interpretation. It is noteworthy that the alternative interpretations chosen were: 'The doctor decides which treatment is right for me' (18%), or: 'The (randomization) process will select the best treatment for me' (14%). The statement, 'Itchy, red skin rashes are unlikely to occur', was misunderstood by 34% of the patients. Thus, the interpretation of a verbal descriptor of probability posed problems for some patients, as did the numerical descriptor (see above).

When the chances for benefits were described, 82% of patients preferred to have a numerical estimate. Of these patients, 59% would like to have seen a verbal descriptor as well. When risks were described, a similar response was seen. These results are consistent with the report¹⁰ that in a survey of 400 people 75% preferred to receive information concerning uncertainty in numerical form.

When we assessed the characteristics of those who agreed and refused to participate in the trial, there were twice as many patients having previous experience with cancer in the group refusing the trial. These patients either recurred or developed a second primary. Although we do not know the extent to which patients understood their prognosis, the failure to respond to therapy may suggest to patients an unfavourable and uncontrollable future course of events. This may result in a more pessimistic view about research protocols on the part of these patients.

What can be said about whether or not informed consent was obtained from the patients participating in this study? If interpretation of statements, including statements incorporated into a consent form, is taken as a surrogate for understanding, then a significant proportion of the patients showed a lack of understanding. There appeared not only to be a lack of understanding of the information provided, but also a lack of understanding of how to make use of it. Evidence for a lack of understanding of the information came from the finding that single-sentence statements were misinterpreted by 26-54% of the patients. The most striking misinterpretation, by 32% of these patients, was that the randomization process would 'select the best treatment for me', or still permit the doctor to decide 'which treatment is the right one for me'. Evidence for a lack of understanding of how to use information came from the information in the consent form that was considered pertinent for a decision about trial entry. Of the 50 patients, the vast majority (74%) did not indicate that both risks and benefits were pertinent. Of the 20 who would not enter the trial, 70% focused only on the risks of therapy. Taking into account not only the misinterpretation of information, but also an apparent lack of understanding about how to use information, it appears that a level of understanding appropriate for informed decision-making was not achieved in this study.

These results are open to criticism on the grounds that they were obtained in a hypothetical situation, and are not representative of the way patients consider the information provided to them when they are offered entry into real trials. Perhaps these patients did not take this hypothetical situation as seriously as they would a real one. Discussions with patients upon completion of the task indicated that, in general, it was taken seriously. Also, patients considering a hypothetical situation are not subjected to the heightened anxiety and stress that might increase the probability of misinterpretation in actual situations. It seems likely that the present results may underestimate, rather than overestimate, the difficulties involved in the achievement of informed decision-making by patients.

What can be done? Perhaps the standard format of consent forms could be composed in a more systematic way, using phrases that have been demonstrated to minimize misinterpretation. Perhaps visual representations could be used effectively to supplement the key concepts being conveyed, such as probabilities; well-designed, user-friendly microcomputer programs might be helpful in this regard. Finally, perhaps the tradeoffs between benefits and risks could be made more explicit.

How might changes in current procedures for obtaining informed consent affect accrual into clinical trials? The tendency in the present study for patients who refused trial entry to focus their attention only on the risks of treatment raises the possibility that they did not take possible benefits adequately into account. Perhaps, more attention to a well-balanced consideration of both risks and benefits would increase, rather than decrease, accrual into trials. If so, the ethical objective of enhancing patient autonomy in decision-making, and the medical and scientific objective of evaluating therapies using rigorously controlled clinical trials, would be in harmony.

Acknowledgments: This work was supported by the National Cancer Institute of Canada.

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(Accepted 8 December 1989)