PATIENTS' WILLINGNESS TO ENTER CLINICAL TRIALS: MEASURING THE ASSOCIATION WITH PERCEIVED BENEFIT AND PREFERENCE FOR DECISION PARTICIPATION

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Abstract—Patients who agree and those who refuse clinical trial entry may differ in attitudes towards decision control and the benefits associated with the trial arms. These differences, if they exist, have implications for the process of obtaining informed consent and for the generalization of the results of a clinical trial. This paper describes the development and initial application of methods designed to detect such differences.

Developmental work involved creating an inventory of instruments designed to determine patients' attitudes towards participating in treatment decision making, permitting random selection of treatment, and undertaking the risks and benefits associated with the various treatments in a trial. Initial application involved modifying these instruments in terms of an actual chemotherapeutic trial for colonic adenocarcinoma, seeking responses to these measures from 60 non-eligible colorectal cancer patients, then determining whether those who would agree to trial entry differed systematically on these measures from those who indicated that they would refuse such a trial.

Twenty-five of the respondents reported that, if faced with the actual decision, they would agree to trial entry; 35 would refuse. Refusers demanded more participation in decision making (Chi-square; P = 0.01) and a greater increment in treatment benefit (t-test; P = 0.0001). Twenty-two of the 35 refusers reported aversion to randomization as their primary reason for trial refusal.

Since their particular content can be modified, these measures may be applicable to all clinical trials. They could be used to study the reasons patients accept or refuse trial entry and to determine if agree-refuser attitude differences undermine the generalizability of a trial's results.

Key words—clinical trials, patients' decision making, patients' preferences, treatment benefits, randomization

INTRODUCTION

The controlled clinical trial stands at the interface between original scientific research and the application of results to patient care. The accrual of patients into clinical trials has been studied from the viewpoint of the clinician-scientist [1–3]; ethical, legal and scientific concerns highlight the importance of also examining the patient's attitudes toward trial entry [4–8].

From a scientific perspective, studying what happens when patients decide whether or not to enter a clinical trial may improve the analysis of the results of that trial. Patients who choose and those who choose not to enter a clinical trial may differ markedly, for example, in their subjective view of the severity and importance of toxic or side effects, or in their attitude toward any possible trade-offs between side effects and benefits (remission or survival). To the extent that these reasons for refusal to enter a clinical trial are unknown, the inferences drawn from the trial results are threatened with bias, since these inferences are based solely on observations obtained from those who do agree to participate [9]. Particularly in trials in which health-related quality of life is an important consideration, such bias may render invalid the use of the trial's results to select the apparent "best" treatment alternative for the general population of patients with that diagnosis.

This issue had not been directly addressed in the relevant literature.

Kemp et al. [10] and Cassileth et al. [4] report that lay adults hold strong favorable opinions about the concept of clinical trials, and Cassileth maintains that these attitudes are comparable to those of cancer and cardiology patients. However, these investigators used multiple choice and open-ended questions to characterize attitudes about trials in general, rather than presenting detailed and explicit information about actual trial protocols to respondents who would find the problem salient.

Mattson et al. [11] particularly sought the reasons for patient nonparticipation in randomized clinical trials for the treatment of sarcomas. Qualitative data collected from 32 nonparticipators
in five protocols indicated that patients’ beliefs about the effects of the treatments upon their functional abilities and quality of life were the primary determinants of the decision to refuse enrolment or to withdraw from these trials. These observations reinforce the argument outlined above for examining the attitudes of nonparticipants towards side effects and benefits. Furthermore, Barofsky and Sugarbaker’s study design highlights the need to develop quantitative methods that would permit such data to be collected in a systematic manner that is also flexible enough to adapt to the unique characteristics of different protocols.

For these reasons, we undertook methodologic work with the primary objectives:

1. To develop a method to determine patients’ attitudes towards undertaking the risks and benefits associated with the various treatments in a trial, in a way that is both comprehensive and adaptable to the unique characteristics of different clinical trials; and
2. To determine whether this method can detect a difference between the attitudes held by those patients who would agree and those who would refuse to enter a particular clinical trial.

A secondary objective was to determine whether different preferences for participating in treatment decision making were associated with differences in willingness to participate in a particular clinical trial. Our interest in this objective stemmed from related investigations into patients’ desires for information and therapeutic choice [13–15].

**PROCEDURES**

**Method Development**

**Preferences for participating in decision making**

To assess preferences for participation in treatment decision making (outside the context of decision making about clinical trial entry), we adapted a questionnaire from the studies reported by Cassileth [16] and Strull [17]. This questionnaire consists of five descriptive sentences ranging from preferring that the physician assume primary responsibility for decision making to preferring that the patient do so. The adapted questionnaire is presented in Table 1.

<table>
<thead>
<tr>
<th>Table 1. Decision Making Preference Questionnaire</th>
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</thead>
<tbody>
<tr>
<td>After they have all the information they need about their illness and possible treatments, some patients prefer to leave decisions about their treatment up to their doctor, while others prefer to participate in these decisions. Please check the statement that best describes what you believe would be ideal:</td>
</tr>
<tr>
<td>— The doctor should make the decisions using all that’s known about the treatments.</td>
</tr>
<tr>
<td>— The doctor should make the decisions but strongly consider my opinion.</td>
</tr>
<tr>
<td>— The doctor and I should make the decisions together on an equal basis.</td>
</tr>
<tr>
<td>— I should make the decisions, but strongly consider the doctor’s opinion.</td>
</tr>
<tr>
<td>— I should make the decisions using all I know or learn about the treatments.</td>
</tr>
</tbody>
</table>

The respondent is asked to select the statement describing his/her ideal level of participation in treatment decision making. Cassileth and Strull present evidence that cancer patients in different age groups [16] and that hypertensive patients and their clinicians [17] provide different responses to this task.

**Attitudes about clinical trial entry**

This involved designing two tasks whose particular content must be modified for the specific trial of interest, although the approaches are applicable to all clinical trials. One task (the “Randomization Task”) was structured to determine patients’ attitudes towards the process of random treatment selection. The second task (the “Trade-Off Task”) was designed to assess the variable of importance for making inferences from a trial’s results—that is, the strength of patients’ preferences regarding the risks and benefits associated with a particular trial’s treatment alternatives.

We will describe these tasks in terms of the versions created for subsequent testing (see Method Application below). These versions incorporated clinical content that was relevant to an actual trial determining the relative effectiveness of a particular chemotherapy protocol in patients with respectable adenocarcinoma of the colon. In earlier work, we developed similar tasks using clinical material pertaining to a radiotherapeutic trial in breast cancer; their subsequent application indicated that the tasks closely simulate the sharply-defined decision problem faced by the patient considering whether or not to enter a cancer clinical trial [18].

**The randomization task**

**General approach.** This task begins with outlining the objective of the trial, describing the treatment arms and their associated risks and benefits, and explaining the use of randomization to select a patient’s treatment. A series of typewritten cards is used to present this information in a standardized sequence. Next the respondent is asked whether or not he/she would be willing to enter such a trial, and an open-ended question is posed to elicit qualitative information about the reasons underlying the respondent’s choice.

Therefore, this task is designed to assess the dependent variable of interest—that is, the outcome of the trial entry decision. To avoid biasing responses in this regard, it always precedes the trade-off task (see below) intended to determine attitudes towards risks and benefits.

**Specific steps.** The randomization task involves eight steps.

1. The subject is told: “Imagine you have a cancer of the large bowel requiring treatment. The first step in treatment involves surgical removal of the cancer. After surgery, there is a standard treatment available that has a probable outcome.”

2. Treatment A card is shown. If the respondent enquires, the interviewer presents standardized information cards regarding the treatment plan if there is a recurrence.
Treatment A card:

Regular medical check-ups
Probable outcome: after 5 years, 40 out of 100 patients will be considered cured.
Treatment risks: none

(3) The subject is told: "There is another, new, treatment available that has a possible additional benefit."

(4) Treatment B card is placed beside Treatment A card. If the respondent enquires, the interviewer presents standardized information cards regarding severity of side and toxic effects and the treatment plan if there is a recurrence.

Treatment B card:

Intravenous (i.v.) chemotherapy: 5-fluorouracil and folinic acid for 5 days, every 28 days, for a total of 6 cycles, plus preventive mouthwash each i.v. day.
Possible additional benefit: 15 out of 100 patients benefit: i.e. after 5 years, 55 out of 100 patients will be considered cured (40 + 15 = 55)
Treatment risks: "very likely": i.e. 80 of 100 patients experience lowered blood count (which could lead to infection and bleeding for 5 of these patients); diarrhea; skin rash; and/or itchy eyes.

"possible": i.e. 30-40 of 100 patients experience temporary sore mouth; hair loss; nausea and vomiting; and/or ulceration of skin at the injection site.
"rare": i.e. less than 1 of 100 patients experience heart damage and/or loss of balance.
85 out of 100 patients receive unnecessary chemotherapy (100 - 15 = 85)

(5) To summarize, the Summary card is placed below the Two Treatment cards.

Summary card:

1. Both treatments may not be equally effective in terms of cure; but
2. to get a possible benefit of increased chance of cure you would get treatment over a 6-month time period, be taking a chance on treatment risks, and be taking a chance on unnecessary chemotherapy.

Therefore: the choice between the standard and the new treatments is difficult to make.

(6) The subject is told: "When the choice is so difficult, often patients are asked if they would be willing to participate in a 'clinical trial'. A clinical trial is a study designed to compare two treatments over a period of time. Such studies use a random selection process to decide which treatment a patient will receive (e.g. choosing one of the two treatments by drawing from an envelope, or by flipping a coin, etc.). So there is a 50:50 chance that either Treatment A or B is selected.

(7) The Clinical Trial card is placed below the Summary card

"Clinical trial" card
Random selection
(flip of a coin)
(envelope draw)
50% Treatment A 50% Treatment B

(8) The subject is told: "If a patient is not willing to participate in such a trial, then he/she receives the Standard Treatment A as usual."

"Imagine that you have been asked to contribute to research by participating in a clinical trial comparing Treatments A and B; that is, imagine you have been asked to allow your treatment to be chosen by random selection. Would you agree to random selection or would you refuse random selection of your treatment? Why would you agree/refuse?"

The trade-off task

General approach. This task also begins with a description of the risks and benefits inherent in each treatment alternative, then the respondent is asked to select his/her preferred treatment. Next, a sliding scale is used to represent visually the probabilities (expressed as percentages, for easier comprehension by patients) associated with each risk/benefit statement, and to permit systematic alteration of these probabilities so that the initial treatment choice gradually appears less desirable while the alternative seems more preferable. The point at which the respondent indicates that he or she would switch to the alternate treatment provides an estimate of how much additional benefit (in this application, increased survival) a respondent would want before accepting adjuvant chemotherapy. Approaches like these, involving trade-offs between probability statements, have been used in decision problems concerned with treatment choice [19-21], but not with clinical trial entry. Besides the probabilities associated with gains and losses, trade-off techniques have also been applied to the absolute amount of gain or loss incurred [22] and to the time spent in a health state [23-25].

Specific steps. The trade-off task involves five steps.

(1) The subject is told: "Imagine you have a cancer of the large bowel requiring treatment. The first step in treatment involves surgical removal of the cancer. After surgery, there are two treatments available (show both Treatment A and B cards). I will be giving you information about each treatment and asking you to choose the treatment you prefer."
(2) Both the Treatment cards described above are shown. If the respondent enquires, the interviewer presents standardized information cards regarding the treatment plan if there is a recurrence under either Treatment A or Treatment B.

(3) A summary, as in step (5) above, is provided.

(4) The subject is asked: "If you had to choose, which treatment would you prefer and why?"

(5) After the respondent has indicated a preference, a trade-off task is carried out to determine the strength of that preference, as described below:

**[If A is chosen:]**

"When there is a 40% chance of 5-year cure in Treatment A and a 55% chance of 5-year cure in Treatment B, you prefer Treatment A because (the reason provided earlier is repeated)."

"Now, let's change the problem somewhat. What if the chance of 5-year cure in Treatment A remained the same, at 40%, but the chance of 5-year cure from Treatment B were 60% while the chance of getting unnecessary chemotherapy in Treatment B were 80%." (Here, a sliding scale is used to represent visually how the increased probability of cure with Treatment A is accompanied by a decreased probability of receiving unnecessary chemotherapy.) Which treatment would you prefer?

If the respondent's choice switches to Treatment B, the 60% switch value is noted. If his or her choice remains Treatment A, the interviewer raises Treatment B's chance of 5-year cure and lowers Treatment B's chance of unnecessary chemotherapy 5 units at a time until a choice switch occurs. Fine tuning is carried out by raising/lowering 1 unit at a time. The subject's final switch value is noted.

**[If B is chosen:]**

"When there is a 40% chance of 5-year cure in Treatment A and a 55% chance of 5-year cure in Treatment B, you prefer Treatment A because (the reason provided earlier is repeated)."

"Now, let's change the problem somewhat." (Here, the same sliding scale is used.) "What if the chance of 5-year cure in Treatment A remained the same, at 40%, but the chance of 5-year cure in Treatment B were 50%, so that the chance of getting unnecessary chemotheraphy in Treatment B were 90%. Which treatment would you prefer?"

If the respondent's choice switches to Treatment A, the 50% switch value is noted. If his or her choice remains Treatment B, the interviewer lowers Treatment B's chance of 5-year cure and raises Treatment B's chance of getting unnecessary chemotherapy 5 units at a time until a choice switch occurs or the treatments are probabilistically identical (at 40% chance of 5-year cure). Fine turning and notation of the final switch value is carried out as above.

The raw probability score obtained at the switch point can be transformed to provide an estimate of how much additional benefit (here, a higher survival rate) the subject would want before accepting the new treatment (here, adjuvant chemotherapy). That is, the raw probability score can be converted to a scale of "survival preference". Other applications may involve different benefits (for example, an extension in the expected remission time) and different incremental ranges, but the general approach to the transformation would be similar [18].

As described above, the raw probability score is first obtained by moving up or down the probability scale (depending on the patient's initial preferred treatment choice) from 55. See Column I below.

<table>
<thead>
<tr>
<th>Raw Probability Score</th>
<th>Survival Increments</th>
<th>% of Total Increments</th>
<th>Survival Preference Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>60</td>
<td>100%</td>
<td>0</td>
</tr>
<tr>
<td>85</td>
<td>45</td>
<td>75%</td>
<td>25</td>
</tr>
<tr>
<td>70</td>
<td>30</td>
<td>50%</td>
<td>50</td>
</tr>
<tr>
<td>55</td>
<td>15</td>
<td>25%</td>
<td>75</td>
</tr>
<tr>
<td>40</td>
<td>0</td>
<td>0%</td>
<td>100</td>
</tr>
</tbody>
</table>

These raw scores indirectly indicate how many survival increments—out of a possible 60—that a patient would want before accepting the more toxic treatment B. The underlying scale of survival point increments is the same for all respondents, regardless of the subject's initial preferred treatment choice. See Column II.

The respondent's required survival point increment is then expressed as a percentage of the total available increments in benefit. See Column III.

Low percentages in Column III indicate that the respondent would require only a small increment in survival to accept adjuvant chemotherapy (Treatment "B"); that is, she/he highly values the survival benefit (despite the risks of side effects), and, to reflect this, the complementary percentage is recorded. See Column IV.

Conversely, high percentages in Column III indicate that the subject would demand a large increment in survival to accept chemotherapy. He thus places a lower value on the survival benefit (relative to the risks of side effects); as before, this is represented by recording the complementary percentage appearing in Column IV.

In this manner, the raw probability scores are transformed to a common scale measuring the strength of preference for the survival benefit offered in this particular clinical trial context.

**Method Application**

**Subjects**

Thirty outpatients with a diagnosis of colon or rectal cancer, with or without metastatic disease, participated in an initial application of this newly-developed approach to detecting attitudinal differences. The purpose of this application was primarily methodologic—that is, to determine if patients who differed in the clinical trial entry decision also differed in their strength of preference for the possible benefit offered by trial participation, as determined by the trade-off
task. We were reluctant to include the inventory in the design of an actual trial before such preliminary testing because of the potential risk of affecting that trial’s accrual rate in unknown ways. Therefore, the respondents selected for this initial application were not eligible for the trial under consideration, and the decision problem was presented as hypothetical in nature. Our experience has indicated that actually having the relevant diagnosis renders this decision problem highly salient to these patients [18].

Patients were interviewed by an experienced research assistant in a room separate from the clinic. Each participant provided sociodemographic data and completed the questionnaires in the same sequence (Decision Making Preference/Randomization Task/Trade-Off Task).

Data analysis plan

Respondents were divided into two groups according to their reported willingness to participate in this trial, as determined by the Randomization Task. The responses to the open-ended question seeking reasons for the trial entry decision were subjected to content analysis. The unpoled t-test was used to test for significant group differences in the means obtained for the survival preference score derived from the Trade-Off Task. Responses on the Decision Making Preference questionnaire were collapsed into two categories, according to whether or not the patient wished to assume any responsibility for decision making (i.e. responses nos 1 and 2 formed one category, while responses nos 3–5 formed the other), then the Chi square test was used to test for group differences in the frequencies of responses in these categories.

RESULTS AND DISCUSSION

Sample characteristics

The demographic, diagnostic, and treatment characteristics of the respondents are summarized in Table 2; they are representative of the population of colon cancer patients attending this clinical setting. Twenty-five respondents reported that they would agree to enter this clinical trial if faced with the actual choice, while 35 indicated that they would refuse.

Differences between ‘Agreers’ and ‘Refusers’

Significant across-group differences were observed in the responses to the Decision Making Preference questionnaire and in the survival preference score derived from the Trade-Off Task. The results of these analyses appear in Table 3. There is a constellation of statistically significant observations that is of particular interest.

Those patients who indicated that they would refuse to enter this clinical trial tended also to report lower scores for survival preference—that is, to be less willing to experience short term toxicity for a possible gain in long term survival. These results are comparable to those of Barofsky and Sugarbaker [12], who observed that patient refusal to participate in sarcoma clinical trials was attributable to aversive attitudes toward particular aspects of treatment. As argued earlier, this association between attitudes and decision behaviour has implications for the generalization of trial outcomes to larger patient populations.

Patients who refused clinical trial entry also tended to be less willing to give away treatment decision making to the physician, when questioned about their preferred decision making role outside the trial context. Given their greater deference to the physician’s point of view, it is possible that cancer patients who agree to enter clinical trials are more susceptible in the clinical investigator’s enthusiasm for the trial [1]. This possibility merits further investigation, since its existence holds ethical implications for the actual conduct of the process of obtaining informed consent to trial entry. Although the design of our study does not permit us to make inferences about the sources of these attitudinal differences, our results indicate that, if these differences actually exist in patients facing a real trial entry decision, they may be detectable with the Decision Making Preference Questionnaire and the Probability Trade-Off Task.

Sub-group analysis

In both decision groups (‘Agreers’ and ‘Refusers’), one respondent declined to identify a preferred treatment choice, and the remaining subjects could be divided into two sub-groups, according to their preferred treatment choice. In Table 4, these four sub-groups are identified and rank-ordered according to their mean survival preference scores. (Note that the Refuse group divides into sub-groups of roughly comparable size, which accounts for the large standard deviation in this group’s reported survival preference scores, as presented in Table 3.) The differences between the two “extreme” sub-groups are of particular interest. Compared with members of Sub-group IV, a larger proportion of respondents in Sub-group I reported a preference for

<table>
<thead>
<tr>
<th>Sub-group</th>
<th>Accept</th>
<th>Refuse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=25</td>
<td>n=35</td>
</tr>
<tr>
<td>Physician dominant</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Patient participate</td>
<td>8</td>
<td>24</td>
</tr>
</tbody>
</table>

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Table 2. Demographic, diagnostic, and treatment characteristics of study respondents (N=60)

<table>
<thead>
<tr>
<th>Mean age: 57 years (range: 33–80 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex:</td>
</tr>
<tr>
<td>M 36</td>
</tr>
<tr>
<td>F 24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cancer diagnosis:</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>colon cancer</td>
<td>33</td>
<td>55.00</td>
</tr>
<tr>
<td>colon cancer with metastases</td>
<td>14</td>
<td>23.33</td>
</tr>
<tr>
<td>rectal cancer</td>
<td>8</td>
<td>13.33</td>
</tr>
<tr>
<td>rectal cancer with metastases</td>
<td>5</td>
<td>8.33</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Current treatment:</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>follow-up alone</td>
<td>42</td>
<td>70.00</td>
</tr>
<tr>
<td>chemotherapy</td>
<td>14</td>
<td>23.33</td>
</tr>
<tr>
<td>radiation therapy</td>
<td>3</td>
<td>5.00</td>
</tr>
<tr>
<td>combination</td>
<td>1</td>
<td>1.67</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. Preferences re. decision participation and survival benefit by Trial Entry Decision Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial Entry Decision Status</td>
</tr>
<tr>
<td>Accept</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>n=25</td>
</tr>
<tr>
<td>Decision participation preference</td>
</tr>
<tr>
<td>Physician dominant</td>
</tr>
<tr>
<td>Patient participate</td>
</tr>
<tr>
<td>Survival preference</td>
</tr>
<tr>
<td>mean score</td>
</tr>
<tr>
<td>SD</td>
</tr>
</tbody>
</table>

References:

[1] [11], who observed that patient refusal to participate in sarcoma clinical trials was attributable to aversive attitudes toward particular aspects of treatment. As argued earlier, this association between attitudes and decision behaviour has implications for the generalization of trial outcomes to larger patient populations. Patients who refused clinical trial entry also tended to be less willing to give away treatment decision making to the physician, when questioned about their preferred decision making role outside the trial context. Given their greater deference to the physician’s point of view, it is possible that cancer patients who agree to enter clinical trials are more susceptible to the clinical investigator’s enthusiasm for the trial [1]. This possibility merits further investigation, since its existence holds ethical implications for the actual conduct of the process of obtaining informed consent to trial entry. Although the design of our study does not permit us to make inferences about the sources of these attitudinal differences, our results indicate that, if these differences actually exist in patients facing a real trial entry decision, they may be detectable with the Decision Making Preference Questionnaire and the Probability Trade-Off Task.

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patient participation in treatment decision making (Chi square test, \( P < 0.05 \)), and would refuse trial entry. These preferences may reflect stable traits within each sub-group that persist across different clinical situations. However, compared with respondents in Sub-group IV, Sub-group I members reported a lower mean survival preference score (t-test, \( P < 0.001 \)) and would prefer medical follow-up alone; these observations imply that each sub-group's decision making/trial entry preferences may be labile states that are dependent on the respondent's perceptions of the context in which they are elicited. The members of these two sub-groups apparently viewed the risks and benefits of the two treatments very differently, and these views were associated with different preferences about decision making and trial entry. The susceptibility of these decision making/trial entry preferences to contextual effects can be tested by presenting information about short term toxicity risks and long term survival benefits in deliberately differing "frames": an experiment investigating this question has just been completed [26].

The reported preferences of the members of Sub-groups II and III were "aberrant", in that their trial entry Agree/Refuse status was not consistent with their preferred treatment choice in the Trade-Off task. Sub-group II respondents would prefer medical follow-up alone, but they were willing to enter this trial and incur the risk of assignment to the adjuvant chemotherapy arm. There were only two individuals in this sub-group; both stated that they would be willing to enter this trial if their physician advised them to do so. The 14 members of Sub-group III would prefer adjuvant chemotherapy, but would refuse trial entry and thus forgo the opportunity of assignment to this treatment. Thirteen of these respondents reported aversion to the randomization process as their primary reason for trial refusal. This aversion may be an artefact induced by our explicit description of randomization. We have subsequently carried out an experiment to determine the effects of describing randomization in different ways on patients' reported willingness to enter a clinical trial [27].

The results of these further experimental studies will guide the development of ways to seek informed consent that will promote information understanding [28] while avoiding the danger of systematically influencing patients' trial entry decision making [29].

CONCLUSION

The primary objective of this study was to develop and apply a probability trade-off method designed to determine if patients who refuse clinical trial entry differ from those who agree to participate, in terms of their strength of preference for the possible benefit to be gained by trial entry.

The version developed here used clinical and probabilistic descriptions derived from an actual trial in which the benefit of a particular chemotherapeutic protocol in colon cancer was assessed in terms of improvements in the probability of survival.

Because of the preliminary nature of the method, its initial application involved patients with the diagnosis of interest but who were ineligible for the actual trial.

With this descriptive content and within the context of this hypothetical (albeit salient) decision problem, the probability trade-off method described here was able to detect differences between agreeers and refusers in terms of their willingness to undergo short term toxicity in order to achieve a possible gain in long term benefit. As noted in the Introduction, the existence of such differences could threaten the validity of the interpretation of the results of a trial in which quality of life is an outcome of primary concern.

In earlier work, we had developed and applied a probability trade-off method that used information relevant to an actual trial involving a different clinical problem (radiation therapy in early breast cancer) and a different risk/benefit trade off (side effects vs reduction in the probability of local recurrence) [18]. The purpose of this earlier study was also different (to determine if the trade-off method could detect differences in the attitudes of patient and non-patient groups); we refer to it here to illustrate that there is accumulating evidence for the method's adaptability. Apparently, the probability trade-off problem can be constructed so as to incorporate descriptions of the unique treatment modalities, risks, and benefits of different protocols.

Thus, the results of our earlier work and of the application reported here indicate that the probability trade-off technique may be readily modifiable and could detect systematic differences in the attitudes held by trial participants and non-participants. Taken together, this work implies that future applications within the context of a real decision, in which eligible patients at the accrual stage of an actual trial are asked to respond to a trade-off question, could fruitfully proceed.

An important issue related to efforts in this direction is the possibility that the explicit and visual presentation of clinical trial information in the manner required by the probability trade-off technique may systematically affect the entry decision itself. An increased refusal rate would be of particular concern to investigators who are primarily interested in enrolling a full complement of trial participants. On the other hand, an interesting ethical dilemma would be

<table>
<thead>
<tr>
<th>Sub-group</th>
<th>( n )</th>
<th>Trial Entry Status</th>
<th>Preferred treatment</th>
<th>Mean survival preference score</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>20</td>
<td>Refer</td>
<td>Check-ups alone</td>
<td>33.0</td>
</tr>
<tr>
<td>II</td>
<td>2</td>
<td>Accept</td>
<td>Check-ups alone</td>
<td>67.0</td>
</tr>
<tr>
<td>III</td>
<td>14</td>
<td>Refer</td>
<td>Chemotherapy</td>
<td>91.0</td>
</tr>
<tr>
<td>IV</td>
<td>22</td>
<td>Accept</td>
<td>Chemotherapy</td>
<td>95.0</td>
</tr>
</tbody>
</table>

Table 4. Sub-group characteristics
created if future work indicates that the probability trade-off technique, compared with usual methods of providing information, fosters more fully informed consent to either accept or refuse trial entry [2, 5, 8] at the cost of an increase in the refusal rate. We have some evidence from related work that this dilemma will not emerge: among 100 women with breast cancer who received written information about a clinical trial in either the usual or an explicit diagrammatic format, there were no differences in the frequencies of the agree/refuse decision [27]; and among 100 cancer patients who received supplementary teaching of trial information either passively, from written material, or actively, using a computer program, a significantly larger number of respondents using the interactive program indicated that they would agree to participate in such a trial [30]. Although these further studies have used hypothetical decision problems, their results imply that trial accrual is not likely to be adversely affected by incorporating explicit and interactive problem representations, like those used in the probability trade-off technique, into real trial entry decision situations.

There are other potential applications of the probability trade-off technique which merit investigation. As noted in the Method Development section, trade-offs between probability statements have been used in assessing treatment preferences outside the context of the trial entry decision problem [19, 20]. However, these efforts have primarily been concerned with determining the effects of "framing" probability information, either positively or negatively, on subsequent trade-off behaviour—that is, the results of the probability trade-off task have been regarded as the dependent variable in these studies. Important insights could be gained by alternative applications. Such applications include experiments in which the probability trade-off technique is regarded as an intervention and is assessed in terms of its effectiveness as a teaching device in the promotion of more fully informed consent or as a decision aid in "bedside" decision making. The designs of such effectiveness studies could include comparisons with decision/teaching aids which address aspects of the clinical problem other than risk/benefit issues; for example, the TWIST method, which focuses upon attitudes towards survival time [31, 32].

In conclusion, the results of the investigation reported here indicated that the probability trade-off technique can detect attitudinal differences between patients who accept and decline clinical trial entry in a hypothetical situation, and that its application at the accrual stage of an actual trial now appears appropriate. Furthermore, analysis of the responses of respondent sub-groups implied that these patients differed in terms of their preferences for participation in treatment decision making and their attitudes towards using a random selection process to make a treatment choice. These descriptive observations have led to further experimental studies to determine if the manner in which the presentation of information about a clinical trial's protocol influences patients' decision making. Finally, we have argued that efforts to assess the method's effectiveness as a teaching or decision aid would be timely.

REFERENCES