Research Participants' High Expectations of Benefit in Early-Phase Oncology Trials: Are We Asking the Right Question?

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ABSTRACT

Purpose

To determine whether patients' expectations of benefit in early-phase oncology trials depend on how patients are queried and to explore whether expectations are associated with patient characteristics.

Patients and Methods

Participants were 171 patients in phase I or II oncology trials in the United States. After providing informed consent for a trial but before receiving the investigational therapy, participants answered questions about expectations of benefit. We randomly assigned participants to one of three groups corresponding to three queries about expectations: frequency type, belief type, or both. Main outcomes were differences in expectations by question type and the extent to which expectations were associated with demographic characteristics, numeracy, dispositional optimism, religiousness/spirituality, understanding of research, and other measures.

Results

The belief-type group had a higher mean expectation of benefit (64.4 of 100) than the combination group (51.6; $P = .01$) and the frequency-type group (43.1; $P < .001$). Mean expectations in the combination and frequency groups were not significantly different ($P = .06$). Belief-type expectations were associated with a preference for nonquantitative information ($r = -0.19$; 95% CI, -0.19 to -0.36), knowledge about research ($r = -0.21$; 95% CI, -0.38 to -0.03), dispositional optimism ($r = 0.20$; 95% CI, 0.01 to 0.37), and spirituality ($r = 0.22$; 95% CI, 0.03 to 0.38). Frequency-type expectations were associated with knowledge about clinical research ($r = -0.27$; 95% CI, -0.27 to -0.51).

Conclusion

In early-phase oncology trials, patients' reported expectations of benefit differed according to how patients were queried and were associated with patient characteristics. These findings have implications for how informed consent is obtained and assessed.

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INTRODUCTION

During the past several years, oncologists, bioethicists, and clinical researchers have engaged in a complex and sustained debate concerning the validity of informed consent in early-phase oncology trials.¹⁻¹⁰

A chief concern is that some patients may fail to understand the low likelihood of direct, personal benefit from participating in a phase I trial.¹¹ This concern stems from data suggesting that many participants in early-phase trials believe the chance of benefit to be much higher than estimates based on historical data.^{7,12,13}

An often overlooked point in this debate is that patients' reports of the likelihood of benefit can take different forms, depending on how the question is asked and the conception of probability the patient

uses.¹⁴ A frequency-type probability refers to the relative frequency of an event in the population of interest (eg, "On average, five of every 100 participants will experience a response to the experimental treatment.") In contrast, a belief-type probability refers to an individual's attitude toward a future event, in this case, the patient's confidence that he or she will personally experience benefit from the experimental treatment (eg, "I am 90% confident that I will be one of the people who will respond to the experimental treatment."). These two types of probability are not simply different ways of framing the same information, but rather refer to two entirely different concepts. Discussions about the validity of consent in early-phase trials generally have disregarded the difference between these two types of probability. However, in preliminary research we

found that patient reports of the likelihood of benefit vary significantly, depending on whether the patient is queried in frequency-type or belief-type terms.¹⁵

In an effort to confirm and extend these findings, we conducted a prospective randomized study to assess the impact of query type on patients' expressed expectations of benefit from early-phase trials. We hypothesized that expectations of benefit reported in response to a belief-type query would be higher than expectations reported in response to a frequency-type query and that asking the question in both ways would help participants understand the difference and lower their reported expectations in response to the frequency-type query. We also examined the extent to which participants' responses were associated with demographic characteristics, numeracy, personality features, religiousness/spirituality, understanding of clinical research, and other measures.

PATIENTS AND METHODS

Participants

We recruited patients with cancer from the Duke Cancer Institute (Durham, NC), Fox Chase Cancer Center (Philadelphia, PA), and St. Vincent's Manhattan (New York, NY). Patients were eligible to participate in the study if they were age 18 years or older; could speak, understand, and provide informed consent in English; and were enrolled onto a phase I or phase II clinical trial but had not yet begun the investigational therapy. We excluded patients if they were enrolled onto a phase I trial of a regimen that included a US Food and Drug Administration–approved agent with a clinical indication for their type of cancer. The rationale for this exclusion criterion was that phase I trials involving standard therapies (eg, in combination with investigational agents) may be expected to afford a higher chance of benefit, so higher expectations of benefit would be of less bioethical concern. The institutional review boards of the Duke University Health System, Fox Chase Cancer Center, and Saint Vincent Catholic Medical Centers approved the study, and all participants provided written consent.

Procedures and Measures

Patients in the study participated in a structured, audio-recorded interview. We randomly assigned participants to one of three experimental groups corresponding to three different ways of asking about expectations of benefit from the investigational therapy, which we developed and pretested in our previous work.¹⁵ In the "confidence" group, participants were asked a belief-type question: "How confident are you that the experimental therapy will control your cancer?" (response options, 0% to 100%). In the "frequency" group, participants were asked a frequency-type question: "If 100 people were to participate in this study, how many could be expected to have their cancer controlled as a result of the experimental therapy?" Finally, in the combination group, participants first answered the belief-type question, discussed the answer with the interviewer, and then answered the frequency-type question. The response of interest in the combination group was the response to the frequency-type question. Thus, an expectation of benefit was solicited from each of the three groups by using a different version of the question.

In addition to items querying participants' demographic and clinical characteristics and previous experience with clinical research, the interviews included several other survey measures. We measured participants' aptitude for numbers by using the Subjective Numeracy Scale¹⁶ and a single item querying understanding of a statement of aggregate probability.¹⁷ We used the Quality of Informed Consent¹⁸ measure to assess understanding of the elements of informed consent in clinical research. We used the Life Orientation Test-Revised¹⁹ to measure participants' dispositional optimism, a personality trait defined in terms of having general expectations of positive outcomes in one's future. Finally, we used the Daily Spiritual Experiences Scale^{20,21} and the Organizational Religiousness-Short Form²¹ as measures of participants' spirituality and religiousness.

Statistical Analysis

We used descriptive statistics to summarize participants' demographic and clinical characteristics. In testing the main study hypothesis concerning differences in expectations by question type and to explore the main and interactive effects of trial phase, we used a linear mixed model and adjusted for the clustering of patients within trial investigator. We used pairwise contrasts in the mixed model to compare the three question groups.

We explored associations between expectations of benefit and participant characteristics separately for belief-type and frequency-type expectations. The collection of belief-type expectations included the responses from the confidence group and the first of the two responses from the combination group. The collection of frequency-type expectations included the responses from the frequency group. To ensure that mean differences in expectations of benefit by trial phase would not bias the estimation of associations, we first converted the expectations of benefit into z scores separately for participants in phase I trials and for participants in phase II trials. We then computed correlations between the standardized expectations of benefit and participant characteristics by using Pearson correlation coefficients for continuous variables, gamma coefficients for ordinal categorical variables, and point biserial correlation coefficients for dichotomous variables.²²

We selected a target sample size of 57 participants per experimental group to provide 80% statistical power to detect differences between the groups of at least 15 points on a 100-point scale after adjustment for clustering within trial investigator (assuming an intraclass correlation coefficient of 0.045). We used SAS version 9.1.3 (SAS Institute, Cary, NC) for all analyses.

RESULTS

Of the 213 patients invited to participate in the study, 171 (80.3%) agreed. The study population included 115 participants (67.3%) enrolled onto phase I trials and 56 participants (32.7%) enrolled onto phase II trials. We randomly assigned 56 participants to the confidence group, 55 to the frequency group, and 60 to the combination group. Table 1 lists the demographic and clinical characteristics of the study population. There were slightly more women than men. Most participants were white (83%), were married or partnered (76%), had at least some college education (65%), and had never participated in a clinical trial (68%). Almost all participants had an Eastern Cooperative Oncology Group performance status ≤ 1 , reflecting little or no limitation in functioning.

Figure 1 shows the distributions of expectations of benefit by question type separately for phase I and phase II trials. Expectations varied by question type ($P < .001$) such that the confidence group had a higher mean expectation of 64.4 (standard deviation [SD], 22.3) than the combination group (51.6; SD, 25.9; $P = .01$) and the frequency group (43.1; SD, 27.1; $P < .001$). Contrary to our expectations, however, the frequency-type responses in the combination group were not significantly lower than—and were in fact higher than—those in the frequency group ($P = .06$). Differences among the groups did not appear to differ significantly between phase I and phase II trials ($P = .34$). Although mean expectations were slightly higher among participants in phase II trials (56.5; SD, 24.0) than among participants in phase I trials (51.7; SD, 27.5), this difference was not statistically significant ($P = .37$). Finally, although it is not apparent in Figure 1, a large number of participants in the confidence group (34%) selected an answer of 50, whereas no such clustering of responses occurred in the other groups.

Table 2 depicts the correlations between participant characteristics and expectations of benefit in the confidence and frequency groups. Belief-type expectations had small but statistically significant

Table 1. Characteristics of the Study Population

Characteristic	No. of Participants (N = 171)	%	Mean	SD
Age, years			60.1	11.8
Sex				
Female	72	42.1		
Hispanic or Latino ethnicity	6	3.5		
Race				
American Indian/Alaska Native	6	3.5		
Asian	3	1.8		
Black	19	11.1		
Native Hawaiian/Pacific Islander	0			
White	141	82.5		
No answer	2	1.2		
Marital/partnered status				
Married/partnered	127	74.3		
Single, never married/partnered	18	10.5		
Divorced	14	8.2		
Widowed	9	5.3		
Separated	3	1.8		
Current living situation				
With others	152	88.9		
Alone	19	11.1		
Education level*				
Eighth grade or less	5	2.9		
Some high school	10	5.8		
High school graduate	42	24.6		
Some college	37	21.6		
College graduate or beyond	74	43.3		
Monthly household income, US\$†				
< 500	6	3.5		
500 to 999	4	2.3		
1,000 to 1,999	17	9.9		
2,000 to 2,999	28	16.4		
3,000 to 3,999	19	11.1		
4,000 to 4,999	17	9.9		
5,000 to 5,999	19	11.1		
6,000 to 6,999	12	7.0		
7,000 to 7,999	5	2.9		
≥ 8,000	33	19.3		
Don't know/prefer not to answer	6	3.5		
First time participating in a clinical trial	116	67.8		
ECOG performance status‡				
0	60	35.1		
1	102	59.6		
2	7	4.1		
3	1	0.6		
4	0			

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

*This variable was missing for three participants.

†This variable was missing for five participants.

‡This variable was missing for one participant.

Fig 1. Expectation of benefit by trial phase and question type. In each box-and-whisker plot, the box represents the interquartile range, the horizontal black line represents the median, and the diamond represents the mean. The whiskers were drawn to the outermost observed values within the lower and upper fences (defined as 1.5 times the interquartile range beyond the 25th and 75th percentiles). Circles represent observations outside the fences. Trial phase is indicated in brackets.

($r = 0.20$; 95% CI, 0.01 to 0.37), and reported more spiritual thoughts and feelings in daily life ($r = 0.22$; 95% CI, 0.03 to 0.38). The only participant characteristic associated with frequency-type expectations was the objective score from the Quality of Informed Consent measure ($r = -0.27$; 95% CI, -0.27 to -0.51), indicating that participants with poorer objective understanding of informed consent information tended to report higher frequency-type expectations.

DISCUSSION

Bioethicists, clinicians, and policy makers are concerned about the high estimates some patients give for their expectations of benefit in early-phase clinical trials.¹⁻¹⁰ Our findings in this study demonstrate that a portion of these high estimates can be explained by the different conceptions of probability conveyed by the questions investigators ask these patients. This concern is greater in traditional phase I trials, given that the historical chance of direct benefit is low.²³ Our findings underscore the importance of distinguishing between the different ways in which uncertainty about benefit can be expressed. Consistent with preliminary findings from the pilot study,¹⁵ participants' expectations of benefit were higher when framed in terms of their confidence in a good personal outcome (ie, belief-type) than in terms of how many of 100 patients would experience benefit (ie, frequency-type). Moreover, the mean belief-type estimate (64.4) was higher than 50 on a 100-point scale, and the mean frequency-type estimate (43.1) was lower than 50. Our previous work has shown that patients view the value of 50 as a psychological dividing line, such that values above 50 reflect greater optimism.¹⁵ Thus, the difference we found in this randomized study reflects a psychologically significant effect.

The difference between belief-type and frequency-type expectations is not a difference in framing. Whereas framing refers to different ways of expressing the same idea,²⁴ frequency-type and belief-type probability statements refer to fundamentally different concepts of probability.^{14,15,25} Patients respond differently when queried by using

relationships with the preferences subscale of the Subjective Numeracy Scale, the objective score from the Quality of Informed Consent measure, the Life Orientation Test-Revised, and the Daily Spiritual Experiences Scale. That is, participants with higher belief-type expectations tended to prefer information expressed in nonquantitative terms ($r = -0.19$; 95% CI, -0.19 to -0.36), had poorer objective understanding of the elements of informed consent ($r = -0.21$; 95% CI, -0.38 to -0.03), had greater dispositional optimism

Table 2. Correlations Between Expectations of Benefit and Participant Characteristics by Type of Expectation

Characteristic	Belief-Type Expectation		Frequency-Type Expectation	
	Correlation*	95% CI	Correlation*	95% CI
Maximum expected benefit	0.13†	−0.06 to 0.30	0.18†	−0.10 to 0.43
Subjective Numeracy Scale				
Total	−0.11†	−0.29 to 0.07	0.04†	−0.24 to 0.31
Ability Subscale	−0.02†	−0.20 to 0.17	0.05†	−0.22 to 0.32
Preference Subscale	−0.19†‡	−0.19 to −0.36	0.01†	−0.26 to 0.29
Understanding of aggregate probability statement	−0.10§	−0.30 to 0.10	−0.15§	−0.39 to 0.08
Highest grade of schooling	−0.08¶	−0.25 to 0.09	0.14¶	−0.10 to 0.38
First time in a clinical trial	−0.004§	−0.19 to 0.18	−0.08§	−0.35 to 0.20
QulC objective score	−0.21†‡	−0.38 to −0.03	−0.27†‡	−0.27 to −0.51
QulC subjective understanding	0.12	−0.06 to 0.30	0.14†	−0.14 to 0.40
LOT-R (dispositional optimism)	0.20†‡	0.02 to 0.37	0.03†	−0.24 to 0.30
Daily Spiritual Experiences Scale	0.22†‡	0.03 to 0.38	−0.10†	−0.37 to 0.18
Organizational Religiousness-Short Form	0.13†	−0.05 to 0.31	0.01†	−0.27 to 0.29

Abbreviations: LOT-R, Life Orientation Test-Revised; QulC, Quality of Informed Consent measure.

*Expectations of benefit were standardized within trial phase before the calculation of correlations.

†Correlation expressed as Pearson *r*.

‡The 95% CI excludes zero.

§Correlation expressed as point biserial coefficient.

¶Correlation expressed as gamma coefficient.

language that conveys these two types of probability, and they appear to understand the conceptual difference between them.¹⁵ A patient's belief-type statement refers to how confident the patient feels about an individual outcome; the frequency-type statement describes knowledge (or a prediction) about a verifiable state of the world. The greater belief-type expectations expressed by participants in this study might be due to a belief that personal feelings of confidence are less vulnerable to a charge of inaccuracy than are knowledge claims about how many people are likely to benefit. Furthermore, many patients value being optimistic,^{15,26} and a belief-type probability statement provides a greater opportunity to express optimism than does a frequency-type statement.

In addition to finding that belief-type and frequency-type expectations of benefit differed in their distributions, we found that they differed in their associations with some participant characteristics. Given our hypothesis that belief-type expectations evoke optimistic attitudes, we expected that belief-type expectations would have stronger relationships with dispositional optimism and religiousness/spirituality than would frequency-type expectations. This hypothesis was confirmed. Participants with optimistic personalities and more daily spiritual experiences tended to express higher belief-type expectations of benefit.

Given our hypothesis that frequency-type expectations appear to reflect knowledge, we expected that frequency-type expectations would have stronger relationships with objective understanding of the clinical trial, education level, and numeracy. Although education level and numeracy were not associated with frequency-type reports of expected benefit, participants with better objective knowledge of the nature of the clinical trial reported lower frequency-type expectations of benefit. However, objective knowledge demonstrated a similar relationship with belief-type expectations.

Of the two types of probability statements we examined, frequency-type statements would seem to be the most appropriate for conveying objective knowledge of the trial in a way that participants can comprehend, as well as for eliciting an accurate measure of that comprehension. Frequency-type probability statements can be based on empirical data (eg, numbers of patients experiencing benefit in

previous phase I trials), and research participants' responses to frequency-type questions can be evaluated as more or less accurate relative to the frequency-type probability disclosed to them during the consent process. This suggests a need for more careful attention to language and a better understanding of the differences between these two types of probability in informed consent discussions.

Nevertheless, even frequency-type reports of expected benefit by the participants in our study were substantially higher than the chance of benefit suggested by historical data—a phenomenon known as “therapeutic misestimation.”²⁸ The ethical implications of this finding depend on the reasons for the misestimation. Such reasons might include difficulty understanding quantitative information during the consent process, encoding the gist of rather than the verbatim characteristics of information during disclosure, or trying to voice an optimistic attitude rather than express true understanding of the chances of success. More research is needed on the relative impact of factors leading to misestimation of frequency-type probabilities. With regard to patients' high belief-type expectations, our findings shift the focus of ethical concern in informed consent for clinical trials to issues other than disclosure, such as whether it is morally acceptable for patients to be optimistic, whether such optimism is beneficial, or whether it represents a cognitive bias that makes patients vulnerable and diminishes the quality of their informed consent.²⁷ We are currently conducting empirical work to address these questions.

Our study has three key limitations. First, to assess the number of constructs we wished to measure without creating undue burden on participants, we used briefer versions of measures—in some cases, a single item. Typically, measures with fewer items are less reliable, which may explain the small correlations we observed. Second, the participants were recruited from three tertiary-care research centers. Although early-phase oncology trials commonly are conducted at large centers such as these, it is unclear how our findings would generalize to clinical trial participants in other settings. Finally, it is important to note that the perceived likelihood of benefit is not the only consideration for patients deciding whether to participate in a

phase I trial and that our framework for categorizing perceptions may miss some of the nuances of research participants' experiences.²⁸

In conclusion, these findings show that the process of obtaining genuinely informed consent in early-phase clinical trials is more complex than has been understood previously, and they suggest the need to continue investigations of how best to advance the science of medicine while maintaining respect for patients who participate in these trials.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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