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The Culture of Faith and Hope: Patients' Justifications for Their High Estimations of Expected Therapeutic Benefit When Enrolling in Early-Phase Oncology Trials

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Abstract

Purpose—Patients' estimates of their chances of therapeutic benefit from participation in early-phase trials greatly exceed historical data. Ethicists worry that this "therapeutic misestimation" undermines the validity of informed consent.

Patients and Methods—We interviewed 45 patients enrolled in phase I or II oncology trials about their expectations of therapeutic benefit and their reasons for those expectations. We employed a phenomenological, qualitative approach with one primary coder to identify emergent themes, verified by 2 independent coders.

Results—Median expectations of therapeutic benefit varied from 50% to 80%, depending on how the question was asked. Justifications universally invoked hope and optimism, and 27/45 participants used one of these words. Three major themes emerged: (1) optimism as performative, that is, the notion that positive thoughts and expressions improve chances of benefit; (2) fighting cancer as a battle; and (3) faith in God, science, or both. Many participants described a culture in which optimism was encouraged and expected, such that trial enrollment became a way of reflecting this expectation. Many reported they had been told few patients would benefit and appeared to understand the uncertainties of clinical research, yet expressed high expected personal therapeutic benefit. More distressed participants were less likely to invoke performative justifications for their expectations (50% vs 84%; $P = .04$).

Conclusion—Expressions of high expected therapeutic benefit had little to do with reporting knowledge and more to do with expressing optimism. These results have implications for understanding how to obtain valid consent from participants in early-phase clinical trials.

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Introduction

Patients entering early-phase clinical trials often operate under what has been termed the “therapeutic misconception,” the mistaken notion that the purpose of the trial is to benefit them as individual patients, when, in fact, the primary study objective is to determine the dose and safety of a novel agent.[1] One aspect of this phenomenon is the observation that patients enrolled in early-phase clinical trials in oncology report much higher expectations of therapeutic benefit than is likely based on reported experience.[2–4] This finding has led some to question the adequacy of the informed consent process, even though several groups have reported that participants in phase I trials do, in fact, know that therapeutic benefit is not the primary purpose. [4–9] Some have argued that patients who participate in research and understand that the trial is not designed for their therapeutic benefit, yet still express high expectations of therapeutic benefit, may not be suffering from a therapeutic misconception.[10] Rather, these commentators suggest 2 classes of expressions of high expectation of benefit—high estimates based on incorrect understanding of the probability of benefit (ie, “therapeutic misestimation”) and high estimates despite a correct understanding that the aggregate probability of benefit is low (ie, “therapeutic optimism”).

Our group has hypothesized that the bioethical questions posed by high estimates of therapeutic benefit may be confounded by linguistic considerations.[11] Patients’ responses to inquiries about their chances of therapeutic benefit are not simply straightforward statements of fact, but must be understood instead as utterances occurring within a discourse that takes place in a specific linguistic context.[12] For example, the question, “What are your chances?” is vague. It might denote a query about a fact regarding aggregate probability in a population (ie, “frequency-type” probability), or it might denote a query about an individual’s beliefs regarding that individual’s future (ie, “belief-type” probability). In support of this interpretation, we recently reported findings from a pilot study that patients expressed significantly higher expectations of therapeutic benefit if they were asked belief-type questions than if they were asked frequency-type questions.[13]

We have also offered a linguistic hypothesis that patients might be “doing other things” (besides reporting their understanding of the facts) with their expressions of high expected therapeutic benefit. It has been reported that hope for personal benefit is a strong motivation for participating in early-phase clinical trials.[14–21] It is not known, however, how patients’ motivations for participation are related to their expressions of expected therapeutic benefit. Their expressions of high expected benefit might subserve indirect speech acts, intended to accomplish other purposes. It is not known whether patients expressing high expectations of benefit are misestimating the probability of benefit or expressing therapeutic optimism. If they are optimistic, it is not known whether such optimism represents a beneficial psychological defense mechanism, a dysfunctional syndrome of denial, or a cognitive bias known as “unrealistic optimism.”[22] These differing explanations have differing ethical implications.

The aim of this study is to explore research patients’ justifications for their estimates of expected therapeutic benefit when enrolling in clinical trials, using qualitative methods to facilitate a comprehensive understanding. We sought to understand what patients mean by the hope and optimism they express in the context of early-phase clinical trials, what they expect to accomplish through the meanings they have constructed, and how these attitudes are related to their estimates of expected therapeutic benefit.

Methods

In preparing a quantitative survey instrument for use in a larger study,[13] we conducted individual, in-depth interviews with a convenience sample of research patients enrolling in early-phase oncology trials in order to understand their justifications for their expressions of expected therapeutic benefit from trial participation. Interview subjects were patients with cancer who had agreed to participate in phase I or II oncology trials at either Duke University Medical Center or Fox Chase Cancer Center but had not yet initiated the investigative treatment. We conducted a total of 45 interviews (which is higher than generally used in qualitative studies)[23,24] in order to augment data stock, maximize data reliability, and facilitate exploratory analyses. All interviews were audio-recorded and transcribed. Participants were paid $75. The institutional review boards of the Duke University Health System, Fox Chase Cancer Center, and St. Vincent’s Hospital Manhattan approved the study.

Interviewers were jointly trained by 2 of us (KPW and DMS). A quantitative interview instrument with closed-ended questions was developed to pilot-test differences between belief-type, frequency-type, and vague questions about anticipated therapeutic benefits of trial participation.[25]

The qualitative portion of the study consisted in the interviewers asking the participants to elaborate on their answers and to probe for justifications of expectations using standardized open-ended questions. All patients were asked 2 of the 3 forms of the questions being pilot-tested—15 were presented the belief-type question first, 15 the frequency-type question first, and 15 the vague question first. For example, a participant would first be asked the frequency-type question, “Out of 100 patients who participate in this study, how many on average will have their cancer controlled as a result of the therapy? (on a 0 to 100% scale).” Next, the interviewer asked the participant how he or she interpreted the question. The interviewer then asked the participant using the following question: “What were you thinking about when you selected your answer of [response]? How did you go about selecting that number?” The participant would then be asked the belief-type form of the question, “How confident are you that the experimental therapy will control your cancer?” and this response would be further probed (see Table 1). The vague form of the question was, “What is the chance that participating in this study will control cancer?” The transcribed responses to these open-ended questions were entered into an ATLAS.ti qualitative analysis database (ATLAS.ti Scientific Software Development GmbH, Berlin, Germany) for textual analysis.

A phenomenological, grounded analytical approach was taken to evaluate participants’ interpretations accurately and to bracket potential preconceptions about how patients justify participation in clinical trials and their expected benefits.[26] By examining the phenomenology of participants’ justifications, we identified recurring themes directly from the narratives and developed substantive and theoretical coding schemes to identify and differentiate the emerging themes.

To ensure the validity of the coding schemes, we used an independent review process. The primary coder developed the preliminary themes and coding schemes using ATLAS.ti. To diminish bias, 2 additional researchers reviewed the transcripts independently. The independent readers corroborated and critiqued the proposed themes and helped to improve the clarity and validity of the coding schemes. Disagreements were resolved by consensus among the 3 reviewers. Once the coding schemes were finalized, the primary coder recoded all 45 transcripts using ATLAS.ti.

ATLAS.ti facilitates the iterative process of creating codes from a large volume of data and allows the researcher to identify meaningful and significant thematic patterns. Using ATLAS.ti, the coder divided the interview transcripts into textual utterances (ie, the smallest pieces of narrative segments that could be interpreted alone, usually 1 to 3 sentences) and coded each utterance by the theme(s) it reflected. Additionally, categorical data such as sex and distress level of the participants were entered into ATLAS.ti for stratified analysis.

We used a sequential, data-transformational design model of mixed-methods research to conduct additional exploratory analyses.[27] Although the coding was based on a grounded theory approach that eschews a priori hypotheses, once coding has been completed, qualitative data can be readily transformed into a quantitative form (in this case, the number of cases associated with each code) and subjected to quantitative hypothesis testing to explore further questions, such as whether subject characteristics are associated with particular themes. Coding data were exported from ATLAS.ti into the SPSS statistical software (SPSS Inc, Chicago, IL) to examine thematic frequencies and to stratify coding data into categorical variables. Based on more than 600 coded utterances from the 45 interview transcripts, using chi-square tests or t tests, as appropriate, we tested associations between thematic codes and the variables of question type, age, sex, race, education, ECOG performance status, and distress level (as measured by a single item, “On a scale of 1 to 10, how much distress have you been feeling in the past week?”).

Results

As shown in Table 2, the participants included equal numbers of men and women and were mostly white. Most participants were married or reported having an intimate partner and had at least some college education. About half had previously been enrolled in another clinical trial, and Eastern Cooperative Oncology Group performance status was generally good (≤2).

Participants varied significantly in their responses to the quantitative questions about expected therapeutic benefit, according to how the question was asked ($P = .02$ from Kruskal-Wallis test). The median estimate of expected therapeutic benefit was 80% for belief-type queries (n = 15), 50% for frequency-type queries (n = 14), and 50% for vaguely worded queries (n = 14). A quantitative analysis of these expectations of therapeutic benefit was reported by Weinfurt et al.[13]

Three major themes were noted in qualitative analysis of the open-ended questions about participants’ justifications of their estimates of expected therapeutic benefit: hope and optimism; battle; and faith.

Hope and Optimism

Almost all participants, at least indirectly, made reference to hope or optimism in justifying their responses to queries about the meaning of their numerical expressions regarding expected therapeutic benefit. A majority (30/45) explicitly uttered the words “hope” or “optimism” in their responses. With one exception (a participant who used the word “hope” in a religious way that explicitly transcended the outcome of the trial), participants used the words “hope” and “optimism” as synonyms referring to their expectations of personal therapeutic benefit from participation in the trial. Representative comments about hope and optimism included the following:

> Participant D24: “‘Cause if you don’t have hope and confidence, what you got left?”

> Participant F22: “It’s just that everything is a hope. And I feel confident that at some point in time they’re going to find the right combination of drugs to get rid of this.”

Expressions of hope and optimism even arose spontaneously in conversations with a few participants when they were asked about the meaning of the phrase “experimental therapy.”

> Interviewer: “And what does ‘experimental therapy’mean?”
>
> Participant D10: “New. Also possibly cutting-edge. Hopeful.“
>
> Participant F38: “Well, it means a great bit of hope to me, because I believe they must have reason for using this chemical on me. Great expectations to do something, you know, I don’t think I’m the first one to try it, but I don’t think I’d be afraid to try something for the first time.”

When participants were specifically asked to explain the reasons for the expected therapeutic benefit they reported at the beginning of the interview, responses fell into 1 of 3 main coding categories: (1) optimism as a performative expression; (2) entering the trial as part of a battle with cancer; and (3) faith, whether in God, medicine, or both.

Optimism as Performative Expression—Many participants (36/45) explained their expressions of optimism regarding the individual therapeutic benefit they expected through participation in the research protocol as “performative” expressions.[25] That is, they believed that by thinking optimistic thoughts and expressing this optimism to others they would actually positively influence the likelihood of experiencing individual benefit.

> Participant D11: “You know, I probably should have said 100 [laughter]. You know, realism with, you know, always being optimistic…. That’s a big part of recovery, that’s a big part of your treatment, is your right attitude and being optimistic and believing that things are going to work.” [Note: This participant said there was an 80% chance the investigational intervention would control her disease.]

Participants often gave further explanations for the belief that expressions of optimism would positively affect the outcome. For some participants, the belief that optimism would change the outcome favorably was justified by a type of folk psychology.

> Participant F4: “I want to feel confident, because you hear people say, well, attitude is a lot…has a lot to do with your, you know, with, with your health, and you know, fighting chance, especially.”

For others, the belief that thinking optimistic thoughts and expressing optimism to others would increase the likelihood of individual therapeutic benefit was something they believed had been proven scientifically.

> Participant F11: “I have friends that are psychologists and psychiatrists, and they said my attitude is better than anything. You have to have a positive attitude. If you sit around and worry about it all day, it’s going to drag you down.”
>
> Participant F15: “According to some research in psychology it probably does affect maybe how you’re going to feel and how you’ll sit with whatever new drug they try on you.”

Battle—Almost all participants (43/45) used metaphors of battle, combat, or competitive sports to describe their reasons for participating in early-phase trials and their expressed expectations regarding the outcome. Even should the prognosis be grim, many viewed their expressions of high expected therapeutic benefit as signs they were not quitters, would always continue the battle, would never "lose hope."

> Participant F11: "I did two tours in Vietnam and I was a cop for 27 years. They didn't get me, so I'm not going to let this get me either."

> Participant F50: "That's the whole key. It's just like, how do you say it, if you're playing a chess game, OK, and you're anticipating a person's moves, OK. I'm anticipating their moves and how do I counteract their moves, OK. So when they come to attack me, I use what they have to be victorious."

> Participant F35: "Oh, yeah, I think you need to be hopeful. You know, without hope you're dead, you're sunk, you might as well stand in the corner and roll over 'til you fall over on your back, legs in the air, just like a cockroach. I mean, there's always hope. Gee whiz, yeah."

Some participants saw participating in this battle as participating in something greater than themselves. While none specifically used the phrase "war on cancer," some comments seemed to reflect this line of thought. These comments often had altruistic overtones.

> Patient F35: "I don't know what I can equate it to. It's trying to achieve saving a million dollars a penny at a time, you know. And that's probably it. Every person contributes their penny, and while the penny itself doesn't amount to much, the accumulative effort becomes substantial."

Faith—Most participants (40/45) explained their expectations of a positive outcome as founded upon some sort of faith. Their faith expressions were of 2 types: faith in a religious sense and faith in medicine. Expressions of faith in individual doctors or in the medical profession or in science were far more common than overtly religious expressions of faith.

Some expressions of optimism based upon faith were straightforward expressions of religious belief in miracles. The expression of faith itself sometimes functioned as performative expressions:

> Participant F50: "Cause I'm going to be their miracle. I believe if you're in the right frame of mind, all this can happen and be…go better, faster, and the body actually heals itself. OK? So whatever they give me is just helping to heal it faster. And that's my belief. And my father in heaven is going to reach down and say, 'Here.'"

Expressions of faith in medicine as a justification for expectations of therapeutic benefit sometimes singled out faith in a particular physician, sometimes faith in medicine or medical science in a general way, and sometimes even expressed faith in the study drug.

> Participant F05: "[The physician] knows my body now and he knows what will work. And there are probably other treatments out there he's tried. But I have complete faith in him that he will come up with the best that is there. Not just because it's a study that's out there and he wants to put me in it just to, you know, get my name in a study and do it. He's trying to pick the best that will work for me."

> Participant F10: "Well, I don't know. I'm just a positive thinker…. I have a lot of faith in the newer drugs."

> Participant F76: "You kind of have a hope, you have a faith in the medical community and this drug. And it you know, there's the hope at the same time."

Expressions of faith as the basis for optimism often combined religious faith with faith in medicine or science.

> Participant F58: “My faith in God is part of it as well. I also have faith in the medical community.”
>
> Participant F50: “God gave us this wonderful thing here, you know [pointing to his head] and I’m using it to help the doctors cure me… And I pray to him that whatever medicine they give me, that they give me the correct medicine, OK, to help cure me.”
>
> Participant F50: “If we could live like brothers, believe in each other as brothers, lift each other up like brothers, help each other as brothers, then it would be perfect. It would be perfect…. We could cure each other.”
>
> Interviewer: “Through our support…”
>
> Patient: “And our prayers. That’s right, OK. But we would probably need doctors to deliver. No?”

Conforming to Social Expectations of Optimism

Some participants (16/45) explicitly described their expressions of faith and optimism regarding the personal therapeutic benefit they expected from the trial in a way that suggested they were conforming to social expectations of how they should behave, what attitudes they should project, and what they should say. They sought to be “model” patients, pleasing the medical community, their families, and even their faith networks. For example, participants often reported that they were told to be hopeful by physicians or nurses who cared for them, both their primary referring medical teams and the staff involved in the clinical trial.

> Participant F15: “I will add to you that when I’d seen my internist back home at a checkup that she knows the latest of what is happening with me and being here that she had said to me don’t lose hope. Don’t give up hope. So hope is vital for a cancer patient.”
>
> Participant F36: “…one thing I do find over here which is very good. I always find that they’re hopeful. Like, if you come over and you’re sort of feeling sorry for yourself…they have another plan, this is something you can do…I think that’s important, you know, that they give you that hopefulness, that there is hopefulness. I mean, they’re going to give it to me when there is not hope too, and they have to do that also, that’s part of it. But…as long as there’s hope there, I think just share it with me, and they have. I’ve always found that to be so. Everybody here that I’ve worked with, the nurses and doctors and fellows, I just have not one complaint.”

Several participants also seemed to suggest that by enrolling in the trial and maintaining an optimistic spirit they were fulfilling the expectations of their families and communities, including those who shared their religious beliefs:

> Participant F24: “…people will tell you, mainly lay people, one of the most important things about fighting cancer is you have to keep a positive attitude.”
>
> Participant D20: “Basically all they say, “Everything’s going to work out.”… So far, about all of my family and friends that I know, I’ve heard, I have yet to hear any of them say anything negative…they do a lot of praying for me. It’s just that I haven’t been a hundred percent as far as doing my part, and I know it’s time.”
>
> Participant F47: “I think half the world is praying for my prolonged life and the fact that I will feel well enough to continue taking care of my mother and helping my

> children, and I can feel, I can feel the peace of all those prayers being offered for me, and it's a wonderful feeling. And that gives me confidence. If the good Lord means me to be here, I will… But you have to help yourself. You can't lay in bed and feel sorry for yourself…"

Some even reported a sense of duty to express positive, optimistic, or hopeful expectations of therapeutic benefit specifically in order to reassure or help loved ones in dealing with the patient's own struggle with cancer.

> Participant D02: "In any sickness, it's good to be positive. And I have been positive throughout the whole thing, although I have had my moments, you know, of course. But I have tried to be very positive. One reason, because of my girls. You know, I didn't want to be all poopy and down and out for them, 'cause they would just be destroyed."

Optimism Despite Realism

Almost all patients (42/45) reported a basic understanding of the fact that the reason the trial was being performed was because the true therapeutic benefit that would be expected in a population of cancer patients receiving the study drug was unknown. They frequently, however, distinguished this realism about the trial (and what might happen to other trial participants), from what they expected would happen to them.

> Participant F44: "Well, I don't expect a lot. I can be hopeful for a lot. But, I mean, experimental is experimental…. I'm optimistic…. Probably I think I'll do better than other people because I'm not false-hope, uptight about what's going to happen. I think that makes a difference."

> Participant F57: "I think every person's different. Every cancer's different. Best guess is, I say maybe 20 percent may have some type of control if it works. You know, I really don't know if this'll work. I really don't, just realistically, I don't care about 100 other patients [laughter]. There's only one I care about, and that's me. And my own opinion, my hopes are high. But I couldn't, I don't know how to answer this. I wouldn't, 'cause I don't know what… You guys can't tell me what the expectations are cause you're still experimenting. And I can't tell you…" [Note: This participant stated he was 50% confident the investigational drug would control his cancer].

Altruism

While it was rarely the primary reason participants gave for enrolling, most participants (30/45) spontaneously expressed an altruistic motivation when asked about their beliefs and expectations about the trial.

> Interviewer: "When you saw 'chance,'what did that mean to you?"

> Participant D24: "It might and it might not help. You know, like I told them to begin with, if it doesn't help me, maybe what they learn from me will help the next person that comes along. I said if God gives me the strength and grace to go through it, if it doesn't help me, maybe it'll help the next…I'll do something to help the next person."

> Participant F24: "I think there's always that hope that by participating you'll hopefully help yourself and help others. "

Associations Between Participants' Qualitative Responses and Characteristics

For exploratory purposes, we conducted analyses of all 45 participants to investigate possible associations between certain types of justification for expectations of therapeutic benefit and demographic and psychosocial factors. We classified participants according to whether they had, during the interview, at least one coded expression in each of the three primary thematic categories of optimism as a performative, battle, or faith. This exploratory analysis was not a primary goal of our study, and the sample size was relatively small for performing statistical hypothesis testing (eg, statistical power of only 0.55 to detect a 30% difference in sex at $\alpha = .05$). Another statistical limitation was that, since we had reached saturation in our qualitative analysis, the number of participants not expressing each theme was very small—hence there was there was little variability. The frequency with which participants gave a response that was coded into one of the three main coding categories was not associated with primary question type (ie, belief-type, frequency-type, or vague), age, sex, race, education level, ECOG performance status, or level of distress. The only significant association we found was that participants who had higher distress (> 5 on a 1 to 10 scale) were less likely to have made performative expressions to explain their optimism (50% vs. 84%; $P = .04$).

Discussion

Human language is complex. It is not merely a mode of expression, but it is used as a tool to get things done. When a patient enrolling in an early-phase oncology trial responds to the inquiry, "What do you think the chances are that this treatment will control your cancer?" and he or she replies, "Eighty percent," a philosopher of language would ask, "What is the patient doing with the phrase, 'Eighty percent'?"[28]

Corroborating previous findings, when we asked our participants who had enrolled in early-phase oncology trials about their expectations of therapeutic benefit, they gave answers that were generally much higher than those historically reported for patients participating in such trials.[2–4,13] When asked to explain how they arrived at their answers, however, we found little evidence that what they were "doing" was reporting misinformed or confused views about data. Rather, consistent with observations reported by Kim et al,[29] what they appeared to be "doing" was expressing attitudes of optimism and faith.

For many participants, expressing optimism was deemed important because they believed expressing hope and having an optimistic attitude would actually improve the likelihood that they would experience a therapeutic benefit. Many based this belief on a type of folk psychology. Such beliefs have been popular from the times of Hippocrates to Percival to Karl Menninger to the present.[30–35] Other participants understood the connection between hope and outcomes as something established by science, even though the actual data are, at best, conflicting.[36,37] Studies reporting that "hope helps" might be more likely to be reported in the media, so that patients come to believe that this is incontrovertibly true. Furthermore, a widespread set of background cultural norms favors an optimistic attitude for patients, influencing their responses to inquiries about their expectations of therapeutic benefit upon enrolling in a clinical trial.[35,38]

Christian scriptures say, "faith is the substance of things hoped for" (Hebrews 11:1). In other words, those who hope must have faith. Our participants, living in a secular age, often based their hopes for therapeutic benefit from clinical trials on their faith in medicine. Sometimes this faith in medicine and science was mixed with religious faith—God and medicine.[39] Other patients only expressed religious faith—that the trial would keep them alive and God would perform a miracle. Another meaning of faith, though, is not belief but trust—faith in a person or group of persons or a human institution. A number of participants who used the word “faith” appeared to be using it in this interpersonal, relational manner, applying it to physicians and cancer centers to justify why it is that they had the hopes they did.

Participants also saw themselves engaged in a battle—a struggle in which surrender was not an option.[18] This metaphor is one of our culture’s dominant metaphors in describing cancer.[33] Lerner,[40] for instance, has documented the history of the celebrated war on cancer, which continues unabated today. Talk about hope and battle has also been linked to cancer patients’ sense of personal agency.[41,42] Individual participants in our study used metaphors from sports or the military, also deeply embedded in our culture, to describe their optimism as the proper attitude in the face of difficult odds.[35,43]

It was clear from these interviews that cultural expectations of faith and hope are not only generated by physicians, nurses, and medical scientists.[33] Families, friends, and religion all encouraged optimism. These cultural norms may be especially well-developed in cancer centers, where optimism may serve as a defense mechanism for staff as well as for patients. Many of the clinical trial participants we interviewed seemed to report both that they had been informed about the uncertainty of the trials’ outcomes, and also that they were encouraged to maintain hope. The latter might serve as the dominant message, even if patients are fully informed at the time of consenting for the trials. It is also likely that the patients are a preselected group, drawn by their faith in medical science to high-profile institutions as potential sources of a “last hope.”

Another cultural expectation seems to be that certain social roles, such as that of spouse or parent, call for expressions of optimism in order to reassure or even “protect” loved ones. Several participants reported that their optimistic expressions were motivated by such familial concerns, with a purpose far different from expressing an understanding of data.

By and large, our participants seemed to understand the purposes of their clinical trials, that the outcomes were unknown or uncertain, and that historically, populations of patients who have enrolled in early-phase clinical trials were unlikely to therapeutic benefit. Only one participant appeared to labor under a full-blown therapeutic misconception, believing that every aspect of the trial was designed for his individual therapeutic benefit (F25: “The purpose is to cure colon cancer”). Despite this, most participants estimated their own chances of individual therapeutic benefit as quite high, showing evidence of a possible therapeutic misestimation rather than a full therapeutic misconception. Yet, in giving their high estimates of expected outcome for themselves, many distinguished themselves from other participants in the same trial, whose chances of therapeutic benefit they estimated to be closer to historically low figures. These patients were optimistic despite their factual knowledge of the low frequency with which patients benefit from early-phase trials, a phenomenon that has been dubbed “therapeutic optimism.”

Most participants also reported a secondary altruistic motive for enrolling in a trial. Many reported a primary hope that they would benefit individually, and a secondary hope that others might benefit in the long run even if they did not themselves benefit individually. Previous studies, using closed-ended questions, have downplayed the role of altruism as a motive.[4,19] More open-ended and qualitative studies, such as ours, suggest altruism has a significant secondary motivating role.[18,21] Notably, we found a hermeneutic association between the way optimistic expressions function as performative expressions for patients as individuals and the concept of engaging in an altruistic battle against cancer. Participants often expressed both justifications for their optimistic expressions in the same utterance. In a sense, both are performative expressions—one expressing the belief that positive thoughts will affect their outcomes as individuals, and the other expressing the belief that their individual battles are part of a greater battle by society against cancer, the outcome of which depends, in part, on their own positive attitudes.

Ethical Implications

This study obviously does not address all of the ethical questions that swirl around the so-called therapeutic misestimation. It does, however, help to define more clearly where the true ethical questions lie.

It does not appear that what most of our participants were "doing" when they reported high expectations of individual therapeutic benefit from participation in clinical trials was giving a confused report on their understanding of trial statistics. To the extent that a patient can say, "I know that historically less than 5% of patients enrolled in phase I clinical trials have benefited," then the potential ethical problem is neither a failure of adequate disclosure by the investigators nor a failure of adequate comprehension by the patient. If this is true, then attempts to improve the informed consent process by new techniques of communication designed to improve comprehension may be missing the mark.

What patients appear to be "doing," in many cases, is expressing faith and optimism. The belief that personal will can effect a change in the course of bodily disease, the conflation of hope and optimism, and the notion that the medical system embodies and defines the limits of hope all may be constructs of a particular historical moment in our particular culture.

It is uncertain what the ethical implications of this faith and optimism might be. On the one hand, it might be important to encourage such expressions. If an optimistic attitude really does improve outcomes, then there might be morally good reasons for encouraging it. If, for most patients, optimism is a critical psychological defense mechanism, then it might also be good to encourage optimism, at least up to the point that it becomes dysfunctional denial. On the other hand, these expressions of optimism might be signs of the cognitive bias known as "unrealistic optimism."[22] That might make patients who are offered participation in early-phase oncology trials especially vulnerable as research subjects, suffering from a cognitive bias that could lead to poor decision making and coercion. It is also possible that these expressions of optimism are signs that these patients are being subtly influenced by cultural expectations both inside and outside the medical research community, pressuring them to enroll in order to prove that they really have not given up hope. Several previous studies have suggested that patients feel family pressure to enroll in clinical trials.[4,15] Our data suggest that the pressure to enroll may be part of a broader expectation that they "think positively," with enrollment in the trial serving as proof that they have not "given up hope."

Limitations

As an empirical investigation, this study cannot answer the ethical questions it raises.[44] Like any qualitative study, it is also difficult to generalize beyond this small group of cancer patients. While our study population reflects the national demographics of cancer trial populations,[45] it is not known how a more racially and culturally diverse population might have responded to the interview questions. Our measure of distress is not validated, but this part of the study was only exploratory and should be investigated more carefully. While we have taken appropriate safeguards against bias, all texts require interpretation and the transcripts of these interviews are a text. Moreover, since we did not observe their interactions with clinicians, we are limited by patients' understandings, memories, and potential recall bias.

Conclusion

Despite these limitations, we found strong evidence that expressions of high expected therapeutic benefit among these early-phase trial participants were more likely to represent expressions of optimism than reports of factual knowledge. These findings also suggest that reports of high expected therapeutic benefit among research participants constitute a complex phenomenon and that studies designed to disentangle a variety of forms of therapeutic optimism, therapeutic misestimation, and therapeutic misconception will need to be carefully designed. Further empirical research is needed before determining the ethical significance of these phenomena.

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Table 1

Sample Interview Schedule[a]

“Out of 100 patients who participate in this study, how many on average will have their cancer controlled as a result of the therapy?” (Response options: 0 to 100 patients)

1 First, pretend that you are helping someone else to answer this question, and the person is not sure they understand the question. To help the person understand, can you rephrase this question in your own words?

> PROBE: What does it mean to be participating in a study of a new experimental therapy?
>
> PROBE: What does “have their cancer controlled” mean to you?
>
> PROBE: What does “on average” mean?

2 [How the patient selected the response and what the response means to the patient.]

> PROBE: What were you thinking about when you selected your answer of [response]? How did you go about selecting that number?
>
> [What kind of story does the patient tell about the justification? Does the patient cite reasons regarding his or her health, the quality of the medical center, etc.? Does the patient cite reasons regarding the need for a positive attitude, hope, etc.?]
>
> PROBE: Imagine someone circling [a number on the opposite end of the scale]. What sort of situation do you think that person might be in?

“How confident are you that the experimental therapy will control your cancer?” (Response options: 0% to 100%)

1 Pretend that you are helping someone else to answer this question, and the person is not sure they understand the question. To help the person understand, can you rephrase this question in your own words?

2 Does this mean the same thing to you as the first question I showed you?

> [If yes] So for you, this [confidence question] is just another way of asking this [frequency question]?
>
> [If no] How are these two questions different?

3 What would your answer be to this [confidence] question?

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[a] Participants were assigned to 3 groups of 15 in which the initial question of the pair of questions began with the belief-type (“confidence”), frequency-type (“out of 100…”), and vague (“What are your chances?”) questions (see text).

Table 2

Participant Characteristics (N = 45)[a]

Characteristic	Participants
Age, mean (SD), y	57 (9.3)
Female, No. (%)	23 (51)
Hispanic or Latino ethnicity, No. (%)	0
Race, No. (%)	
Black or African American	4 (9)
White	40 (89)
No answer	1 (2)
Marital/partnered status, No. (%)	
Married/partnered	34 (76)
Widowed	5 (11)
Single, never married/partnered	3 (7)
Divorced or separated	3 (6)
Current living situation, No. (%)	
With others	39 (87)
Alone	6 (13)
Highest grade or level of schooling completed, No. (%)	
Eighth grade or less	3 (7)
Some high school	1 (2)
High school graduate	10 (22)
Some college	14 (31)
College graduate or beyond	17 (38)
Monthly household income, No. (%)*	
< $500	1 (2)
$500 to $1999	9 (20)
$2000 to $3999	7 (16)
$4000 to $5999	6 (14)
$6000 to $7999	5 (11)
≥$8000	9 (20)
Don’t know/prefer not to answer	6 (13)
First time participating in a clinical trial, No. (%)	22 (49)
ECOG performance status, No. (%)	
0	28 (62)
1	15 (33)
2	2 (4)
3	0
4	0
5	0

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

[a] The variable was missing for 2 participants.