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Unrealistic Optimism and the Ethics of Phase I Cancer Research

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Abstract

One of the most pressing ethical challenges facing Phase I cancer research centers on the process of informed consent. Historically, most scholarship has been devoted to redressing therapeutic misconception—i.e., the conflation of the nature and goals of research with those of therapy. While therapeutic misconception continues to be a major ethical concern, recent scholarship has begun to recognize that the informed consent process is more complex than merely a transfer of information and therefore cannot be evaluated only according to how well an individual understands such information. Other components of decision making operate independently of understanding and yet still may compromise the quality of informed consent. Notable among these components is unrealistic optimism, an event-specific belief that one has a better chance of receiving benefit than others similarly situated. In this article, we consider responses to interviews with parents who had recently completed an informed consent conference for enrolling their child in a Phase I cancer clinical trial to examine how this influence manifests and how investigators might address it during informed consent.

Keywords

unrealistic optimism; Phase I; clinical trials; research ethics; cancer

INTRODUCTION

Children and adults with terminal cancer may seek to enroll or be actively recruited to participate in Phase I trials of investigational drugs. The scientific goals of these studies are to determine an appropriate dose for Phase II and to assess toxicity of the drug. Efficacy is not a primary endpoint. Because understanding these goals and endpoints is ethically mandatory for adequate consent, much effort has been put forth to improve the quality of information transfer and to better assess subject understanding.[1–3] Yet, the hopes of these patients for clinical benefit remain a major motivating factor for participation. Scholars wanting to understand this phenomenon have focused largely on the notion that harboring such high expectations of benefit is the result of having received bad information or of not having understood good information that was provided during the consent process. The underlying assumption seems to be that if participants really understand the scientific goals of Phase I research and are adequately informed about overall response rates they would not give as their reason—or at least their primary reason—for enrolling any motivation other than a desire to help advance scientific knowledge or to benefit others. For many scholars, hope or optimism, understood as a disposition toward positive thinking, is not incompatible

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with adequate understanding of the nature and purpose of Phase I research and is therefore ethically unproblematic. When optimism is unrealistic, however, some scholars have begun to consider that it may unduly influence a participant's decision-making.

To better understand the frequency and influence of UO, we examined transcripts of informed consent conferences (ICC) and post-ICC parental interviews gathered as part of a larger NIH funded multi-center project on pediatric Phase I informed consent (POIC). The goals and methods of this project are outlined elsewhere.[4] Rather than a full report of data gathered in the larger project, this paper reflects some of the important insights we have gleaned from one instance of UO—namely that, while not common among the cases examined, UO is an ethically important concept. Moreover, while the empirical research conducted in the POIC related to informed consent, the ethical question in this paper centers on investigator integrity. We ask: If a physician-investigator discovers unrealistic optimism during an ICC for a Phase I cancer trial, should she ever prevent the patient from becoming a subject in the study? To begin our exploration of this question, we first focus on defining UO. We then examine a case of UO ascertained from our research. Finally, we conclude with reflections and guidance for investigators who may face this dilemma.

DEFINING UNREALISTIC OPTIMISM

The concept of unrealistic optimism in the science of decision-making has been a topic of academic research in social psychology for over 30 years.[5] Stated simply, unrealistic optimism "occurs when people perceive their own personal outcomes as being more positive than those of other people in similar circumstances."[6] The initial research focused on discrete future life events such as likelihood of enjoying a first job or of getting divorced within the first five years of marriage. Extension of this work has recently turned to examining how this bias manifests in making decisions about medical treatments. Probability and numeracy are considerations with regard to both risk and chance for benefit in this context. Whether, how, and the extent to which unrealistic optimism plays into the decisions about research participation is a new and promising area of inquiry. One of the challenges of translating this work on unrealistic optimism into the context of decision-making for participation in research, more specifically participation in Phase I research, is the level of uncertainty involved for predicting numeric estimates of both risk and chance for benefit.

Social psychologists have labeled some optimism as 'situational' or 'comparative' to distinguish it from a more global attitude of positive thinking, which is referred to as 'dispositional optimism.'[7] To be sure, not all instances of comparative optimism are unrealistic. It is only unrealistic when there are in fact no good reasons for an individual to consider that he has a greater likelihood of experiencing positive outcomes or avoiding negative outcomes compared to others in the same or similar situation. So, for example, a non-smoker who makes an accurate judgment about her comparative risk of lung-cancer as being lower than that for a smoker demonstrates comparative optimism that is not unrealistic. By contrast, a heavy smoker who believes her risk of lung cancer is lower than others who have a similar tobacco history because she "just knows it in her heart" does indeed have UO.

Because the idea of unrealistic optimism has only recently entered into bioethical discourse, there is limited understanding of the full spectrum of ethical implications of its occurrence. In fact, earlier considerations of optimism—which most likely refer to forms of dispositional optimism—portray optimism as ethically unproblematic and in some instances an outlook that should be fostered for its potential benefits for sick patients.[8–11] So, for example, Horng et al, consider "therapeutic optimism" as "always [ethically] tolerable because hope

does not compromise the autonomy of a decision to participate in research."[9] The notion of compromising autonomy is critical here, and helps explain why the majority of the literature looks at problems caused by errors associated with either a lack of information or a misunderstanding of information provided. A basic conception of autonomy requires that an individual be able to form ideas about what he or she values and be able to pursue those ideas without interference. An individual who is not adequately informed about the purpose of a clinical trial, or who does not understand how the study differs from routine medical care, cannot be said to be acting autonomously. Her ability to decide whether participating in a study is consistent with her values is compromised because she is reasoning from false beliefs.

As Jansen points out, distinguishing dispositional (and ethically unproblematic) optimism from unrealistic optimism allows one to see that UO is the result of a bias that may be ethically problematic. First, this bias is cause for ethical scrutiny because it can interfere with the process of autonomous decision-making. It is important to note that UO does not necessarily hinder "understanding … [but] may interfere with the appreciation and processing of information related to risks and benefits."[12] A second ethical concern is raised by the potential for unrealistic optimism to "directly interfere with voluntary or autonomous decision-making … typically operat[ing] behind the back of those who are subject to it, thus potentially interfering with the voluntariness component of IC."[12] These concerns serve to establish good reason to take a closer look at unrealistic optimism in the context of research participation. Jansen has completed one such study in a recent examination of UO in early-phase adult cancer trials.[13] In what follows, we push further into the nature of UO in Phase I cancer trials and suggest strategies investigators might take in addressing UO.

UNREALISTIC OPTIMISM IN POIC

To identify possible occurrences of unrealistic optimism in the POIC study, we looked at the responses to several of the questions asked during parent interviews that address estimates of medical benefit. These questions asked parents 1) whether most patients who participate in Phase I cancer trials get medical benefit from participation, 2) what percentage of patients who participate in this trial will get medical benefit, and 3) what chance their child has of getting medical benefit from participating in this trial. The second and third of these questions allow for a comparison of respondent's beliefs about their own chances of benefit versus the chance of benefit believed to apply to other participants. We are able to approximate the existence and extent of unrealistic optimism by making this comparison. In contrast to Jansen's study sample, these individuals had completed an ICC but may not have decided yet (formally, at least) whether to provide their permission for their child's participation. This is important because the expressions that may be evaluated as illustrating unrealistic optimism are more likely to be the result of how parents are incorporating or "appreciating" information given to them than the result of something like post-hoc rationale for already having decided to participate.

The following dialogue between interviewer and parent illustrates several key points:

Do most patients who participate in Phase I clinical trials get medical benefit from participation?

Patient's Mother: Do I think it works for most kids, is basically what the question is.

Research Assistant: Yeah.

> Patient's Mother: Um … I don't really know the statistics. Um, I think it's worth it for the kids that it does help. And I hope T. – you know of course I hope T. is one of those. That's kind of the outlook we have is you know, if he's given a ten percent chance he's going to be in that ten percent, you know, and that's kind of my outlook on things and I try to keep him that way. Um, so I would say … I mean if I had to answer that question I would say … based on what I know about this disease, probably not, most kids. But the ones that it does help I think that it's worth it. And if it's increasing you know, the – how many kids its helping then it's definitely worth it.

What percentage of patients who participate in this Phase I clinical trial do you think will get medical benefit from it?

> Patient's Mother: I think enough that they think it's worthwhile to keep it a trial. (laughter). Which … with the disease that T's battling, I mean it – honestly I don't think it's most. It's probably on the lesser side but it's probably more than other things that are available.

What is the chance that your child will get medical benefit from participating in this Phase I clinical trial?

> Patient's Mother: Um … I think his chances are good. Because this trial is a drug that is in the same family of the drug that helped him previously. Um, the [drug] he took before and it completely – I mean it put him into remission. And this is [a similar drug] which, you know, we talked about yesterday, is it's in the same family. Um, so I feel like that's good. I feel like that's good. I feel like it gets him a good chance.

In this example, we see the kind of contrast between assessing the likelihood of benefit for other participants and for oneself that raises a red flag warning about possible unrealistic optimism. In this particular case, the patient's mother had indicated in a response to a prior question that she had an accurate understanding of the scientific goals of the study: "to find out how much of this drug can be given safely." Free from therapeutic misconception, it is highly unlikely that her expression of optimism is based on a misunderstanding that the purpose of the trial is to benefit her child directly. Instead, it seems that her expression of optimism is grounded in the same kind of biased reasoning a smoker may use when he says "I'm less likely than other smokers to develop lung cancer because I exercise and eat healthy"—namely, overlooking that these specific features may be true of other smokers as well. In the case of the smoker, he may continue to engage in a risky behavior due to an error in comparative appreciation of the risks of smoking.[14] This would be a clear case of unrealistic optimism as we have defined it here. In the case of the patient's mother depicted above, her belief that her child has a "good chance" of medical benefit while benefit is "probably on the lesser side" for other participants is based on a failure to consider that other participants may too have been on a similar drug in the past. It may in fact be true that having been on a similar drug in the past increases her child's likelihood of receiving benefit from this drug but that fact would be true for any other participants in the study who had benefited from a similar drug in the past. In other words, she is inflating her belief about the likelihood of benefit because she believes that there is something "exceptional" about her situation that distinguishes her from others similarly situated when in fact this same feature may be true for others as well.

REDRESSING UNREALISTIC OPTIMISM, OR WHAT DO WE DO IF WE FIND IT?

Provided that at least some instances of UO are cause for ethical concern, the next step is to consider how the IC process can be modified to prevent or correct the bias created by unrealistic optimism. Given earlier research results which demonstrate the absence of a strong correlation between understanding and unrealistic optimism, taking steps simply to improve participant understanding is unlikely to prevent or reduce UO.[15, 16]

With so many variables to consider, it is also unlikely that those instruments which can be used to identify unrealistic optimism would be practical solutions during IC conferences—an already complex process of understanding and subsequent decision-making.[16, 17] However, knowing that some prospective Phase I research subjects exhibit unrealistic optimism, and having a basic understanding about how unrealistic optimism influences decision-making can help sensitize investigators. Investigators are then better positioned to be vigilant about addressing UO when it does manifest at the individual level. Investigators already are (or should be) assessing subjects' understanding by asking both open- and close-ended questions during IC. Adding one or two comparative risk/benefit questions to this assessment may be an efficient way to alert an investigator to the possibility of UO. Because UO may be operating outside of a person's conscious awareness, attempts to uncover and correct it must successfully bring it out from behind the curtain. In practice this would not be overly difficult nor would it require excessive additional time to the IC process. Below is a brief sketch for how this might play out during an ICC:

"Can you tell me in your own words the purpose of Phase I research?"

"What would be involved if you decided to participate in this study?"

- these questions and others like them should already be standard during ICC to assess an individual's understanding of the nature and purpose of Phase I research and of the risks/burdens of participating

"Are there any benefits to participating in Phase I research?"

- again, this may already be standard as a way to assess understanding, but it is also important as a first step toward revealing and addressing UO

"What percent of participants benefit (in the way(s) just described, especially medical benefit/tumor response) from participating in Phase I studies?"

"What percent benefit from this study?"

- provides an opportunity to address therapeutic misestimation as well as to establish a point of comparison for what follows

"What is your percentage likelihood to benefit from participating in this study?"

- if actual percentages are hard to establish for the participant, could ask greater or less than
- if individual indicates a greater than others likelihood, probe further by asking

"Do you know of others who participated?" "Imagine that your brother/sister/best friend were facing a similar situation. How does your likelihood of benefit compare?"

- this latter question is important should the individual give indication of the possibility of UO; research indicates that UO is reduced the closer or more familiar the point of comparison [18, 19]

On a case by case basis, these questions taken together enable the investigator to discern whether the expression of a high expectation of benefit is the result of 1) poor understanding of information, 2) the act of conveying something besides understanding (e.g., a speech act intended to express a parent's commitment to being a "good parent" by doing everything possible for the child),[20] or 3) is a manifestation of unrealistic optimism. If it appears to be UO, the investigator could then probe further and attempt to clarify that no one individual has a greater or lesser likelihood of benefit compared to others in the study. Doing so helps establish for the potential participant additional factors such as comparative risk are important and relevant to their decision about participating. In extreme cases, where a participant clearly agrees to be on the study as a result of UO, investigators may-as a matter of ethical integrity-have to prohibit study enrollment.

Initially such focused attention may reveal more instances of UO than we are currently aware of, but, in doing so, it would also provide the opportunity for an investigator to better protect potential subjects from research risk. It requires that investigators understand better the position from which potential subjects or their parents are in, what factors are at play in decision-making, and how to draw them out. Should UO become apparent in this process, investigators would be in a unique position to help participants reason more clearly.

CONCLUDING REMARKS

Respect for persons is paramount in conducting research on human subjects. This requires investigators and other research staff to take steps to ensure that participants have the opportunity to provide their consent/permission/assent to the proposed experimental procedures or drugs. It also demands that investigators have the integrity to either provide further guidance to enable adequate consent or prevent those individuals from participating who demonstrate a lack of understanding about the purpose of the research and/or the nature of the scientific goals as compared to routine medical care. Such considerations have received much attention in the literature, including studies intended to clarify key concepts (e.g. therapeutic misconception) and interventions intended to improve communication during ICC so as to reduce the frequency and severity of poor understanding. In this article, we argue that there are aspects of the IC process that operate outside of rational understanding but that have the potential to challenge autonomous choice nonetheless. Clinical researchers and ethicists are coming to recognize that "good informed consent" entails more than the transfer of information. Subsequently, decisions about whether to enroll are now more clearly understood as complex events involving trust, hope and other elements that may be difficult to measure. Ethical scrutiny of IC to date has focused almost exclusively on improving the content of IC—both consent documents and conferences—to enhance understanding. Recent research and theoretical inquiry has demonstrated, however, that individuals can receive good information, understand it, and still be acting out of compromised autonomy when factors such as unrealistic optimism influence their decision-making about participating in a research study.

To address these concerns, investigators are situated as the front-line defense against reasoning that is unduly influenced by unrealistic optimism. Neither IRB oversight nor the IC document can protect participants in this way. It is a function that can be accomplished only in conversation between investigator (or other study staff) and whoever is providing consent/permission. Identifying unrealistic optimism and distinguishing instances where it is ethically problematic from instances where it is merely dispositional optimism or the expression of some other speech act becomes an exercise of practical wisdom. It requires that investigators know when to foster hope and when to curtail unrealistic optimism. This concept highlights the importance of investigator integrity—a matter of virtue, wisdom and practical ethics.

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