

**Therapeutic Misconception, Unrealistic Optimism,
and Hope in Phase I Oncology Trials****By David B. Resnik**

Consider the following scenario: A patient with advanced lung cancer that has not responded to radiation and chemotherapy has run out of treatment options. He is considering foregoing further aggressive treatment in favor of palliative care so he can live his remaining days (estimated to be three to four months) in relative comfort, surrounded by family and friends, without having to endure the harsh effects of more chemotherapy. He discusses palliative care options, including hospice, with his oncologist, who informs him that he has an opportunity to enroll in a Phase I clinical trial of a new drug that could cure his cancer or stop its progression. The oncologist tells him that there is only a small chance (5%) that the new drug will be effective against his cancer but that it is worth a shot. The patient jumps at this chance, hoping that this new drug will benefit him. He tells himself that he will be among the 5% for whom the treatment works. Unfortunately, the drug does not help the patient and he dies from its side effects and the progression of his disease six weeks after enrolling in the study. His family regrets his decision to pursue aggressive experimental treatment instead of hospice care.

Patients with advanced cancer often face choices like the above when they have exhausted all other treatment options. While Phase I oncology trials offer patients experimental drugs that might work, they raise difficult ethical issues for investigators, human subjects, and institutional review boards (IRBs) because the odds patients will benefit from participation are usually exceedingly slim.

Phase I oncology trials collect data about safety and pharmacology and seek to establish a maximum tolerable dose (MTD) level. Dosing typically begins at 10% the lethal dose established in rodents and escalates gradually until the subject experiences dangerous toxicity or intolerable side effects (Eisenhauer et al. 2000). Although Phase I studies are not designed to benefit participants, cancer patients might derive medical benefits from participation, such as shrinkage of tumor size, halt of metastasis, or enhanced longevity (Miller and Joffe 2008). Although the Phase I testing period typically lasts 6 to 12 months, subjects' participation ranges from a few days to a month. A drug must complete Phase I successfully before Phase II and III testing can begin (Eisenhauer et al. 2000).

One of the ethical issues raised by Phase I oncology trials concerns the balance of risks to benefits (Miller 2000, Miller and Joffe 2008). Federal regulations require that, "Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result (Department of Health and Human Services 2009, 45 CFR 46.111(2))." Because oncology drugs are usually highly toxic, most commentators argue that it would be unethical to enroll healthy volunteers in these studies. Subjects should include only cancer patients who have exhausted other treatment options and have only several months to live because they might derive medical benefits from participation that would justify their high risk-exposure (Agrawal and Emanuel 2003, Miller and Joffe 2008). However, the chances of patients benefitting from participation are usually so small that some have questioned whether the risks are reasonable in relation to benefits (Miller 2000). According to a comprehensive study of 466 Phase I oncology trials involving 11,935 participants, response rates averaged 10.6% and mortality related to toxicity was 0.5%. In addition, 14.3% of participants had at least one episode of a life-threatening or disabling toxic event (Horstmann et al. 2005).

Other studies have yielded response rates ranging from 4.2% to 6.3% and mortality rates from 0.5% to 0.57% (Agrawal and Emanuel 2008).

Low response rates in Phase I oncology trials are chiefly due to the fact that these studies are not designed to test drug efficacy (Miller 2000). The primary purpose of Phase I oncology trials is to generate safety information, which is needed for Phase II and III testing. As noted above, patients might receive varying doses that may not correspond with the optimal dose for treatment, and they usually do not remain in the study long enough to derive significant treatment effects (Miller 2000).

Another important ethical issue is informed consent. Federal regulations require that investigators obtain "legally effective informed consent of the subject or the subject's legally authorized representative (Department of Health and Human Services 2009, 45 CFR 46.116)." Many commentators have argued that informed consent for Phase I oncology trials is often defective because patients do not adequately understand or appreciate the nature of the research or the benefits and risks of participation (Miller 2000, Miller and Joffe 2013). Commentators have distinguished between two types of problems with consent that might occur when cancer patients enroll in Phase I oncology trials. One of these is known as "therapeutic misconception" (Henderson et al. 2006).

First described by Applebaum and colleagues in the 1980s, therapeutic misconception occurs when research subjects do not understand that the primary purpose of a study is to gain new knowledge rather than to benefit the study participant (Appelbaum et al. 1982, 1987, Henderson et al. 2006). Although clinical researchers have known about therapeutic misconception for several decades, the phenomenon continues to persist despite efforts to educate patients about the goals of clinical research (Glannon 2006). For example, a systematic review of 88 articles on therapeutic misconception in psychiatry found that rates among subjects ranged from 12.5% to 86% (Thong et al. 2016). Pentz et al. (2013) interviewed 95 subjects in Phase I oncology studies and found that 68.4% had therapeutic misconception.

One reason why therapeutic misconception is difficult to dispel, especially in oncology, is that cancer patients often are motivated to enroll in studies to benefit medically from participation (Henderson et al. 2006), and the expectation of personal benefit can lead subjects to confuse research and therapy. For example, Dolly et al. (2016) surveyed 301 patients in Phase I oncology trials and found that 84% rated the possibility of tumor shrinkage as the most important reason for enrollment, followed by lack of alternative treatments (56%). Overall, 47% said they expected their tumor to shrink and 14% expected to be cured. Other studies have also found that a high percentage of cancer patients enroll in Phase I studies with expectation of personal benefit (Agrawal and Emanuel 2008).

The expectation of personal benefit can also lead to a second type of problem, known as "unrealistic optimism," which occurs when patients significantly overestimate their chances of a successful outcome for a treatment (Horng and Grady 2003). For example, if the chances of cure from a treatment are 5%, but a patient believes that her chances are 50%, we could say that the patient is unrealistically optimistic. Unrealistic optimism is a type of bias that can compromise consent by interfering with a patient's understanding of the balance of the benefits and risks of participation. Jansen et al. (2011) interviewed 88 patients in Phase I oncology trials and found that most had some type of unrealistic optimism related to the benefits of participation. For example, 62.5% were unrealistically optimistic about their chances of benefitting medically from participating, and 59.7% were unrealistically optimistic about the prospects of having their cancer controlled (Jansen et al. 2011). Jansen et al. (2011) argue that unrealistic optimism is not a type of misunderstanding but a problem with applying information correctly to decision context.

They characterize unrealistic optimism as a failure to adequately appreciate information concerning benefits and risks (Jansen et al. 2011).

Unrealistic optimism is different from hope, which can be defined as “the feeling that what is wanted can be had or that events will turn out for the best” (Dictionary.com 2018). One can be hopeful that an event will occur without being unrealistically optimistic. For example, one may buy a lottery ticket hoping that one will win yet acknowledge that the chances of this happening are minuscule. Likewise, a patient can be hopeful that a treatment will work yet also be realistic about its chance of success.

Hope plays an essential role in helping cancer patients (and their families) deal with the diagnosis of cancer, cope with illness and suffering, and adapt to changing expectations concerning life plans (Chi 2007). Hope is also positively associated with quality of life (Chi 2007) and can give patients a sense of control (Butt 2011). Factors that can enhance hope include religion, spirituality and familial and personal relationships (Butt 2011).

Unlike therapeutic misconception and unrealistic optimism, hope is an informed and rational state of mind that, in and of itself, provides a benefit to study participants. A patient might be willing to endure aggressive therapy for the sole purpose of maintaining hope when the other option is despair (Butt 2011). A patient might accept significant physical pain and discomfort to fend off that mental anguish, especially when many people believe that a positive state of mind increases the odds of achieving good health.

Many patients opt for aggressive cancer therapies that are not experimental and are known to be unlikely to succeed. The only difference here is that the probability of success is based on hard evidence rather than scientific prognostication.

Physicians dispense placebos to give patients hope. Studies have demonstrated that placebos can work even if the patient is informed that they are receiving a placebo (Mundt et al. 2017). A Phase I oncology trial can be considered a very elaborate form of placebo, but one that a patient might choose to obtain of the benefit of hope.

Hope is thus a legitimate potential psychological benefit of research participation that IRBs should not discount when assessing the benefits and risk of study participation. Although hope, in itself, does not justify imposing serious risks on patients, it should be considered in conjunction with other benefits to the subject or society.

However, since hope can easily lead to therapeutic misconception and unrealistic optimism, the consent process must ensure that a hopeful decision is based on a realistic understanding of the odds of success (Miller and Joffe 2013). Clinical investigators should not take advantage of participants’ hopes that they will be the small group of patients for whom the treatment works.

Clinical investigators and research staff who talk with cancer patients about participating in Phase I studies might be concerned that they will take away their hope if they emphasize the low chances of successful treatment. Studies have shown that a more realistic understanding of one’s prognosis is associated with reduced hope (Helft et al. 2003), so it is conceivable that candidly discussing the chances of successful treatment with a patient who is considering enrolling in one of these studies might undermine his or her hope. However, since investigators are obligated to obtain effective informed consent from patients prior to enrolling them in Phase I studies, they must find a way to help patients understand the risks and benefits of research participation and alternative options (such as palliative care) that does not take away their hope. Investigators and staff who are trying to meet recruitment goals must be aware of their own biases related to the study and guard against their tendency to oversell the benefits of participation (Henderson et al. 2006).

IRBs also face dilemmas when they review Phase I oncology protocols and consent forms. Ideally, the protocol should undergo a thorough scientific review before it reaches the board to provide IRB members with the information they need to assess ethical and safety issues related to research design (Resnik 2015). The scientific review may be conducted by the study's sponsor, the host institution, or both. The scientific review should address issues such as: results from prior animal, cell and chemical studies; the dosing regimen; tests, procedures, measurements and variables; inclusion/exclusion criteria; clinical monitoring; data and safety monitoring; and adverse event reporting. IRBs should pay attention not only to the potential risks of the study but also to its benefits, if any. The protocol should include information about the effects of the drug when used to treat cancer in animals, as well as its potential efficacy in human beings (Kimmelman and Henderson 2016).

IRBs should carefully review the informed consent document to ensure that it candidly discusses benefits, risks and alternatives, including the option of foregoing aggressive treatment (Miller and Joffe 2013). The informed consent document should clearly state that the purpose of the study is to gain knowledge about the safety of the medication, not to benefit the participant, and it should not overemphasize therapeutic goals or effects. Although research indicates that consent forms in Phase I oncology studies generally comply with ethical and regulatory requirements (Horng et al. 2002, Malik and Mejia 2014), patients might still fail to adequately understand or appreciate risks and benefits due to therapeutic misconception and unrealistic optimism (Glannon 2006). IRBs should consider requiring investigators to include language in consent documents designed to dispel therapeutic misconception and warn participants about how unrealistic optimism might impact their decision-making.

Since the consent process encompasses various interactions between investigators, staff and participants, IRBs should carefully review other communications with participants, such as advertisements, recruitment materials, phone scripts, and letters. IRBs should also consider monitoring consent discussions to ensure that investigators and staff are communicating appropriately with participants and addressing their questions and concerns (Miller and Joffe 2013). They could also interview participants to assess their understanding of the benefits and risks of participation. For example, some studies ask participants to take a quiz after they sign the consent form to evaluate their comprehension of the study and correct any misunderstandings they might have (Nishimura et al. 2013).

Terminally ill patients with advanced cancer that has not responded to conventional treatment face complex, emotionally vexing ethical dilemmas concerning their options related to medical therapy and research participation. Some of these patients might decide to forego aggressive treatment to minimize pain and suffering during their remaining days, while others might cling to the shred of hope that some form of therapy, including experimental drugs or alternative medicine, will work for them. Investigators and research staff who are conducting Phase I trials of oncology drugs must deal with ethical issues related to balancing risks and benefits and obtaining valid, informed consent. Investigators and staff should be mindful of the ethical challenges inherent in their research and take appropriate steps to address them so they do not take unfair advantage of desperately ill cancer patients. Likewise, IRBs should carefully scrutinize Phase I oncology protocols, consent forms, and other documents to protect the welfare, rights and dignity of human research participants.

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