

False Hopes, Informed Consent: The Problem of Therapeutic Misconception and Stage I Clinical Trials

Jennifer Cable

Keywords: clinical trials, dying, therapeutic misconception

INTRODUCTION

In America, with our closely held values of optimism and perseverance, we are very often loath to confront death and dying; cancer patients are told to fight, to hold on to a positive attitude, to nurture faith and hope. Our doctors are trained to heal us, to cure us, but rarely to gently guide us toward acceptance of our own mortality. We will grasp at a chance, any chance, to keep fighting, to turn things around. We believe that medicine will aid us in this fight; never counsel us to give up fighting. And when we hear “probability,” we think, “a chance.”

No issue so brightly illuminates these themes as the participation of terminal cancer patients in Stage 1 clinical trials. Having exhausted all other treatment methods, these patients are offered a chance to continue chemotherapy, with a new experimental regime. The researchers explain that the only purpose of a Stage 1 trial is to determine appropriate dosing levels, and few patients, if any, will see any therapeutic benefit. While patients may fully understand the purpose of the trial, they simultaneously believe that they will be the exception, that they will reap the benefit. Enrolling in the trial is an expression of hope for one’s future, not an expression of altruistic sacrifice. Patients may have intellectually understood the purposes and demands of participation, but they have fundamentally misunderstood their chance of benefit from the study.

ANALYSIS

Patients enrolling in many types of clinical trials can be affected by what has been termed therapeutic misconception. These patients confuse the goal of the trial with the goals of individual treatment: The goal of a clinical trial is to gather sufficient data over a population; the goal of a clinical intervention is to provide benefit to the individual patient. The patient as subject mistakenly believes that the goal of the trial is to provide treatment that will be beneficial in treating the patient’s illness. In a Stage 1 clinical trial, as in a placebo control trial, this misconception is troubling due to the strong possibility that the individual patient will not receive the intervention in sufficient dosage to be effective, if he receives it at all. When a patient enrolls in such a study because he has exhausted all other options, and is terminally ill, the moral dimensions of therapeutic misconception and its impact on informed consent must be addressed.

In technical terms, the requirements of informed consent have been met; researchers have informed the patient of the significant risks of enrolling in the trial and have explained that the likelihood of the patient receiving a direct benefit is very low. However, the patient is motivated to participate in the trial by a false hope in the possible benefit. Even when a researcher is completely truthful, the layperson’s understanding of the facts presented may be

colored by a psychological need to express hope, cultural expectations around illness (especially cancer), or an overestimation of the probability of benefit.

Sulmasy et al. distinguish between therapeutic misestimation, in which the patient has a high expectation of therapeutic benefit and incorrectly understands the probability of benefit, and therapeutic optimism, in which patients have a high expectation of therapeutic benefit but understand correctly that the aggregate probability of benefit is low.¹ Sulmasy et al. show that patients may not be engaging in a “full-fledged” version of therapeutic misconception (i.e., “the purpose of this trial is to cure ovarian cancer”), but instead overestimate the possibility of benefit, either on the whole or for themselves. However, patients reported that their primary motivation for enrolling in a Stage 1 clinical trial was for an individual benefit, with a secondary altruistic motive to further research that will help others suffering from the same disease. Although there is certainly a spectrum of therapeutic misconception, in all of these cases the researcher must confront the psychological and emotional components of participation in Stage 1 clinical trials if fully informed consent is to be obtained.

Jansen et al. report that unrealistic optimism is also endemic in Phase I, Phase I/II and Phase II clinical cancer trials, but it has no significant relationship to the participants’ understanding of the trials’ purpose (it is not “full-blown” therapeutic misconception); this suggests that patients can continue to engage in unrealistic optimism even after being fully informed and educated about the content of a trial.² Kass et al. emphasize the importance of how oncologists use language to represent the trial to potential participants; in their survey of oncologists’ communication with patients about involvement in Stage 1 clinical trials, they found that although oncologists explain that Stage 1 trials only measure safety and dosing, they also refer to the trials as “treatment with uncertain therapeutic effects.”³ This resulted in 17 percent of patient respondents saying that the purpose of the study was to cure their cancer, with 17 percent correctly stating the purpose as measuring dosing and safety. Researchers concluded that this misconception could be addressed with more precise language on the part of clinicians and researchers. Although these are all relatively recent studies, this is not a new issue in Stage 1 clinical trials, as a recent survey of 25 years of scholarship on this subject has shown.⁴

Typical standards of informed consent in this case must be expanded to ensure that research is not conducted on terminally ill subjects whose consent is predicated on the false belief that they will benefit from participation. It is deeply troubling that such patients might spend their last years or months dealing with the inconvenience and pain of undergoing experimental treatment when there is no possibility of benefit, instead of spending that time with friends and family. Some individuals would place a high value on contributing to research that furthers the scientific body of knowledge of their own disease, yet it’s more likely that most patients would not choose to spend their limited remaining time as subjects in clinical trials if they did not believe they might offer them some benefit. This raises an important question: Is therapeutic misconception in some ways necessary to conduct Stage 1 clinical trials, especially in oncology? Is it therefore acceptable? I believe it is possible to both confront therapeutic misconception and continue Stage 1 clinical trials. Therefore, researchers and clinicians must address therapeutic misconception if Stage 1 clinical trials are to be conducted ethically.

Some would argue that it might not make sense to confront therapeutic misconception if it is a powerful expression of hope and faith, or if it provides a psychological benefit to a patient. However, this sort of popular pseudo-science (promulgated in bestsellers like *The Secret*) has no basis in reality. Coyne et al. showed, in a study of more than 1,100 participants with head and neck cancer, that emotional well-being is not correlated with better overall survival rates.⁵ More interesting is the argument that some patients may feel obligated to express optimism to support their families, or because of cultural expectations to “fight” cancer, or a belief that a positive attitude will lead to a positive outcome.⁶ If this is the case, optimism may be more performed than believed, and there is less of an ethical obligation for the researcher to confront it in the informed consent process. However, research consistently shows a sizable portion of patients continuing to engage in genuine therapeutic misconception, believing that the purpose of the trial is to provide them with an individual benefit.

Some say that it may not benefit individual patients to indulge in unrealistic optimism but it will benefit patients as a whole. There is, after all, a necessity to develop new treatments, especially in the area of terminal cancers. Agrawal and Emanuel argue that in fact patients sometimes do benefit from Stage 1 clinical trials; it is not pure delusion on the part of the patient to enroll in a trial hoping for some personal benefit.⁷ They write that patients with advanced cancer who enroll in Stage 1 trials do so as an expression of their personal values, and that more than 70 percent of patients understand that they may not directly benefit, even if they hope that they will personally benefit. I believe the distinction between understanding and hope is a valid one, but Agrawal and Emanuel employ this language to argue against “the critics” of Stage 1 clinical trials. I don’t believe that 70 percent is high enough to satisfy concerns of informed consent, and they do not adequately confront the ethical problems posed by therapeutic misconception.

Although I have focused mainly on the mind-set of the patient, researchers play a significant role in reducing or propagating therapeutic misconception. The role of language and communication in the conversations between oncologist and patient was discussed earlier; oncologists themselves presented trials as a sort of treatment, adding to the therapeutic misconception.⁸

Researchers may be tempted to overlook therapeutic misconception expressed by their patients when enrolling patients in trials that will further their research. They may also genuinely believe that participation in the trial might positively affect their patients’ outcomes (as Agrawal and Emanuel argue that some Stage 1 trials do). Often, over years of work with a patient, an oncologist may come to closely identify with that patient’s struggle and encourage her onward, sometimes instilling in her a false hope for improvement. Oncologists are human, and, like the rest of us, they find it difficult to confront the reality of death and dying; better to push patients to enroll in trials than inform them that there is little more to be done than make hospice arrangements. For both patient and oncologist, if there is a chance, even if very slim, they will feel compelled to try.

In *Experiments on Man*, Henry Beecher recommended that there be a clear separation between the roles of clinician and researcher if research is to be performed ethically. Such a separation of roles when it comes to Stage 1 clinical trials would help to combat therapeutic misconception. The patient must have a source of expert opinion whose aim is not the furthering of research but his health and well-being. By ensuring that no doctor is both researcher and clinician, we can more effectively guide patients to a full understanding of the burdens of participation and the slim probability of benefit. Importantly, as independent parties, we can stress that the goal of trials is not to provide benefit to patient themselves (although this may be a fortunate side effect). Further, palliative services should be available to patients before they decide to give up treatment (many insurance companies insist that patients be in full hospice care); professionals in palliative care could discuss end-of-life planning with patients and help them to decide if participation in a clinical trial is an appropriate use of their remaining time. A simple scale of independently administered questions for potential participants could test whether patients are engaged in therapeutic misconception; these patients could then have another information session about the trial, or they could be considered unsuitable subjects. Institutional review boards should discuss this issue with researchers to ensure that all methods of informed consent address the problem of therapeutic misconception.

CONCLUSION

Some may argue that this will overburden an already highly bureaucratic system and increase the cost of developing new drugs, costs that would then be passed on to consumers and taxpayers. However, all of these recommendations make use of pre-existing resources in hospital and clinical settings. And the new healthcare law will require end-of-life counseling, through which more holistic and unbiased advice can be offered to the patient. In the end, our primary goal should be to satisfy the necessary conditions for ethical research. Research methods and hospital bureaucracy should evolve to meet ethical requirements; ethics should not be distorted to fit the needs of

research or bureaucracy. By confronting the problem of therapeutic misconception, we can ensure that consent is truly informed and that participation in Stage 1 clinical trials is ethical.

An ethical procedure for informed consent and enrollment in these trials is possible—a procedure that does not take advantage of individual patients' false hopes for benefit or their reluctance to confront the reality of terminal disease—if several modifications are made to the existing system.

¹Sulmasy, D. P. et al., "The culture of faith and hope," *Cancer* 116, (2010): 3702–3711. doi: 10.1002/cncr.25201

²Lynn A. Jansen, Paul S. Appelbaum, William M.P. Kelin, Neil D. Weinstein, William Cook, Jessica S. Fogel, and Daniel P. Sulmasy, "Unrealistic Optimism in Early-Phase Oncology Trials," *IRB: Ethics & Human Research* 33, no.1 (2011): 1-8

³Nancy Kass, Holly Taylor, Linda Fogarty, Jeremy Sugarman, Steven N. Goodman, Annallys Goodwin- Landher, Michael Carducci and Herbert Hurwitz, "Purpose and Benefits of Early Phase Cancer Trials: What do Oncologists Say? What do Patients Hear?" *Journal of Empirical Research on Human Research Ethics: An International Journal* 3, no.3 (September 2008): 57-68

⁴Paul S. Appelbaum, Charles W. Lidz, Franklin G. Miller and Jonathan Kimmelman, "Twenty-Five Years of Therapeutic Misconception," *The Hastings Center Report* 38, no.2 (March - April 2008): 5-7

⁵Coyne JC, Pajak TF, Harris J, Konski A, Movsas B, Ang K, Watkins Bruner D; Radiation TherapyOncology Group, "Emotional well-being does not predict survival in head and neck cancer patients: a Radiation Therapy Oncology Group study," *Cancer* 110, no.11 (December 2007): 2568-75

⁶Sulmasy, et al

⁷Manish Agrawal, Ezebiel J. Emanuel, "Ethics of Phase 1 Oncology Studies: Reexamining the Arguments and Data," *JAMA* 290, no.8 (2003): 1075-1082

⁸Kass, et al