

# Misunderstanding in Clinical Research:

## *Distinguishing Therapeutic Misconception, Therapeutic Misestimation, & Therapeutic Optimism*

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Understanding is a requirement of informed consent,[1] which is itself fundamental to ethical clinical research.[2] Data show that many research subjects misunderstand various aspects of the research in which they participate, and investigators, study coordinators, and IRBs are also suspected to share these misunderstandings. Interview studies with subjects in phase I cancer trials, for example, reveal that many of them confuse the aims of research with the aims of clinical care,[3-6] and both subjects and investigators overestimate the expected benefit of phase I trial participation.[7-10] Ethicists have pointed to these misunderstandings as cause for alarm by invoking the therapeutic misconception.[11] Unfortunately, therapeutic misconception has been used loosely to refer to any number of misunderstandings that subjects may have in the research context. This imprecise use of the term can itself cloud our assessment of when informed consent is compromised. Different types of misunderstanding are possible, and in this paper, we distinguish and discuss two of them in order to demonstrate how misunderstandings of different components of research carry distinct ethical implications for informed consent. We further distinguish the concepts of misunderstanding and optimism.

### Illustrative Cases

Mark is a 63-year-old retired engineer with advanced colon cancer. He wishes to participate in a phase I clinical trial that is testing the safety of a new chemotherapeutic agent. Before enrollment, as the primary investigator interviews Mark in order to assess his understanding of the research, Mark reports that the purpose of the trial is to find out how well the chemotherapy will shrink his tumor. Even though the actual purpose of the trial is to discover the maximum tolerated dose of the agent in humans, he claims that the trial "is designed to help people who have no other options," and that the research doctors "have [his] best interests in mind." While the risks of the untested agent exceed those of standard chemotherapy, he feels that the possible risks are "no worse than the treatment [he has] already tried." He estimates the probability of benefit to be at least 30%. The investigator's estimate of potential benefit is 5%, based on previous meta-analyses of similar phase I cancer trials.

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Susan is a 45-year-old journalist who also suffers from advanced colon cancer. She volunteers for the same phase I cancer trial as Mark. In the pre-enrollment interview, Susan states correctly that the purpose of the trial is "to find the highest dose of the drug that is safe in humans." Moreover, she mentions that she has considered the possibility of being assigned either to a dose that is too low to have a therapeutic effect on her cancer or to a dose that is high enough to cause severe side effects. Nevertheless, she states that this is a "low risk research trial," and estimates the probability of benefit to be around 30%.

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Thomas, a 57-year-old painter with advanced colon cancer, wishes to enroll in the phase I trial as well. He recognizes that safety testing is the purpose of the trial and estimates harm and benefit with probabilities similar to those of the investigator. However, he hopes that he is "one of the 5%" to receive benefit from the tested agent.

Which, if any these cases, is ethically problematic? Mark, Susan, and Thomas demonstrate different degrees of understanding. Both Susan and Thomas have a better understanding of the research and its differences from clinical care than Mark does. Mark and Susan seem to be overestimating the probability of benefit and underestimating the probability of harm in the trial. Thomas appears to have an accurate understanding of the probabilities, but is optimistic that he will beat the odds. What approach should IRBs or investigators take in addressing these misunderstandings?

### Understanding in Informed Consent

To approach these questions, we must recognize why informed consent is important as well as how understanding contributes to it. Informed consent is important because of the value we place on respecting individuals' autonomous decisionmaking.[12] This respect involves making sure that an individual's decision to volunteer for research includes four elements: 1) competence, 2) provision of information, 3) understanding, and 4) voluntariness.[13]

For the sake of conceptual analysis,

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Figure I.

| Concept | Definition | Ethical Significance | Example |
|---|---|---|---|
| **Therapeutic Misconception** | The research subject conflates research with clinical care. | *Rarely* tolerable because understanding the nature of research is necessary for an autonomous decision to participate in research. | Mark believes that the purpose of the Phase I cancer trial is to help him personally. |
| **Therapeutic Misestimation** | The research subject underestimates risk, overestimates benefit, or both. | *Sometimes* tolerable because understanding the exact probability of harm and benefit may not be necessary for an autonomous decision to participate in research. | Susan estimates that she has a 30% chance of benefit in the Phase I cancer trial. A meta-analysis of similar studies shows that benefit accrues to 5% of subjects. |
| **Therapeutic Optimism** | The research subject hopes for the best personal outcome. | *Always* tolerable because hope does not compromise the autonomy of a decision to participate in research. | Thomas hopes that he will be one of the 5% who benefit from the Phase I cancer trial. |

let us assume that Mark, Susan, and Thomas were competent enough to make decisions, their decisions to participate were voluntary, and the research team provided accurate information on the purpose of the phase I trial, its high risk, and its low probability of benefit. Under these hypothetical conditions, understanding is the critical concern. What kind or degree of understanding must Mark, Susan, or Thomas have to autonomously decide to participate in the trial? Understanding in the context of informed consent includes having an accurate grasp of the available options and the consequences of choosing one option over any others. To deliberate meaningfully over options, research subjects should understand what those options entail. If they misunderstand aspects of the research and its consequences, these misunderstandings are ethically salient insofar as they compromise an autonomous decision to participate in research.

## Therapeutic Misconception: A Warning Flag

In clinical research, patient-subjects often confuse research with clinical care. Appelbaum and colleagues have termed this misunderstanding "the therapeutic misconception."[14] The therapeutic misconception operates when a subject believes that "every aspect of the research project ... [is] designed to benefit him [or her] directly." Although a subject may benefit directly from research participation, the primary purpose of clinical research is always the production of generalizable knowledge.[15] Failure to understand this fact is ethically troubling, especially when the design of a trial is inconsistent with the research subject's expectation that personal care will be maximized and individualized.

In their original characterization of the therapeutic misconception, Appelbaum and colleagues invoke experience from a randomized, placebo-controlled trial for schizophrenia.[16] In this trial, some subjects understood the abstract concept of randomization to a placebo, but did not apply this concept to their *own* group assignment within the trial. Because they believed that the investigator would provide them with the best possible care, they could not conceive of being personally assigned to the placebo group. The subjects' expectation for personalized care conflicted with the actual design of the trial.[17]

In a similar way, Mark has a therapeutic misconception that conflicts with the design of the phase I cancer trial. He states that the purpose of the trial is to test whether the chemotherapeutic agent will shrink his tumor, when in fact the purpose is to test for safety. While a doctor in the clinical setting might adjust the dose of Mark's medication in order to increase efficacy or minimize side effects, the research investigator is restricted from doing so by the trial's dose escalation design. There is incongruence between Mark's beliefs that decisions about his medications and care will be made according to his personal best interests and the reality of research procedures that are required to answer a scientific question.

A decision to participate in research when the nature of the research has been misunderstood raises concerns about the autonomy of that decision. If a person does not understand the nature of research and how it differs from clinical care, then that person has a distorted representation of the research project and is making a decision about something that is different from the actual project at hand. Thus in most cases we want subjects to understand the nature of research and its distinction from clinical care for their enrollment to be ethically acceptable.

A solid understanding of a study's purpose and design can reinforce an understanding of the difference between research and clinical care. While subjects often need not understand the scientific or procedural details, the more features of the trial diverge significantly from what one would expect in clinical care, the more fully subjects should understand the purpose and procedures of the trial. For example, the use of procedures

such as randomization to a placebo or dose-escalation might conflict with what the subject would expect in the clinical care context. The same holds for such research aims as determining toxicity or provoking psychiatric symptoms.

Conversely, as features of a research trial more closely resemble those of clinical care, the less important it may be that a subject understand the specific research purpose and procedures. There may even be circumstances in which the therapeutic misconception, that is, a genuine conflation of research with clinical care, may be tolerated. For instance, in a phase III trial testing the comparative efficacy of a new agent against standard treatment, procedures and care may be close to or no different from those provided in the clinical care context. Thus even if the subject does not fully understand the research nature of the trial, the differences between what the subject experiences in the trial and in the clinical care setting are small. Although a genuine effort should still be made to redress this therapeutic misconception, if unsuccessful, it may be acceptable in some cases to tolerate the misunderstanding.[18] Additionally, a high prospect of personal benefit from the trial may support tolerating a subject's therapeutic misconception, since significant health benefits are most likely to be consistent with the subject's overarching goals.

Although a therapeutic misconception compromises the autonomy of a subject's decision to participate in research, because, by definition, it represents inaccurately the object of that decision, may not always be unacceptable. When efforts to correct a therapeutic misconception have failed, the compromised decisional autonomy of the subject may in some cases be compensated for by other factors, such as a high prospect of benefit and/or a lack of substantial conflict between the subject's expectations and the various features of research participation.

## Therapeutic Misestimation: Another Form of Misunderstanding

The therapeutic misconception is not the only type of misunderstanding that subjects may have in research, however. In the case above, Susan did not misunderstand the research purpose or difference between research and clinical care, but rather overestimated the probability that she would receive benefit in the trial and downplayed the risks of the experimental agent.

Studies demonstrating that subjects in phase I cancer trials are motivated by expectations of benefit suggest that participants may overestimate the probability of benefit and underestimate risk in a similar way.[19] This form of misunderstanding is descriptively and ethically distinct from the therapeutic misconception. We call it the "therapeutic misestimation." While the therapeutic misconception involves misunderstanding the *nature* or *intent* of clinical research, the therapeutic misestimation involves misunderstanding the *probability* of direct benefit or harms that may result from participating in research.[20] We suspect that the therapeutic misestimation may manifest itself as an overestimation of benefit, an underestimation of risk, or both together.[21]

The therapeutic misestimation is frequently combined or confused with the therapeutic misconception. Macklin characterizes the therapeutic misconception as "the belief that ... research is a promising treatment intended to benefit subjects,"[22] while King claims that the therapeutic misconception results from the assumption that "clinical research offers a reasonable potential for direct benefit to subjects."[23] Distinguishing the two concepts is useful when considering instances in which one exists without the other, as in Susan's case.

A therapeutic misestimation can exist along with a reasonably accurate representation of the nature and purpose of a research project. Conversely, a therapeutic misconception might exist despite a realistic expectation of risks and benefits. Although the therapeutic misconception and misestimation can co-exist in the minds of subjects, recognizing two separate elements of misunderstanding allows one to identify the different ways in which those elements can compromise the autonomous decisionmaking of patient-subjects.

■ *How Do Research Subjects Understand Probability?* Is the "therapeutic misestimation" a misunderstanding per se or merely an optimistic interpretation of probability data? To answer this question, it is helpful to consider the possible ways in which research subjects understand and interpret concepts of probability. Currently, little is understood about how research subjects understand probability and the role it plays in their decision to participate in clinical research.[24] However, the existing literature on presentation of risk in *clinical* settings suggests that both patients and clinicians commonly misunderstand statistical data expressed in the form of percentages.[25] Certain modes of presentation increase understanding, but patient preferences do not always include these modes.[26]

Given the complexity of understanding probability and the dearth of empirical data in the research setting, we suspect that investigators and research participants may interpret probability data differently and that participants may be predisposed to interpret probability data in their own favor.

First, subjects may question whether a probability estimate applies to themselves as individuals.[27] When using group data to predict the chances of an event happening to an individual, the assumption is that the individual and all members of the group are similar. However, there is always the possibility either that an individual has certain qualities that members of the group lacked, or that the group was heterogeneous for important, as yet undiscovered traits that affect the outcome. In clinical research, the usual outcome measures are physical responses, and subjects' intuitive awareness of factors that separate them from other people may

make them reluctant to accept the probabilities that investigators provide. Whether or not they have actual reason to disregard a probability estimate, subjects may be inclined to interpret those estimates to reflect a more optimistic outlook.

Second, it is also possible that subjects interpret a probability estimate in terms of odds, whereas researchers interpret it in terms of frequency.[28] While both interpretations are statistically "correct," it seems as if the odds interpretation might lead subjects either to "spin" a probability estimate in their favor or simply to be more willing to accept risk. For example, for a 50% chance of liver damage, from an odds perspective a subject may believe rightly that there is no greater confidence in an outcome of liver damage than there is in an outcome of no liver damage, and thus may be more willing to accept the risk. In contrast, an investigator may view the data as the expected frequency of liver damage in her subject pool, expecting approximately half of her subjects to experience this side effect. From this perspective, she may feel that subjects should be less willing to accept the risk. We speculate that an odds interpretation leaves more room for individual subjects to "hedge their bets."

Of course, the intuition that patient-subjects' tend to disregard or misestimate probabilities is empirically unproven and we should be careful not to support any ethical conclusions with nonexistent data. In any case, even if subjects *do* tend to misunderstand probability data, this tendency is a weak justification for tolerating it. A better understanding of how subjects (and investigators) understand probability should serve to make IRBs and investigators more attuned to misestimation and more informed about possible strategies to correct it.

## Therapeutic Misestimation: A Threat to Informed Consent?

The ethical importance of a therapeutic misestimation should be assessed in regard to two important elements: the magnitude of misestimation and the personal relevance of a misestimated risk or benefit to the subject. There are cases when a therapeutic misestimation is indeed problematic. For example, in a chemotherapy protocol that presents a 90% chance of hearing loss, a cellist should demonstrate a reasonable expectation that his participation will most likely result in deafness. If he expects a 10% chance of hearing loss, this estimate may be so unrealistic as to compromise the choice that he has made.

We suspect that the larger the misestimation, the more likely it is to misinform the subject's decision to participate. In addition, the relevance of a particular harm (or benefit) to an individual's life, such as hearing loss to a musician, augments the importance of that risk in the decisionmaking process. When the likelihood of an outcome is grossly misestimated and/or that outcome holds special significance for the individual, the subject most likely chooses among misrepresented options and the validity of his or her consent may be compromised. A large or personally meaningful misconstrual of risk/benefit probabilities can be an ethically significant concern, and should be met by further efforts to ensure that the patient-subject comprehends the actual risks and benefits of participating. One might plausibly argue that Susan's expectation of harms and benefit from the phase I cancer trial was not so large or personally meaningful as to compromise her decision.

The therapeutic misestimation may be especially problematic in trials in which the risk is high or severe and the probability of benefit is low. Because it is possible that individuals may interpret probability estimates in problematic ways, the onus of risk-benefit calculation is more appropriately placed on the research team and the IRB. Ethically and by regulation, research should be designed in a way that minimizes risk and enhances the possibility of benefit. The need to carry out high-risk, low-benefit studies, especially when they involve subjects who might understandably have therapeutic expectations, as in phase I cancer research, requires that researchers recognize and address the possibility that subjects—and investigators themselves—may engage in therapeutic misestimation.

■ *Optimism versus Misunderstanding.* Misunderstanding, especially in the form of misestimation, can be confused with personal optimism. In both clinical care and research settings, patients and subjects naturally hope for the best outcome. In practice, it may be difficult to separate this sense of hope from a therapeutic misconception or misestimation. Yet it is possible, and may be therapeutically important, for patient-subjects to maintain optimism, while demonstrating an understanding of both the nature of research and the probability of important risks and benefits. In the third case above, Thomas appears to have neither therapeutic misconception nor a therapeutic misestimation, but maintains a personally optimistic outlook.

Optimism alone should never be ethically problematic. An optimistic outlook likely makes a positive contribution to the healing process.[29] A patient-subject is still a patient, even in the context of research,[30] and if participating willingly and with understanding, she or he can hope for the best medical outcome without compromising the research partnership. In this way, personal optimism should be supported and encouraged in the research setting.

Nevertheless, optimism can contribute to misunderstanding, just as misunderstanding can sustain optimism. In reality, it may be extremely difficult to ascertain whether a research subject misunderstands the prospect of benefit or has simply adopted an optimistic outlook along with an awareness of the facts. An awareness of these concepts and careful discussion with subjects can help a research team identify and preserve hope in the process of improving patient-subjects' understanding of research.

## A Three-Way Ethical Distinction

We have distinguished three separate but related concepts: thera-

## Figure 2.
## Critical questions and strategies for IRBs and Investigators

| Type of Misunderstanding | Factors that increase the possibility of misunderstanding | Strategies for minimizing the possibility of misunderstanding | When persistent misunderstanding might be tolerated after efforts have been made to correct it |
|---|---|---|---|
| **Therapeutic Misconception** | • Studies in which the research design approximates clinical care<br>• Subjects who have limited options for treatment<br>• Subjects who are invited to participate in research by regular medical physician or team | • Explicit and clear descriptions of research purpose, procedures, and features and their difference from clinical care, e.g., placebo-controls, randomization, dose-escalation, extra bloods or scans<br>• Careful and comprehensive discussion of alternatives and voluntary nature of participation<br>• An explicit plan for assessing subject understanding of research purpose and procedures<br>• In some cases, recommendation for consent to be obtained from a researcher uninvolved in patients care or for consent monitoring | • High similarity to clinical care in research design or procedures, e.g., Phase III trials<br>• High or exclusive chance for personal benefit, especially when there is low risk |
| **Therapeutic Misestimation** | • Studies in which the prospect of benefit is low or unlikely<br>• Subjects who are hoping for treatment | • Specific information about the probability and magnitude of possible risk and benefit, when data are available<br>• A clear distinction between uncertainty due to lack of data and uncertainty associated with evidence-based probabilities<br>• Comparison with risks and benefits of other options<br>• Presentation of probability data in a variety of forms<br>• A clear plan for assessing subject understanding of various risks and the prospect of benefit and distinguishing misestimation from optimism | • When the misestimation of benefit or risk is not too large and not the primary factor in the subject's decision to participate |

peutic misconception, that is, conflating research with clinical care; therapeutic misestimation, misunderstanding the probability of benefits and/or harms in research; and therapeutic optimism which refers to hope for the best outcome. (See Figure 1.) We offer some critical questions for IRBs to consider in reviewing protocols, as well as strategies to prevent and minimize a therapeutic misconception or misestimation (Figure 2).

Both the nature of research and the probability of harms/benefits are important to a person in deciding to participate in research. But misunderstanding these elements can compromise the individual's decision to participate in research in different ways or to different degrees. Whereas understanding the nature of research is integral to understanding research as an option, the probability of harms/benefits is merely one aspect of that option, and misunderstandings here may be less problematic. A therapeutic misconception fundamentally misrepresents the choice of research participation, whereas a therapeutic misestimation affects the subject's decision to participate only insofar as it shapes significantly his or her expectations about personal health outcome.

Therapeutic misconception undermines the autonomy of subject decisionmaking and thus is ethically problematic. Therapeutic misestimation compromises a subject's decisionmaking when it involves a large alteration of probability or when it concerns a personally significant outcome of the research. Therapeutic misconception should be tolerated only when factors counterbalance the compromised autonomy of the decision, as when

there is significant prospect of individual benefit and/or the study is procedurally similar to clinical care. Therapeutic misestimation should be tolerated in situations when modest misestimates do not compromise a reasonable awareness of possible outcomes. Therapeutic optimism should be tolerated in most cases, and even actively preserved.

Despite our willingness to tolerate therapeutic misconception or therapeutic misestimation in some cases, it is always preferable that participants not misunderstand at all what they are getting into. Efforts should always be made to minimize misunderstanding. And even when therapeutic misconception or therapeutic misestimation might be ethically tolerable, neither should be encouraged. To actively contribute to misunderstanding on the grounds of its presumed therapeutic effect or administrative convenience violates our commitment to partnership with subjects in research.

## Encouraging Meaningful Consent

Researchers should encourage patient-subjects to make a meaningful choice when deciding to participate in research. Attaining this goal requires that investigators promote clear understanding of the nature of research as well as realistic estimates of risk and benefit. Current empirical data on research subjects' understanding of research participation does not sufficiently distinguish between therapeutic misconception and therapeutic misestimation, which may confuse efforts to correct these different forms of misunderstanding. Studies to date also obscure the difference between misunderstanding and optimism. By utilizing more precisely the concepts of therapeutic misconception, therapeutic misestimation, and therapeutic optimism, we can begin to differentiate more precisely when misunderstanding is ethically problematic and how to tailor our efforts to correct it.


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19. See: ref. 3, Daugherty et al. 1995; ref. 4, Joffe et al. 2001; ref. 5, Daugherty et al. 2000; ref. 6, Yoder et al. 1997; ref. 7, Itoh et al. 1994; ref. 8, Von Hoff & Turner 1991.

20. A therapeutic misestimation could conceivably exist in the clinical care setting as well, although we focus here on the therapeutic misestimation in research.

21. It is also possible for potential subjects to underestimate the chance of benefit or overestimate risk. In these cases, 'misestimation' may contribute to a decision not to participate in research. This situation may occur in individuals or populations that are suspicious of research. In this paper, we only discuss the decision of subjects to participate in research

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