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# Communication and Miscommunication in Informed Consent to Research

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# Communication and Miscommunication in Informed Consent to Research

## **Abstract**

Biomedical ethics require that research subjects be aware that the drugs they take or procedures they undergo are designed to fulfill the conditions of the experiment and not to benefit a subject's health. This apparently straightforward distinction between research and treatment is a source of much controversy and misunderstanding. Ethicists have labeled this problem the "therapeutic misconception." This misconception and, more broadly, informed consent have been studied extensively. Nonetheless, the therapeutic misconception persists among research subjects. This paper argues that one factor overlooked in the persistence of the therapeutic misconception is the effect of the theoretical paradigm that guides the practice and analysis of informed consent. The paradigm poses an idealized model of communication that ignores social context. This paper examines informed consent practices associated with a cancer research trial to demonstrate an alternative approach to studying informed consent to research. Through analysis of informed consent session transcripts, it demonstrates the importance of taking account of not only what is said, but how and by whom it is said.

## **Keywords**

genetics, biomedical research, informed consent, biomedical language

## **Comments**

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## Communication and Miscommunication in Informed Consent to Research

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### Introduction

#### *Therapeutic Misconception*

Informed consent sessions are meetings in which biomedical investigators discuss details of proposed research with potential subjects. This exchange precedes enrollment in research and is accompanied by a document, the consent form, which provides a detailed version of the information that has been discussed. The form requires a subject's signature, which, in turn, is meant to represent his or her voluntary and informed agreement to participate in the experiment being proposed. The informed consent session and form describe the experiment's risks, benefits, and alternatives as well as several other conditions, such as the subject's right to withdraw from the experiment and confidentiality protections. Among the

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most important requirements for informed consent to research is that the subject understand that the procedures or medications constitute research, not treatment.

The apparently simple distinction between treatment and research has generated persistent controversy concerning informed consent to research because it is often the case that despite going through informed consent, research subjects erroneously believe that they are agreeing to treatment. This confusion, dubbed the *therapeutic misconception*, need not hinge on a literal mislabeling of research as treatment; although the word *treatment* is often used to describe research (Appelbaum, Roth, and Lidz 1982; Fried 1974). More importantly, it represents a confusion of goals. Whereas the goal of medical care is symptom relief or cure for the patient, the goal of research is hypothesis testing for the investigator. Thus, a *patient's treatment* is based on what is *best for* the patient's health, while a *subject's management* is based on what is *best for*, or required by, the research design. For example, in certain experiments, the drug dosage given to a subject is based on the cohort to which randomization assigns him or her; in others, it is based on the order in which the subject enrolls in the research. In neither case is the drug prescribed or procedure chosen based on an assessment of the individual subject's medical needs. The subject's erroneous belief that it constitutes the therapeutic misconception. Informed consent to research is meant to dispel the therapeutic misconception by explaining to potential subjects that the proposed procedures are research, not treatment.

Despite two decades of warnings about the need to beware of the therapeutic misconception, studies show that it continues to be a problem among a wide variety of research subjects (Appelbaum 2002; Appelbaum et al. 1987; Daugherty 1999; Emanuel 1995; Freedman 1990; Miller 2000; Vanderpool and Weiss 1987). The persistence of the therapeutic misconception is often attributed to patients who so desperately seek treatment that they distort or ignore statements that the proposed drug or procedure is research and insist on believing that it is being recommended specifically to benefit them (Ferguson 2003; Sugarman et al. 1998). However, this explanation, and perhaps the persistence of therapeutic misconception itself, might have as much to do with the theoretical paradigm underlying informed consent and its analysis as with the influence of wishful thinking by subjects.

### **The Transmission Model of Informed Consent**

The importance of informed consent to biomedical ethics and the relative temporal boundedness of the informed consent session and form have made it a popular research topic. Articles on the topic number in the thousands (Sugarman et al. 1999).<sup>1</sup> Most of these articles provide no explicit theory for the approach to conducting or improving informed consent that they advocate. Implicitly, however, most of them rely on a theoretical paradigm dating back a half century (Shannon and Weaver 1949), called alternately the transmission model, or the sender-receiver model, of communication. Although the subject of considerable criticism (Fiske 1982), this model persists as a popular commonsense view of communication generally in U.S. society and specifically within biomedicine.

The transmission model of communication was developed by telecommunication engineers who sought to conceptualize data transmission in a way that allowed for its standardized measurement, such as in "bits per second," and contributed

to efforts to improve transmission through telephone cables and radio waves. The model assumes stable senders and receivers and unambiguous messages, as would be the case if the message itself were an electronic pulse. Successful communication occurs when the message sent is the message received, or when the exact number, size, and rate of pulses received matches those sent. Any other result is a failure and is attributed to “noise” or “distortion.” Introduced as a model for electronic transmissions, it gained popularity as a way to explain human communication as well. Applied to people, the model implies that ideal or effective human communication should mimic the stability and clarity of electronic pulses. As a result, the model cannot incorporate the influence on social interactions of time, personal relations, purpose, or expectations, except as sources of noise or distortion.

Implicit reliance on this model has fostered the idea that informed consent is about the transfer of research trial-related information from the investigator to the subject. This model casts successful transmission as the endpoint of informed consent and leads to its evaluation based on measures of extent, accuracy, and duration of information recall (Booth 2002; Edwards et al. 1998; Mayberry and Mayberry 2002; Sullivan 1998). Informed consent is not without the need to transfer information, and this model has been productively applied to the topic. For example, research guided by this model is the source of advice to analyze reading grade level of informed consent materials as a way to improve informed consent, as well as of proposals to use different media such as videotapes, illustrations, and computer programs (Meade 1999; Silva and Sorrell 1988).

A 2002 study that analyzed 272 phase 1 cancer trial consent forms (Hornig et al. 2002) suggests that admonitions to investigators to communicate more clearly and completely have been taken to heart. The study found that the consent forms described protocols accurately and made clear that they concerned research, not treatment. As the authors note, however, improved consent forms do not necessarily mean that subjects are well informed. Rather, it means that if problems persist in subject understanding, we need to look somewhere other than to the reading level or clarity of consent forms.

There is no single theoretical alternative to the transmission model of communication. Research that implicitly or explicitly rejects it focuses instead on social context and interpretation. Some of the earliest work on informed consent to research, for example, demonstrated that the setting of informed consent—typically a hospital or clinic—encourages patients to assume that they are being offered treatment. (Appelbaum, Roth, and Lidz 1982; Katz 1984; Meisel and Roth 1981). Other research has examined the pitfalls encountered when applying this model in non-Western cultures (Kaufert 1990), and more recent studies have examined the language of informed consent. For example, research has examined the label “gene therapy” for a set of experiments that test whether a novel procedure can transfer genetic material to a desired site in the human body. These experiments have no therapeutic intent, and might more accurately be called “human gene transfer” research. The use of the word *therapy* implies treatment where none is provided (Churchill et al. 1998; Lysaught 1998). Human gene transfer<sup>2</sup> research has also been the focus of an inquiry into how investigators use the word “benefit.” (Henderson and King 2001). This inquiry shows that sometimes investigators use it to refer to the popular definition, “something that has a good effect,” as in a drug that might ease a patient’s symptoms, and, at other times, to refer to a desired

outcome of an experiment, such as killing tumor cells. Killing tumor cells is also logically a “good effect.” However, in the world of biomedical research, for “tumor cell kill” to be labeled a benefit, it need be only large enough to be measured and not necessarily large enough for the subject to physically experience improvement. The label of benefit, then, absent an elaboration of what kind of benefit, can imply vastly different outcomes for a subject.

As this research suggests, the language of informed consent is complex and multilayered and prone to the kinds of miscommunication that are routine among people of notably different backgrounds or occupations (McTear and King 1991). Miscommunication is particularly likely when parties involved in an interaction have markedly different expectations or goals for that interaction. The transmission model of communication assumes that sender and receiver share goals and expectations, otherwise transmission fails. Up to a point, those present at an informed consent session do share expectations. They are there to discuss research participation. But if we ask participants the classic framing question, “What is going on here?” subjects and investigators are likely to produce rather different answers (Bateson 1972).

The subjects in the research trial discussed here are terminally ill and are eligible for this trial only because they have a cancerous tumor that has recently recurred. The news of the tumor’s recurrence has been confirmed to the patient for the first time at the consent session, or announced only a few days or weeks previously. The implication of the recurrence, that the patient has exhausted known treatments, is likely to dominate his or her answer to the framing question. The investigators’ answer is likely to be dominated by the need to enroll subjects in their experiment. This is not to suggest that the investigators are unsympathetic to the patient’s plight. They are working to solve this patient’s problem, even if solutions are likely to be available only to future generations. Rather, the point is to emphasize the radical disjuncture between the frames that each party sets around this interaction. What one party is trying to get rid of, what is indeed killing one party—the tumor—is what the other party needs to continue his or her work: diseased tissue. Much effort is expended to conceal or sidestep this divergence in expectations. It is this sidestepping that fosters the therapeutic misconception. The required circumlocutions supply the misinformation that patients draw on when they create accounts to sustain the interpretation (or misconception) that they are being offered treatment. Precisely how this happens varies among research trials. The investigators’ contribution to the therapeutic misconception in the trial analyzed here is directly linked to the distinctiveness of phase 1 trials, which will be described before turning to analysis of the consent session transcripts.

## **Background and Setting of Research**

### *Phase 1 Trials*

A phase 1 trial is the first experiment of a drug using human subjects instead of animal models. These trials are subject to extensive regulation by the Food and Drug Administration. They have several features that distinguish them from other sorts of biomedical research and that directly influence the content and significance of informed consent.

First, and foremost, the primary purpose of a phase 1 trial is to determine whether the experimental drug is toxic to humans and to establish the highest possible dose a human can tolerate before it becomes toxic. Thus, unlike most human biomedical experiments, a phase 1 trial does not assess a treatment's effectiveness. Rather the aim is to discover at what point it becomes harmful.

The second distinct feature is reflected in how a phase 1 trial is designed to test toxicity. Initially, a very small dose of the new drug is given to a small number of subjects. This initial dose is calculated at 1/1000 of the dose at which the animal model experienced toxicity. If no toxicity is observed, more subjects are enrolled and the dose is increased by a power of 10. If this group withstands the new dose, then another group is enrolled. Subsequent increases occur until investigators think they have reached the maximum-tolerated dose in humans (Daugherty et al. 1995). This staging is referred to as "dosing" or "dosing cohorts." It is designed to make research move gradually and to give investigators ample time to detect toxic effects, should they emerge, while their harm to subjects is still minor.

The third feature is a logical outcome of the dosing design. The effort to minimize toxic effects also minimizes all effects. In other words, there is no intended benefit in these trials. This is true no matter how benefit is defined, whether as in popular parlance of feeling better or living longer, or in research jargon meaning reduced tumor size. While lack of benefit is the logical outcome of a phase 1 trial design, its absence remains controversial (Kodish, Lantos, and Seigler 1990; Lipsett 1982; Markman 1986; Miller 2000; Schain 1994).

A fourth feature, present in only some phase 1 trials, is that the experiment must be conducted on "sick volunteers," that is, people who have the disease that the experimental drug aims to treat. In certain serious diseases, such as advanced cancer, this requirement carries with it the additional limit of enrolling only patients who have exhausted all existing treatments. This limitation is based on the premise that someone with a terminal illness should be allowed to participate in an experiment only when no other treatment is available. In summary, a phase 1 trial enrolls people, sometimes terminally ill patients, as subjects in experiments to assess the toxicity to humans of drugs previously tested only in animals.

The phase 1 gene transfer trial reviewed here tested a method for sensitizing cancerous tumors to respond to treatment by a class of relatively benign drugs. The trial was designed to assess a technique needed to move the altered genetic material from test tube to tumor. This transfer is the necessary first step for a novel cancer treatment based on the hypothesis that a genetically altered virus could trigger tumor cells to produce a particular protein, which would then sensitize cells to an existing, approved antiviral drug. This antiviral drug could then be administered to subjects and, it was hoped, kill the tumor cells in the same way that it kills the virus against which it was originally designed to act. The advantage of this treatment, if successful, is that it would provide a way of targeting cancer drugs to a tumor site and avoid the systemic damage associated with current chemotherapies.

### *Research Design and Analysis*

The analysis presented here is based on observations of 16 informed consent sessions with potential subjects who were considering enrollment in this trial. The

consent session observations are part of a larger project examining recruitment and enrollment in phase 1 trials. Both the cancer gene transfer trial and the study of research recruitment and enrollment took place at a cancer clinic in a large university medical center.<sup>3</sup> Our inquiry into phase 1 research recruitment and enrollment began with interviews of patients who were considering enrollment in research at the cancer clinic. The research nurse who coordinated the patients' visits identified potential subjects for our study and asked them if they wanted to participate in an interview about their experience with biomedical research.

Thirty-one patients approached by the research nurse agreed to be interviewed. During these interviews, patients were asked if the interviewer could attend the patient's informed consent session if the patient decided to pursue research participation. Of these 31 patients, 16 decided to participate in informed consent sessions for the gene transfer trial. All 16, in turn, agreed to allow the interviewer to observe the consent session. The author or a research assistant conducted the interviews and attended the informed consent sessions.

The investigators who conducted the gene transfer protocol included two oncologists, a surgeon, and a medical geneticist. Typically, two or three investigators were present at each informed consent session. The investigators had previously consented to be subjects in our study of phase 1 trial recruitment and enrollment and had agreed specifically to be observed during informed consent sessions for this gene transfer trial.<sup>4</sup> Eleven informed consent sessions were tape-recorded and extensive handwritten notes were taken for five sessions. The tapes were transcribed and the notes and transcriptions were entered into a QSR NUD\*IST 4 database. A coding scheme was developed that focused on government-regulated content in informed consent to research, such as risks, benefits, and trial design. Descriptive coding such as conducted here minimized the likelihood of coder disagreement. Each interview was coded by one member of our research team, reviewed by a second, and a subset of codes checked by a third. Differences among coders were rare and were resolved through discussions among the coders.

## Results

### *Overview of Informed Consent Sessions*

The informed consent sessions typically began with a review of the patient's medical history and current state. The investigators discussed with the patient and his or her family the patient's symptoms, medication levels, and the size and location of the tumor. This discussion provided an opportunity for the patient to ask questions about the condition and for investigators to frame the tumor's return as evidence that standard treatment appeared to no longer help the patient.

Once the review of the patient's condition was complete, the investigators turned to the availability of options for the patient and introduced the gene transfer trial. Their opening statement typically included a statement that gene transfer is experimental, a description of the ideas behind gene transfer, and a description of what participation would require of subjects.

The length of the opening statement and of the consent session as a whole often depended on the extent that potential subjects or their family members asked questions. When there were few questions, the sessions concluded rapidly, often



**Table 1**  
**Office of Human Research Protections (OHRP) elements of informed consent to research discussed in gene transfer trial consent sessions.**

<b>Informed Consent Elements</b>	<b>Number of Sessions where Element Discussed</b>	<b>Percent of Sessions</b>
Statement that study involves research	16	100
Description of risks	16	100
Description of benefits	16	100
Disclosure of alternative treatments	13	81
Statement of confidentiality	1	6
Explanation of compensation for injury	0	0
Whom to contact with questions	16	100
Statement that participation is voluntary	15	94
Statement of right to withdraw	1	6

with a discussion of how soon the patient could become a subject in the trial. Other sessions took longer because the family had many questions or because they introduced topics that the investigators' did not typically cover (i.e., discussions of different research protocols or of specific symptoms and how they could be ameliorated). Potential subjects who raised more questions tended to get more information about the study design. All of the consent sessions lasted at least a half hour and several lasted more than an hour. While this is longer than most informed consent sessions for research, it is not atypical of sessions for novel protocols, such as gene transfer.

#### *Requirements for Informed Consent to Research*

Government regulation of human subjects research<sup>5</sup> lists eight basic elements that informed consent to research must address and several additional elements that are required depending on certain features of the research. Analysis of the 16 transcripts shows that the sessions covered nearly all of the required elements. (See Table 1 for a list of the elements of consent that were required for the gene transfer trial and in how many sessions they were addressed.) All patients were told that the proposed activity was research, all were told that the benefits of participation were unknown, and all were told that the research involved risks. Most of the sessions included a discussion of alternative treatments, conceived of primarily as other phase 1 trials. The investigators did not use the word *voluntary* in consent sessions, but in nearly all of the sessions they indicated that the decision whether to enter the research trial was up to the patient and his or her family.

There were also elements of informed consent that the researchers did not routinely address in the informed consent session, including confidentiality, compensation for injury, and whom to contact with questions or in case of injury. The right to withdraw from the research was mentioned in only one session. All of these topics, however, were covered in the written informed consent form, as were

all of the topics described above as having been routinely covered in the consent sessions.

This analysis indicates that the informed consent sessions met prescribed standards. Furthermore, the transcripts indicate that for the most part investigators used fairly simple language. The investigators displayed a consistent willingness to restate explanations in response to questions and repeatedly encouraged patients to consider carefully the decision to participate and to discuss the research with friends, family, and other medical practitioners. However, the problems with communication in the consent sessions were created less by complex or missing information, or by time pressure or overt coercion, than by the way that investigators framed the meaning or apparent significance of certain features of the trial.

### *Framing*

Framing has been used in anthropology, communication studies, and political theory to distinguish a certain kind of interaction or to distinguish certain aspects of interactions (Graber 1989; Marteau 1989; Tuchman 1978). A general definition might explain *frame* as the background expectations that we bring to an interaction, or that motivate an account or a narrative. *Framing* is the way we impose those expectations or promote one account over others. At its simplest level, framing uses inclusion and exclusion to juxtapose and arrange elements in order to signal or impose a particular account or frame. The concept is useful in analyzing informed consent interactions because it focuses attention on what is left out as much as on what is said and because it emphasizes the importance of examining the expectations that patient and investigator bring to the interaction. The following sections address the investigators' contribution to the therapeutic misconception by analyzing how they discuss benefit, the difference between research and treatment, and dosing.

*Benefit.* "Rhetorical parity," a term recently proposed to describe how investigators discuss research benefits, refers to statements that imply that two outcomes are equally likely when they are not, such as the possibility of clinical success and failure (Miller 2000). For example, while the investigators stated in every interview that the benefit from participation was unknown, they sometimes presented this information as if that benefit could be substantial. Investigators would say that the protocol might be beneficial, might have no effect, or might have a detrimental effect, but not that the chances of benefit were minute, especially for the first group of subjects enrolled in the trial:

In choosing among the options we have, it is the best. It combines surgery with a new therapy. There is the potential for additional benefit over surgery. You can still have other therapies afterwards if this does not work. There are three possible outcomes. One, you could have no effect. Two, you could have toxic effects. Three, it could work wonderfully and you'll live to be 100. I don't think that that is going to happen, but those are the options we have to work with. There are risks, but it is FDA approved [IIG].<sup>6</sup>

None of the options available will make the tumor go away. In this, this treatment is not different. It is different in that we do not know the side effects. There is a

risk to you. You have to balance the risk and the possibility of benefit, small. It may work, it may not work. You need to ask yourself are these risks acceptable to me? Given the options, given the risks. [H1O1]

In the first example, the investigator states clearly that the possible risks and benefits are unknown, but then asserts that the protocol “could work wonderfully and you’ll live to be 100.” This is a wildly improbable outcome of enrolling in the lowest dose of a phase 1 clinical trial for a subject with terminal cancer, and this is information that the researcher knows but does not disclose. In the second example, the investigator turns the decision over to the subject, which is the correct procedure for an informed consent session. However, absent an explanation of the research design, a problem described in more detail in the discussion on dosing below, the subject has no basis on which to judge whether the experiment “may work” or “may not work.”

*Research and Treatment.* In a move similar to rhetorical parity, investigators blur the difference between “research” and treatment by casting unlike as like. Investigators referred to the trial as research or as “experimental” in every informed consent session, however, they did so in a conversational manner that assumed the meaning of “experiment” was already clear to the subjects.

There’s the risk that we may not be able to get all the tumor out, there’s the risk that this is an experimental therapy. [S1S]

Another thing that we are doing here, which is a research approach, an experimental approach to [these] tumors, is something called gene therapy, which involves injecting a virus that carries a certain gene into the tumor then removing the tumor a week later. [X2O1]

This gene therapy is a new way of treating [this kind of] tumors. It’s experimental. We don’t know if it’s going to be good. . . . Now when we say that this is new we mean that it is experimental. [Q1O1]

You would have the tumor removed so you would have that part of the treatment and then you would have the additional treatment of the gene treatments plus the drug. [X2G]

Although each of these statements mentions that what is being proposed is research or is experimental, the significance of this fact is left unstated (examples #1 and #2), or it is explained simply as something “new” (example #3), or as an add-on to standard treatment (example #4). Most often when investigators referred to the protocol as experimental, they used the label as a way to explain why its benefits were unknown (in 14 of 16 sessions) (example #3) or why its risks were unknown (in eight of 16 sessions) (example #1), not to explain that there would be no benefit.

A misunderstanding between treatment and research is especially likely when a trial involves both therapeutic and experimental procedures or medications. When this is the case, the investigator needs to cover two contrasting topics in the informed consent session: (1) recommending a particular avenue of therapy; and (2) raising the possibility of enrolling in a research trial (which includes the therapeutic

procedure as one part). This trial called for two surgeries, one to administer a drug directly into the tumor and one to remove it. The second surgery is both part of the research and a standard procedure for patients at this stage of disease. This “debulking” surgery provides temporary symptom relief but has no curative effect. In nine of the 16 consent sessions, the investigators refer to surgery as beneficial without specifying which surgery.

At the time of the second surgery the surgeon takes out as much tumor as he can and he injects another dose of the virus into the remaining tumor cells, the tumor bed. In your case the tumor is fairly large so we definitely could not get it all out but he would get out some of it. And that could be a benefit to you just to debulk the tumor. [A2S]

There is no question that removing some of the tumor if you can get a reasonable amount out does prolong life in this particular disease. [C2O1]

Just removing the bulk of this can give you more time. Whether the virus in addition adds anything to that, we still don't know. It's still much too soon to say that. [K2G]

As the third example shows, the investigators often contrasted the known benefit of removing the tumor with the unknown benefit of the gene transfer trial. However, they did not always make clear the benefits of debulking surgery alone or whether the patient could have that surgery without participating in the trial.

*Dosing.* In studies of clinical trial informed consent, a subject's understanding of randomization is often taken as evidence of a broader understanding of the difference between research and treatment. This assumption is based on the reasoning that if a subject grasps that his or her assignment to a particular medication or procedure is by chance, he or she is also unlikely to think that the regimen will be of direct benefit. For this reason, some consent forms now include a detailed explanation of randomization. The design of phase 1 trials prevents the use of randomization, and instead subjects are enrolled in dosing cohorts. Including an explanation of these cohorts and of dose escalation in phase 1 trial informed consent has been recommended (Freedman 1990), but happens only rarely (Hornig et al. 2002).

The key to the research design of a phase 1 trial is that the first group of patients is given a very low dose and that then the dose for each subsequent group is increased by a power of 10. A complete explanation of the research design requires explaining the entire design, regardless of which group the subject will be enrolled in. A partial explanation would be to describe only the dose given to the group that the subject will be enrolled in, perhaps also the dose of the previous group, but to omit saying that a higher dose will be given to subsequent groups. The complete explanation of dosing would make clear that the dose being given to the subject was based on the objective of the experiment—to identify the limits of toxicity—not the medical needs of participants.

Dose was mentioned in 11 of 16 informed consent sessions. (A summary of the pattern of dose level and discussion of dose is provided in Table 2). None of the prospective subjects for the lowest dosing level were told that multiple dosing

**Table 2**  
**Dose level and statements to subjects about risk and benefit.**

<b>Dose Level</b>	<b>Total Enrolled</b>	<b>Dosing Mentioned</b>	<b>Multiple Doses Discussed</b>	<b>Told Lower Dose Equals Less Risk</b>	<b>Told Higher Dose Might Mean More Benefit</b>
Lowest (1)	6	4	0	3	0
Middle (2)	7	4	3	1	2
Highest (3)	3	3	3	0	3

levels existed. This was the case also for one of four prospective subjects at the middle level, but for none at the highest level.

Only one subject entering at the lowest dose was told the reason for starting with a low dose was, “for safety’s sake.” More typically, investigators mentioned dose to this cohort as a way to assert that the study was unlikely to be risky. For example, during an exchange explaining the objective of the consent session, the patient’s spouse queried: “So, it’s [gene therapy] new here?” One of the oncologists answered that several similar studies were being conducted at the cancer center right then, and the second oncologist added,

Oh, yes. We have another cancer gene therapy trial here where they’re going to be getting a thousand times the dose of the drug that you’re getting. So you really don’t have to worry about the dosage. [N1O2]

During another session with a subject eligible for the lowest dose, the genetics researcher contrasted chemotherapy’s systemic toxicity with the targeted effect of gene therapy and cast as reassuring the low dose this subject would receive.

Well, in animals receiving doses 100 to 1000 times more that you would get, they did OK. The virus went into normal tissue and they were fine. No animals died. [K1G]

These statements from the lowest dose sessions address dosing without explaining its significance by leaving out two important pieces of information. First, the investigators did not inform the subjects that they would be receiving lower doses than future study participants. While they point to animals and participants in other human studies receiving much higher doses, they do not explain why the dose they are proposing to give to these subjects is so much lower. Second, while investigators used dosage to stress the low risk to this cohort, they left out the corresponding implication that a low dose meant a low probability of benefit.

In contrast, when dose was discussed with patients receiving higher doses, researchers stated that they expected the higher dose to have greater potential benefit:

It works incredibly well in the test tube, it works incredibly well in animals, but people are different. We can’t find out until we treat enough patients. We have treated three patients at the lowest dose of the virus. The next patient that we treat will get a higher dose of virus and we really think that that’s likely to be effective. [Y2G]

We started this at a very low dose of the virus to be safe. We had three patients at the lowest dose, three patients at the next dose and so forth. So we are now getting up to doses where we think there is a better chance of really controlling the tumors. The patients at the lowest dose all had regrowth of tumors. The patients at the next dose some of them are doing fine. They are all living. Some of them are doing fine. Some of them have had the tumors grow back. And then the very high dose, the highest dose, we are just beginning to follow those patients. [K3O1]

And we are now reaching doses of the virus where we expect if there is going to be some benefit; we will begin to see it. We have treated most of the patients at lower doses. We gradually increased our dose for reasons of toxicity. And the one thing we can definitely say is that there is no unusual toxicity. . . . So we don't anticipate any problems; we cannot yet say if our treatment is affecting the tumor growth. Some of the patients have had tumors grow back, some have not. But they have all been at, except for one patient, they have all been at the lower doses. [L3O2]

Subjects slated to receive the lowest dose were not told that future subjects would receive higher doses and subjects slated to receive the highest were not told that a higher dose entailed greater risk. Interestingly, dose was least often mentioned in sessions with subjects slated to receive the second or middle dose level, perhaps because it was least clear to investigators how best to use the information about dosing.

By selectively emphasizing certain features to certain patients, investigators were able to transform the experiment's dosing design into a desirable feature for all groups, despite its rather different real implications for each group. Explanations of how the trial fit into the larger picture of the approval of experimental therapies followed a similar pattern. For example, when investigators mentioned the FDA, it was not to explain its role determining the safety of the experimental procedures. Rather, investigators were more likely to describe the involvement of the FDA as evidence that the current study is safe. In an exchange between the surgeon and a patient concerning possible side effects of the trial, the patient followed up on a comment made by one of the oncologists about the risk that the altered virus, once injected in the tumor, could spread to other parts of the body, to which the surgeon replied:

Right, that's always a theoretical concern. The practicality is that, it's. . . . We've not seen it in any of the animal studies or any of the humans treated thus far. But you know the FDA, you have to cover all bases. [A2O1]

Similar references to the FDA occurred in these passages:

FDA has standards, and we get their approval at every stage, even though we don't have to, we do. They are the top standard for safety. So you don't have to worry about everything being as safe as it can be. [N1O2]

Anyway and you know and I know there's a lot. You have to have gone a long way before you can even get the FDA approval on people. [E3O1]

While the FDA requires phase 1 trials to determine whether a new drug is toxic, the researchers refer to the FDA to reassure patients that the experimental drug won't be too risky. While statements about a drug being "not toxic" and "not

risky” are similar, they are not the same. The choice to frame statements in terms of “reducing risk” rather than “determining toxicity” allows investigators to refer to the FDA drug approval process as a protection without directly explaining the implications of the stage in the approval process at which subjects are recruited.

### *Mixing the Unproven with the Known*

Descriptions of the actual procedures that the subject will undergo are the source of additional confusion in the consent sessions. Certain steps in the experiment can be described accurately in declarative statements, such as “We give five different injections with the needle,” because they are known routines, well understood and controlled by the investigators. The combined effect of all of the steps, however, is unknown. Indeed, determining the combined effect is the objective of the experiment. Will the “five different injections with the needle” deliver the altered gene into the tumor? Will the tumor cells absorb it? And will, or at what point will, its effects become toxic? Sometimes investigators signal the distinction between the certainty of each procedural step and the speculative nature of the sum of the steps, or the trial’s outcome, by using the word *hope*, as in, “we are hoping that we are injecting this gene into tumor cells.” But just as often, investigators slide between the known and the unknown without indication.

The following passage opens with a declarative statement about the hypothesized role of the virus—that the virus will successfully transfer the altered gene into the tumor cells. The next two sentences signal the contingency of this result with the words *hoping* and *hope*. The next 11 lines describe the method being tested—whether the altered virus can be transferred by injection into the tumor site, whether the tumor (but not the surrounding tissue) will absorb the injection of altered virus, whether this absorption will lead the tumor to become sensitive to the chosen antibiotic and whether, when the antibiotic is administered, the result of this sensitization will be that the destruction of tumor cells by the antibiotic. Interspersed in the description of the hypothesized effects are factual, descriptive statements, such as, “It is an antibiotic.” The passage ends with a summary of the experiment and the intended outcome as killing tumor cells—not assessing toxicity—this time prefaced by the words, “we believe,” which underscore the investigators’ confidence in the outcome. (Italics indicate hypothesized results of procedures.)

This virus is carrying a gene, *it acts as a vector, or a carrier to carry a certain gene, a bit of genetic material*. When we inject it, *we are hoping that we are injecting this gene into tumor cells*. We can’t inject it into every single tumor cell *but we hope that we are getting enough tumor cells*. *That gene that we are giving you permits the tumor cells that get injected to make a protein called thymidine kinase. That protein makes the cells sensitive to a drug*. We give that drug in the vein. *When it gets to the tumor cells that have this new gene, those cells die. So there is a reaction with this drug and that gene. The rest of the cells in your body that don’t have that gene are not affected by this drug, so the drug is safe except to the cells that have that gene. So we are changing the tumor cells in such away that they will be killed off by this drug*. It’s not a chemo drug. It is an antibiotic that kills off [altered] viruses and we are giving you a [altered] virus gene into those cells to fool those cells into behaving like [altered] viruses so when this drug comes in it kills them just as though they were [altered] virus

*cells. We believe that once that gene is in there and it produces this protein that that protein spreads out among the other tumor cells that weren't injected then those cells around it can also be killed. [Y2G]*

In this consent session, the investigator explains why and how he thinks gene transfer might work to kill tumor cells. This explanation belongs in the consent session, but by intermixing statements about steps in the experiment with statements about what he eventually hopes gene transfer protocols will achieve, he is framing the contingent as the inevitable. He creates a picture of effectiveness that undermines concurrent statements that the investigators don't know whether the gene transfer will be beneficial. Furthermore, such passages focus attention on future therapeutic outcomes, obscuring any reminder that the trial's objective is to assess toxicity in humans. The difference between the known and the unproven is further blurred in other consent sessions when investigators switch from talking about "*the tumor*" and "*the cells*" to describing the hypothesized effects of gene transfer to "*your tumor*" and "*your cells*." This change personalizes the description of what the gene transfer trial might do and suggests that the investigator believes that it *will do* these things for *this* subject.

## Conclusion

Therapeutic misconception was identified more than 20 years ago and described as an urgent problem that needed fixing. Repeated attempts have been made to improve informed consent and to mitigate this misconception. These attempts apparently have had some influence on reducing the complexity of consent forms (Hornig et al. 2002). At the same time, recent research suggests that more than 70 percent of subjects enrolled in a wide variety of trials continue to confuse the goal of research with the goal of treatment (Appelbaum 2002). This outcome suggests that some of the efforts to improve informed consent to research might have misidentified their target. Therapeutic misconception focuses attention on the subject. Misconception implies misinterpretation and misinterpretation suggests that the problem lies with the party receiving or interpreting the message. Review of consent session transcripts, however, confirms the need to examine the investigators' contribution to misunderstanding.

Investigators play an active role in creating and sustaining the confusion between research and treatment and precisely how and why they do this begs examination. As for how they do it, this article showed that investigators discussed, without explaining, several important topics, including benefit, the difference between treatment and research, and dosing. They do this by casting unlikely outcomes as plausible, alternating between the scientific and popular meanings of terms, and selectively highlighting different features of the proposed trial.

Why investigators foster therapeutic misconception among subjects is not a question pursued by this research, but is important to address. The question suggests that it might be intentional. Deliberate deception by researchers desperate to enroll subjects might play a role in a small number of cases, but reducing this phenomenon to trickery or scapegoating researchers ignores its complexity. Still, intentionality introduces the question of awareness, and this is a more difficult issue. Could these researchers have said what they said and *not* have been aware



that they were misleading subjects? One answer could be that they were not aware because they believed that the experiment really would benefit the patients—that the investigators suffered from their own therapeutic misconception. This interpretation has begun to surface in the literature (Appelbaum 2002; Joffe and Weeks 2002; Miller 2000). Further research might examine how investigators assemble and sustain their own therapeutic misconception and to what extent it varies in different research settings or with different subjects. Developing this interpretation would require explaining how investigators integrate what they know about dosing and randomization into formulations about the likelihood of subject benefit. This explanation could provide a useful starting point for a practical account of the rational and irrational features of scientists' beliefs about risk.

Alternatively, the answer might be that these researchers could have said what they said and not have been aware that they were misleading subjects because their assumptions about communication are similar to those of the transmission model of communication. If investigators think of the consent session as Table 1 characterizes it—as a list of points to review—the fact that they covered virtually all of the relevant features would constitute a valid informed consent. This interpretation corresponds with a common theory of scientific or biomedical language as powerful because it is capable of achieving objectivity through precision, clarity, and rigor (McCullough 1989). This theory insists on the primacy of the descriptive function of language, which is at once a source of the remarkable power of the scientific method—sustaining the capacity to replicate and extend findings—and a source of comfort to investigators, in that its objectivity and precision provide a sense of control over the language, which perhaps extends to a sense of control over the experiment. Investigators can soothe doubts they might have about exposing people to experimental procedures with the knowledge that they have described what the experiment requires, using words and phrases that in scientific communication signal “this is research” and that the rest of what is said is just so much noise.

## NOTES

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1. A MEDLINE search conducted on August 21, 2003, found 4,623 articles with the words “informed consent” in the title. (For a more select list see Sugarman et al. 1999).

2. I use the phrase “gene therapy” when discussing how investigators presented the protocol analyzed here because this is the phrase investigators used. Elsewhere, the phrase “gene transfer” or “human gene transfer” will be used to describe the research.

3. To preserve the confidentiality of the subjects and the investigators, the exact type of cancer is omitted here, as well as the name of the hospital where the research occurred.

4. The research reported on here received IRB approval from the University of Pennsylvania and all subjects, including subjects in the gene transfer trial and investigators who ran the trial, provided informed consent to their participation.

5. Government regulation of human subjects research is overseen by the Office of Human Research Protections (OHRP) and the mandated requirements for informed consent are given in the Code of Federal Regulations, Part 46, Protection of Human Subjects, often referred to as the “Common Rule.”

6. Passages quoted are identified by a code that denotes the subject, the dose level to which he or she was assigned, and the investigator making the comment. Subjects are denoted by randomly assigned letters of the alphabet and dose levels are denoted by 1, 2, or 3. Investigators are identified as follows: the surgeon by "S," the medical geneticist by "G," and the two oncologists by "O1" and "O2." Thus, the identification code "B2S" refers to a comment made by the surgeon, about subject "B," who was enrolled at the second dosing level.

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