This section focuses on the ethical, legal, social, and policy questions arising from research involving human and animal subjects.

Why Is Therapeutic Misconception So Prevalent?

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Abstract: Therapeutic misconception (TM)—when clinical research participants fail to adequately grasp the difference between participating in a clinical trial and receiving ordinary clinical care—has long been recognized as a significant problem in consent to clinical trials. We suggest that TM does not primarily reflect inadequate disclosure or participants' incompetence. Instead, TM arises from divergent primary cognitive frames. The researchers' frame places the clinical trial in the context of scientific designs for assessing intervention efficacy. In contrast, most participants have a cognitive frame that is personal and focused primarily on their medical problems. To illustrate this, we draw on interview material from both clinical researchers and participants in clinical trials. We suggest that reducing TM requires encouraging subjects to adjust their frame, not just add information to their existing frame. What is necessary is a *scientific reframing* of participation in a clinical trial.

Keywords: therapeutic misconception; informed consent; clinical trials; research ethics

Nearly four decades ago, Charles Fried argued that a physician's fundamental ethical obligation is to provide "personal care," prioritizing the interests of the individual patient.[1] Subsequently, Appelbaum and his colleagues[2] identified "therapeutic misconception" (TM) as a research participant's failure to appreciate that participation in clinical trials does not primarily involve receiving personal care. Unlike clinical care provided in routine settings, treatment provided in a clinical trial cannot follow the ethical precept of personal care.[3] Were clinical trials designed to provide personal care, they would never use placebos, constrain dosage adjustments, limit adjunctive treatments, randomize patients to different treatment arms, or blind physicians to individual patients' treatments. All of these methods deviate from Fried's basic principle—individualization of treatment to the needs of each patient, with the patient's interests coming first.

Since the initial description of TM, researchers have attempted to determine its prevalence,[4,5] how to measure it,[6,7,8,9] what factors are associated with its occurrence,[10] and whether it impacts the quality and validity of informed consent.[11,12,13]

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Despite proposals that informed consent interventions be directed at reducing the occurrence and impact of TM, most intervention studies have attempted to improve the understanding and recall of disclosures and have not addressed the issue of TM per se.[14,15,16,17]

Researchers have struggled to reach consensus on what constitutes TM. Some of us have suggested[18] that two dimensions of misconception are (1) the belief that treatment will be individualized to the specific needs of the participant and (2) an unrealistic expectation of personal benefit, based on misunderstanding of the nature of the clinical trial. Others have added to this list the failure to realize that research is the primary purpose of the clinical trial[19] or have distinguished different dimensions of the phenomenon.[20]

Other controversies have focused on the level of TM that is problematic and whether "evidence" of TM might be an artifact of measurement or data interpretation. Kim and colleagues[21] suggested that participants' reports of being motivated by therapeutic benefits did not necessarily reflect a failure to understand the scientific nature of the trial. Sulmasy and colleagues[22] argued that patients' reports of potential therapeutic benefit were expressions of optimism and faith that did not hamper their understanding of the purpose of research. Most would acknowledge, however, that some degree of TM exists in many participants in clinical research. However, the literature on TM has not explored social science models of the phenomenon that would facilitate testing, refinement, and the development of ways to address the problem.

In this article, we propose a model for understanding the prevalence and persistence of TM. We hypothesize that TM results not merely from inadequate disclosure or from the ignorance or incompetence of research participants. Rather, *TM arises from divergent primary cognitive frames*. The concept of framing is based on the work of the pioneering sociologist Erving Goffman.[23] As Goffman uses it, the concept of cognitive framing refers to an individual's understanding of "what is going on here." Cognitive frames allowed Goffman to build a unified theory of how we understand the differences among, for example, theatrical performance, play, deception, and "reality."

When designing a clinical trial, the researcher's cognitive frame places the trial in the context of scientific designs for assessing the efficacy of the intervention. In contrast, participants' cognitive frames are personal and focused primarily on their health problems. This is *not* to imply that researchers lack concern about research participants *or* that participants are necessarily unaware that they are participating in research. Rather, we hypothesize that the *primary* cognitive frames of researchers and participants differ quite dramatically, and that this divergence is the social context in which TM can emerge.

We illustrate this hypothesis using interviews from a study of both clinical researchers and clinical trial participants in Phase 2 and 3 randomized clinical trials at four medical centers. The details of the methods, participants, and primary results from that study are described elsewhere.[24] We use these examples only to illuminate our model; confirmation must await research designed specifically to test it.

Researchers' Primary Cognitive Frame: Science

In designing clinical trials, researchers generally approach the studies from what can be called a "scientific" cognitive frame that is based on an *abstract* concept of

how to assess the efficacy of a treatment. This frame regards cases as units that need to be managed according to a protocol that guides the activities of the researcher. A predetermined number of these units needs to be studied to answer the research question, and because the treatments being compared should have equivalent groups of participants, participants should "be assigned" treatments at random. Neither the treating physician nor the participant should know which medication the participant is getting, so that their perceptions of the efficacy of the treatment are not biased by their expectations. Dosages are restricted to a predetermined range so that the intervention is clearly defined, and any other medications that might affect the outcome are prohibited.

This frame is independent of specific patient needs. Although clinical researchers are typically quite concerned about the well-being of their participants, benefits to any *particular* participant are not a central focus. Our interviews with researchers included statements with which they could agree or disagree. One of these was the following: "Researchers should only participate in trials that are likely to help the subjects who take part." Responses, especially from researchers who participated in the design of the trial, suggest that their primary cognitive frame is focused on conducting scientifically valid trials.

> **Participant (P) 101**: Well, you never know if it's gonna help so I guess I'm kind of neutral on that but I believe that that's not the point . . .
> **Interviewer (I)**: What is the point of the study?
> **P 101**: Well it's to find out if the treatment is going to help.

> **P 104**: I disagree. There can be overall benefit to other populations or to future patients. There's nothing wrong with no direct benefit studies, provided the appropriate procedures are followed. . . . So if you only would participate in studies if it would help all of your patients . . . then I will be going home and be retired.

> **P 106**: You can't make that determination. If the researchers are of the opinion that it works, then they are not in clinical equipoise and . . . they're biased, and so they should not participate in that study.

As a general principle, then, researchers do not design trials primarily to benefit the participants; rather, they do so to answer a scientific question.

Participants' Primary Cognitive Frame: Personal Needs

In contrast, the participants in research studies whom we interviewed perceived the research largely from a "personal" frame. Whereas the scientific frame regards participants as units needed to assess intervention effectiveness, participants generally focused on the study from the point of view of the individual units (i.e., themselves) and their personal medical needs. They were coming for help with a problem and saw the study in that context. They almost always understood that there was "research" involved and could often repeat some features of the design, but they typically lacked the big-picture understanding of why various research methods were being used. In this personal frame, it is not obvious, for example, why the physician providing the treatment should not know

what treatment is being provided or why someone could not be given another medication along with the experimental one if that might be of help. Thus, many participants either ignored design features or invented reasons for them that were consistent with a focus on their own expectations of personal benefit.

We asked all participants about the purpose of the study. They often stated that the purpose was to help both the participants *and* patients in the future. When probed, they would usually say that the primary purpose was to help the patients in the study, or they would make statements such as, "By helping me it will also help others in the future." Following are some examples of such statements:

> **I:** So what is your understanding of this study? Is it focused on getting the best treatment for you or is it to help people in the future?
> **P 247:** Well of course I wanted the best treatment for me. Secondarily, I said it's nice to give something to humanity.
> **I:** And the researchers . . . their goals . . . are your treatment or future treatment?
> **P 247:** Oh I'm sure it's my treatment, but then it adds to the statistics and I'm sure it helps them somehow.

The following participant was a patient with recurrent breast cancer participating in a Phase 3 trial.

> **I:** And would you say the study is primarily designed to help participants in the study or to collect data to help people in the future?
> **P 325:** Well see now I would say both. I think it's both. I mean obviously you wouldn't want to study a bunch of people that aren't gonna benefit from it and I think . . . really I feel like they're really after what's working for me.

A participant in a Phase 2, randomized, nonblind chemotherapy trial for metastatic, hormone-refractory prostate cancer said:

> **I:** And what is your understanding of the purpose of the study that you're doing with Dr. X?
> **P 321:** To try and find the best treatment for me and also to kind of research and see if it can help anybody else that might be in similar positions that I'm in . . .
> **I:** And how will decisions about your treatment be made in Dr. X's study?
> **P 321:** Well it's kind of a combination between Dr. X and myself and my girlfriend and anyone else that's involved. You know if I have to talk to my daughters or whatever so it's kind of a discussion but she's pretty open about the possibilities both ways.

Conflicting Frames: The Example of Eligibility

A good example of the conflict between different frames relates to eligibility. For clinical trial researchers, the concept of eligibility is built into the design of the trial. Researchers usually design trials to include tightly defined groups of participants in an effort to reduce extrinsic sources of variability and to get a "clear signal" from the intervention.

The participants whom we interviewed often did not view eligibility as a feature of a trial. Instead, they tended to see it as a question of whether they, personally, would be likely to benefit from getting the experimental intervention.

> **I:** [Asking an agree-or-disagree question] The reason I was asked to be in this study is that it will provide me with the best treatment available.
> **P 210**: And I met the criteria for being a part of the study. So I agree. . . . I've had anemia and having normal heart functioning and a somewhat enlarged heart, I met the criteria that he was looking for to put me on the medication. . . . Dr. X . . . came to see me and we started talking and he looked over my records and he saw that . . . I met the criteria for one being anemic or having the heart functioning which wasn't pumping enough blood . . . and he felt that this kind of research might be very effective in helping me overcome the anemia.

Similarly:

> **P 206**: When Dr. X was my rheumatologist and I was referred to him from a doctor in the, at the medical center in [city] and he felt I'd be a good candidate for it.
> **I:** And what were the reasons that he said you'd be a good candidate for it?
> **P 206:** Because my [condition] was chronic and acute and that because of this long-term ulcer I had that was not healing. . . . I was sure it was gonna help. I was sure it was gonna help.
> **I**: Based on . . .
> **P 206:** Just the fact that Dr. X felt I was a good candidate. The fact that the first, you go through a very detailed process where they give you a little bit of the drug and make sure you don't have any side effects and take blood every hour. And the fact that it went so smoothly just, I thought it was gonna help. I still do.

Secondary Cognitive Frames

We have described the primary cognitive frames that most research clinicians and most participants use to orient themselves in dealing with clinical trials. However, both parties have secondary cognitive frames as well. Clinical researchers, particularly those who are actively involved in delivering the interventions, are also committed to their "patients." The formal ethical commitments of clinical trial design require protecting participants, and many of our researcher-interviewees insisted that they would never put participants at risk.

> **P 107 (nurse):** I'm always a patient advocate first . . . we spend . . . I don't want to say extra time but they do get more one-on-one with the health-care professional. We take our time . . . we do a lot of patient teaching in terms of dietary, exercise . . . but I think first and foremost we are here for the patient and give them a positive experience so hopefully they will want to continue in research . . .

> **P 225 (physician, researcher):** Let's say I'm recruiting for a study and the person is eligible for my study but I happen to know of another

> study that would better meet their needs. Should I put them in my study or should I tell them about this other study that might be more suited to them? I want people in my study. Mine's a good study. It's a perfectly good study! It's scientifically valid and I want to keep my numbers up! So there's a tension to, well, should I send someone somewhere else? We actually have done that. We actually have sent people away who were technically eligible but we did not think that was the right thing for them.

Many of the participants also see what is going on as part of research—even if many have a limited understanding of what that implies. Thus, when asked whether the primary purpose of the study was to help people in the study or people in the future, many responded "both." Participants' secondary frames include research as a goal. For example, a participant in a Phase 3 trial to investigate whether either of two treatments will help prevent cancer from metastasizing said:

> **I:** [Asking an agree-or-disagree question] My own treatment for cancer will almost certainly be better as a result of participating in this study.
> **P 212:** Agree.
> **I:** The reason I was asked to be in this study is that it will provide me with the best treatment available.
> **P 212:** Agree . . .
> **I:** And so what led you to sign up for Dr. X's study?
> **P 212:** Well a couple things . . . I think clinical trials are wonderful and I do believe that they are what changes the medical field.

The Personal Frame and Therapeutic Misconception

The Likelihood of Benefit (What Do I Get Out of It?)

Unrealistic expectations of benefit based on a misunderstanding of the nature of clinical trials have always been central to the concept of TM. Because participants focus on their own medical needs and believe that clinical investigators do the same, it is not surprising that they think that the experimental medication or procedure would be a good (or the best) option. Often they do not understand that researchers are studying a new treatment precisely because its effects are uncertain.

The following segment is from an interview with a participant in a trial addressing metastatic pancreatic cancer (for which the median survival time is less than one year).

> **I:** So what kinds of things did you consider when making this decision?
> **P 428**: Well I felt it would help me.
> **I:** Felt it would help you?
> **P 428:** Yeah. I felt it would cure, but I guess it's . . .
> **Spouse:** . . . you know, when you're told that you have a certain sickness that's not curable and the only cure is the chemo, what else can you really do but accept the chemo and . . . when they suggested the study which would help even more than what the standard treatment would be . . . like it would be being able to get cured faster . . . to be more helpful. Instead of just one chemo, two chemos could probably help even better.

Research Ethics

This interview segment was from a participant in Phase 3 of a study medication for ALS.

> **I:** Okay. And how do you think that being in this study might help you?
> **P 229:** It's gonna stop the disease. . . . That is the reason. There is no other reason to be in this study.

Individualization

A second part of the concept of TM concerns how the individualization of treatment within a study is different from ordinary treatment. When we asked participants how treatment in the study was different from treatment as usual, including how the treatment that they received would be selected, they often said there would be no difference, even if they had just finished accurately describing randomization, placebos, and so on. Participants rarely spontaneously pointed out key differences.

The following participant was in a Phase 4, double-blind, placebo-controlled trial of a medication for dysthymic disorder. The participant interpreted placebo use as essentially the same as the trial-and-error procedures in standard care.

> **I:** Okay. And how would your personal treatment be different if you were not in this study?
> **P 257:** You know, I think it would be comparable, because it's a process of elimination . . . with depression medications. I mean, I have lots of friends that are depressed . . . that each, individually, have tried a number of different antidepressants . . . because they do often try more than one medication before they find one that is beneficial, I think that this is comparable to the type of treatment I would get in private practice.

Some participants thought the doctor decided which group they would be in based on what would be best for them. Participant 405 was in a Phase 4, randomized study to compare three standard surgical procedures for damaged cartilage. His conviction that he would get the best treatment led to his ignoring what he was told about randomization.

> **I:** And so you said they're comparing three different procedures. How did they decide which treatment you end up getting in the end?
> **P 405:** That was decided by the doctor when he went in during the surgery. It wasn't decided before . . . he uses whatever procedure he thinks is best for that particular patient.

In an effort to clarify the impersonal nature of randomization, clinical researchers sometimes tell participants that the treatment is decided at random "by a computer." However participants' personal frame often leads them to interpret this as the computer "choosing" or "deciding" which treatment they will receive based on the participants' personal treatment needs. This interview segment is from a participant in a Phase 3 trial for metastatic pancreatic cancer:

> **P 414:** Yeah, he told me it would be randomized depending on my blood work and x-rays and stuff, and studies that I had done, the randomization goes by that.

I: Goes by the blood work.
P 414: The blood work and the scans and whatever, things they were doing, that all goes into the decision . . .
I: And you talked a little bit about the randomization, about how they decide; any more details about that?
P 414: No, all I know is they take your studies and go over them, and they put them into a computer I guess and they put all the factors in the computer, and the computer comes up with, okay he should be on this . . . according to the data they've gotten on you.

Participants sometimes made statements that seemed to indicate a clear understanding of the procedures of the clinical trial, only to make a contradictory statement that reflected a frame focused on individual treatment. The participant in the following segment was in a Phase 3, randomized, double-blind, placebo-controlled trial of an enhanced treatment for opioid addiction.

I: Okay. And does everybody get the [study medication]?
P 426: No.
I: How do they decide who gets the [study medication]?
P 414: Um, I'm pretty sure it's by random but just . . . either one third gets the [study medication] or one third doesn't get it and the other two thirds will get a placebo or . . . so like you don't know if you're getting it or not.
I: You don't know.
P 414: No. Yeah, the dosage is random too, I'm pretty sure. Because it said on the guideline thing that you're either gonna get the [study medication] or you're not gonna get the [study medication] and the people that get it are either gonna get like 5 milligrams, 15 milligrams, or like 30 milligrams. You're not gonna know.
I: Okay so it [the guideline] dictates what you're gonna get.
P 414: Yeah.
I: The doctor doesn't look at you and say: I think he should get ten. It's whatever you . . .
P 414: Well it might be. The doctor has gotta have something to do with it but . . .
I: Okay. Sure.
P 414: I can't, I don't think they're gonna be just like, yeah give him this . . . just picking out of a hat.

Discussion

Therapeutic misconception remains a frustrating puzzle in the ethics of clinical research because it is a persistent misunderstanding of a situation. Whereas previous work has described the conflicting statements that participants make regarding their perceptions and expectations of research,[25,26] the present work proposes a novel model of the mechanism by which TM arises: it emerges out of the conflicting, yet somewhat overlapping, cognitive frames of researchers and participants. We suggest that participants bring a primary frame in which they assume that the research is focused on their personal needs. Within this cognitive frame, participants attend to disclosures based on their personal concerns and assume that, like the clinical care they previously received, the research is both designed and intended to benefit them. The presumption that

physicians will render personal care is thus transferred to a situation in which personal care is constrained by specific research methods that may be difficult for the average participant to understand.

However, given that TM is in conflict with the underlying rationale and methods of most clinical trials, the question is how to explain its persistence in so many clinical trial participants. We suggest that a critical piece of the explanation lies in the secondary frames that both parties have. The clinicians, especially those delivering the interventions, are invested in the idea that they are helping their participants. Moreover, there are aspects of care in research studies that *are* superior to ordinary treatment settings. Researchers often give more time and attention to participants than they would receive in an ordinary clinical setting. Participants may receive more frequent assessments or more in-depth testing; even if such testing is being done primarily for research reasons, these practices may better monitor participants' conditions. Moreover, as specialists in the treatment of particular disorders, researchers often believe that they are superior to nonresearchers in diagnosing and treating the disorders they study. Thus, clinical researchers find it easy to be reassuring about the benefits of participation.

Participants' secondary frames also contribute to the persistence of therapeutic misconception. Most participants recognize at some level that research is taking place and endorse the value of helping others. Ironically, this partial recognition of the research nature of the study reduces the cognitive dissonance that participants might otherwise experience during consent disclosures. This secondary framing allows participants to acknowledge that not everything taking place in a clinical trial is meant to benefit them directly, while still maintaining the view that the key aspects of their treatment are undertaken with their needs in mind. Observations that would otherwise clash with their therapeutic orientation are thereby reconciled, and the threat to the primary frame decreased.

Our model suggests skepticism about the likelihood of diminishing TM simply by adding information during the informed consent process. More information, even if clearly presented using the latest in educational technologies, is likely to be interpreted in the same personalized cognitive frame. Nor will simply describing the elements of trial design necessarily change participants' personally oriented cognitive frames. What is necessary is a *scientific reframing* for participants of what is involved in a clinical trial.

The problem is that the elements of information typically provided to participants in a consent process do not make sense by themselves. Research participants who are not scientifically trained have difficulty interpreting specific aspects of research participation—such as randomization or blinding—when these aspects are presented in the typical, isolated format of "informed" consent. Such information can only be fully understood in a scientific frame in which investigators try to minimize nonexperimental influences. If one does not understand these concepts and how they are applied in biomedical experiments, it is easy to ignore or reinterpret information that does not fit well into one's personal cognitive frame. Thus, participants may pay minimal attention to information about randomization, double-blind procedures, placebo use, and the like, rationalizing that, "after all, medicine is a highly technical business and regular people cannot be expected to understand all of it. I know that the doctor will do his or her best for me."

How does one help participants to recast the information into a scientific frame? Not easily. There is little research on how to transform cognitive frames, and most of this has to do with how people discover deliberate deception.[27] There is essentially no research on which to draw that specifically concerns the prevention of TM.[28] Thus, we can only suggest approaches based on our data and experience.

First, it is important to set the frame at the *beginning*. Researchers obtaining consent from participants should begin by explaining clinical trial methodology in a top-down manner. Not only should features of the trial (e.g., randomization or double-blind procedures) be described, but the reasons behind their use should be explained. Only if participants understand the scientific reasons underlying the methods will they be likely to resist the assumption of personal care.

Second, requests for participation in a clinical trial should be made in a way that explicitly undercuts therapeutic assumptions, for example, "We don't know which is the best approach—that's why we are doing this study." If participants have a basic grasp of the reasons behind the methods being used, they should have a framework into which to fit such information.

Third, the impact of contextual factors in sustaining participants' personal frame needs to be acknowledged and mitigated. Everything about a medical setting will evoke participants' expectations of personal care. Although this may not always be feasible, the treating physician preferably should not obtain consent, and the discussion should occur somewhere other than a treatment setting. The person who explains the study should avoid the symbols of clinical medicine, including a white coat or a stethoscope around the neck.

This article has suggested a model for understanding the emergence of TM and has emphasized the importance of attending to the cognitive frames with which participants understand clinical research—not merely the information they receive. The approaches we suggest to modifying those frames should be subject to empirical testing before widespread implementation. If the ideal of informed consent—that people can make informed and meaningful decisions about research participation—is to be realized, some means of reducing the therapeutic misconception must be found.

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