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Time to Stop Worrying about the Therapeutic Misconception

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ABSTRACT

Work on the therapeutic misconception suggests that investigators should ensure that potential research subjects understand the fundamental differences between clinical research and clinical care. Yet, what potential research subjects should understand depends on their circumstances and the study in question. This analysis implies that researchers and review committees should stop attempting to define, measure, and dispel the therapeutic misconception, and instead should focus on what potential subjects should understand to participate in individual studies.

Clinical research is similar to clinical care in many ways. Both clinical research and clinical care have the goal of improving health and well-being; both involve giving medications to individuals who are ill; both take place in hospitals; both involve doctors and nurses. Clinical research also differs from clinical care in many ways. Clinical research is designed to collect generalizable information to benefit future patients; clinical care is designed to benefit present patients; clinical research uses many methods not found in clinical care such as randomization and double-blinding; clinical research is subject to more regulation and review than clinical care is.

The many similarities between clinical research and clinical care can make it difficult to recognize their differences.[1] This possibility raises ethical concerns when individuals who are involved in research assume that they are involved in clinical care. For example, individuals with cancer who are offered a pill to take by a doctor wearing a white coat who works in a hospital may assume that they are patients being offered standard clinical treatment, when actually they are being invited to participate in research by an investigator who is testing an experimental medication. This tendency to confuse clinical research with clinical care has been called the *therapeutic misconception* (TM).[2] The TM is especially problematic when it results in individuals failing to understand the things they should understand to decide whether to participate in research. Persons with cancer who think they are being offered clinical care, when they are actually being invited to participate in research, may fail to understand that, if they agree, they will undergo extra procedures purely for the purposes of research.

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Empirical studies report that individuals enrolled in clinical research—and individuals thinking about enrolling—often fail to understand the ways in which clinical research differs from clinical care.[3] These data are regarded by proponents of the TM as indicating that research subjects often fail to understand the things that they should understand, thus calling into question the ethical appropriateness of a good deal of clinical research.[4] The conclusion that the TM may be undermining the ethical appropriateness of a good deal of clinical research has led to substantial work on the TM: how to define it, how to measure it, and how to eliminate it.[5] There have, in contrast, been surprisingly few analyses of the value of all this work on the TM: to what extent should subjects understand how clinical research differs from clinical care?[6] What impact is work on the TM likely to have on subjects' informed consent, and, in turn, on the ethics of clinical research?

This article argues that work on the TM is implicitly based on a mistaken method for determining what things research subjects should understand. Work on the TM begins with the principle that the subjects of some studies need to understand specific differences between research and care. It concludes that most or all subjects need to understand the same differences between research and care. A good deal of work on the TM thus focuses on trying to identify some difference (or differences) between research and care that are relevant to informed consent for most (or all) subjects.

This approach effectively ignores the issue that what research subjects should understand depends on the study in question and the circumstances of potential subjects for that study. What potential subjects should understand to enroll in one study may be irrelevant to what other potential subjects should understand to enroll in a different study. Such a "task-specific" approach to determining what research subjects should understand suggests that the differences between research and care are relevant to informed consent for some trials, as proponents of the TM claim, but which differences potential subjects should understand varies by the study in question. In these situations, attempts to ensure appropriate consent by identifying the fundamental or enduring difference between research and care distorts what subjects should understand. A task-specific analysis also indicates that the differences between research and care are irrelevant to informed consent for many trials. In these cases, emphasis on the TM may distract potential subjects from the things that they should understand.

Emphasis on the TM can lead commentators to exaggerate the differences between research and care in an attempt to identify some way in which most (or all) research studies differ from clinical care.[7] It can lead to claims that research is always riskier than clinical care, that research always uses unproven methods, that clinical care always uses proven methods, that researchers do not try (or intend) to benefit subjects. In fact, research is often less risky than clinical care; research often uses proven methods; clinical care often uses unproven methods; researchers typically try to help their subjects.

Finally, the TM represents only one possible way to fail to understand clinical research. The TM may be more interesting theoretically than the possibility that subjects fail to understand because they are anxious, distracted, or overly impressed with doctors. Yet, these other possibilities are present for essentially all research studies. Hence, arguments that investigators and review boards should be especially attentive to the TM may result in a failure to address more common sources of misunderstanding.

Taken together, these considerations suggest that emphasis on the TM is more likely to undermine than promote research subjects' informed consent. This conclusion suggests that it is time to stop attempting to define, measure, and dispel the TM. Instead, commentators, researchers, and review committees should focus on what potential subjects should understand to give informed consent for specific studies.

ANALYSIS

The Therapeutic Misconception

The TM was coined in an article published in 1982, which reported the results of interviews with 31 research subjects. Of the 31 subjects, 13 were participating in a study on the effect of social skills training for chronic schizophrenics,

and 18 were participating in a study on the comparative efficacy of two medications for borderline personality disorders.[8] The authors found that many of the subjects failed to understand important features of these two studies. Of the 13 subjects enrolled in the social skills study, 10 thought that everyone would receive training, even though the informed consent form explained that one of three groups would receive the regular day-hospital program.[9] One subject seemed to think that she was receiving standard medical care rather than participating in a research study.[10]

The authors recognized that the ethical appropriateness of clinical research typically depends on subjects understanding the study in question and consenting to participate in it. Yet many of the individuals interviewed did not seem to understand the things they should understand to give informed consent. At first glance, the solution to this problem might seem straightforward: explain to research subjects the things they should understand, but don't understand. For the woman who did not realize that she was enrolled in research, tell her that she is. For the subjects who failed to understand that one of the three groups would not receive social skills training, explain this to them.

This straightforward approach is likely to be effective for many research subjects. When it is, focus on the TM is unnecessary and may be counterproductive. Before we get to that, it is important to note that the authors of the original study found something very interesting: the individuals they interviewed sometimes had difficulty understanding ostensibly simple facts about the studies for apparently deep and complicated reasons. Some subjects did not understand because they wanted to believe they would receive effective treatment and get better. Others did not understand because they did not recognize that, in order to collect generalizable information, researchers sometimes use methods—such as randomized assignment, placebo-control groups, double-blind procedures, and fixed treatment protocols—that are not used in clinical care.

The finding that mistaken assumptions about the nature of clinical research in general make it difficult for subjects to understand has led to the view that there are fundamental differences between research and care that most (or all) subjects need to understand. In this way, attempts to determine what research subjects should understand, that are rooted in the TM, lead commentators away from a task-specific analysis of what potential subjects should understand to a comparison between clinical research in general and clinical care in general. Much of the current work on the TM focuses on identifying the fundamental differences between care and research, measuring how often subjects fail to understand them, and finding ways to help subjects better understand them.[11]

Which Differences?

Trying to determine the likely impact of work on the TM is made difficult because its proponents do not agree on which difference (or differences) between research and care subjects should understand: "Empirical studies have clearly documented the presence of TM but, reflecting lack of agreement in the conceptual literature, they have not defined or measured it in the same way."[12] Recognizing this disagreement, accounts of the TM tend to focus on two differences between research and care. First, many accounts focus on fundamental differences in the *methods* of research and care: "Studies repeatedly have shown that clinical research subjects have trouble appreciating the implications for their clinical care of participating in a clinical trial. When this failure is based on a lack of appreciation of the impact on individualized clinical care of elements of the research design, it has been called the 'therapeutic misconception.' "[13] Second, a number of commentators focus on the difference in *purposes* of research and care. The U.S. National Bioethics Advisory Commission (NBAC) argues that the TM involves "the belief that the purpose of a clinical trial is to benefit the individual patient rather than to gather data for the purpose of contributing to scientific knowledge."[14]

Finally, some commentators regard both differences in methods and difference in purposes as relevant to the TM: "We use three variables to construct a composite measure of therapeutic misconception, tapping misconceptions about the purposes of early phase research and

the potential for direct medical benefit in these trials."[15] Given these different accounts, the present analysis will consider the extent to which potential subjects should understand differences in *methods* between research and care, the extent to which potential subjects should understand differences in *purposes* between research and care, and the extent to which they should understand *both* of these things.

Relationship to Valid Informed Consent

Proponents of the TM sometimes claim that research subjects should understand the differences between research and care because such understanding is necessary for ethically valid informed consent.[16] According to this view, it is ethically impermissible to enroll individuals in research who do not understand these differences. The things that research subjects should understand to give valid consent for clinical research are sometimes called the *essential elements of informed consent.* It is widely agreed that the essential elements typically include at least: (1) that enrollment involves participation in research, (2) procedures, (3) risks, (4) potential benefits, (5) alternatives, and (6) voluntariness.[17] One way to support the view that understanding the difference(s) between research and care is necessary to valid consent would be to argue that these differences represent an additional essential element. That is, proponents of the TM could argue that, in addition to the other essential elements (for example, procedures, risks, potential benefits), the differences between research and care are themselves things that research subjects must understand to give valid consent: "Appreciating the distinctions between research and usual care is critical for informed consent for research, and its absence has been denoted a 'therapeutic misconception.' "[18]

Because some proponents seem to endorse this approach, we will consider it briefly. However, this option makes the TM seem largely stipulative and mysterious. It seems plausible to claim that it is ethically permissible to enroll subjects in research only when they understand the risks, potential benefits, and that enrollment is voluntary. It seems less clear why most (or all) potential subjects would need to understand the differences between research and care in order to give valid informed consent. Perhaps, for this reason, most proponents of the TM endorse other arguments, which we will consider in detail below.

The second approach is to argue that understanding the differences between research and care is relevant to valid consent because a failure to understand the differences undermines subjects' understanding of one or more of the essential elements of informed consent. For example, proponents of the TM sometimes argue that failure to understand how the methods used in research differ from the methods used in clinical care is "a critical handicap to the subject's ability to engage in an accurate assessment of benefits and risks."[19]

The third approach by proponents of the TM is to argue that understanding the differences between research and care, while not strictly necessary to valid consent, is ethically valuable. It might be ethically permissible to enroll individuals in research who do not understand the differences between research and care, but it is ethically much better for research subjects to understand these things. This option gains plausibility from the view that a greater understanding of the activities in which we are involved typically is better than less understanding.

Differences in Methods

As noted, work on the TM tends to identify what potential subjects should understand by drawing a comparison between clinical research in general and clinical care in general. One of the few and prominent differences between research and care at this level of abstraction is that clinical research uses methods to collect generalizable knowledge—randomization, fixed treatments, double-blinding—not used in clinical care. Evaluation of what potential subjects need to understand through the lens of the TM thus suggests that potential subjects should understand these differences in methods.

The widely endorsed essential elements of informed consent include the procedures used in a study, as well as their risks and potential benefits. If research subjects understand these things, it seems that they understand all that they need to know about the methods used in a study. For this reason, it seems implausible to

argue that the general differences in methods between research and care are themselves another essential element of consent. A more plausible claim, one endorsed by proponents of the TM, is that understanding differences in methods is helpful or important for understanding the widely endorsed essential elements of consent. In particular, it is often claimed that understanding differences in methods is important for an adequate understanding of the risks and potential benefits of research participation.

To consider a specific example: individuals may have the option of receiving an unproven (off label) treatment from their doctor, or receiving the same treatment as part of a research study that is investigating the impact of the treatment on their condition. Imagine that those who enroll in the study will undergo three standard blood draws for clinical reasons and three extra blood draws purely for research purposes. Understanding that the subjects in this study will undergo six blood draws total, and also understanding the risks and potential benefits of these blood draws, does not seem sufficient for valid consent.[20] To understand the risks of the research, potential subjects should understand that they would not undergo three of the blood draws if they received the treatment from their own doctor. This example reveals that research subjects sometimes need to understand differences in the methods of research and care to understand the risks of research participation. To this extent, emphasis on the TM agrees with a task-specific analysis of consent. However, a task-specific analysis suggests that the subjects in the present case need to understand a specific difference between research and care—a difference in three blood draws—which is irrelevant to consent for most research studies.

A task-specific analysis also reveals that there are many studies for which potential subjects do not need to understand any differences between the methods of research and care in order to understand the risks and potential benefits of research. First, the methods used in some clinical research studies do not differ from the methods used in clinical care. For example, natural history studies often attempt to mimic clinical care and determine the outcomes of standard treatment. In these cases, fundamental differences in the methods of clinical research in general and the methods of clinical care are irrelevant to valid consent. Similarly, for many rare diseases, there are no established treatments, and the methods used in research often represent the standard of care.[21]

Second, even when there are fundamental differences in the methods of research and care, they may be irrelevant to valid consent. Phase I studies of new treatments for many conditions are typically conducted using healthy volunteers. These studies use methods that are very different from the methods used in clinical care. Yet, these differences are irrelevant to healthy volunteers who are not candidates for clinical care. Similarly, Phase I oncology trials often are limited to patients who have exhausted all standard treatment options. These individuals have the condition in question, and the methods used in these studies can be very different from the methods used in standard cancer care. Yet, these differences are irrelevant to potential subjects who have no standard care options.

Third, work on the TM often assumes that differences in the methods of research and care are necessarily contrary to potential research subjects' clinical interests. It is natural to make this assumption when one attempts to determine what potential subjects should understand through the lens of the TM, which looks at the differences between research and care in general. The goal of clinical care is to promote the interests of individual patients. This suggests that the methods used in clinical care are likely best for promoting patients' interests; hence, deviations from these methods are likely to undermine patients' clinical interests. One study attempting to measure the TM found, "More than 85% of subjects responded to questions about risks and disadvantages of participating in clinical trials without referencing any of the disadvantages that are inherent in the methodologies of clinical trials."[22]

Perhaps the paradigm example of a difference in methods that is assumed to undermine subjects' interests is that clinicians choose treatments for patients using individualized clinical judgment, while many clinical trials rely on randomization. To assess the impact of randomization on subjects' interests, it is important to

recognize that clinical trials typically use randomization only in the setting of *clinical equipoise*—that is, randomization is used when it is not clear which of two or more treatments is better clinically. There are very few data evaluating the impact of randomization on subjects in the setting of clinical equipoise. The data that do exist suggest randomization is not associated with increased risks or decreased benefits.[23] Explanation of the differences in methods between research and care is not relevant to understanding the risks or potential benefits of participation in these cases. Indeed, one might hypothesize that emphasizing randomization may lead potential subjects to assume mistakenly that research poses greater risks, or decreased potential benefits, than clinical care.

The present considerations underscore the extent to which work on the TM ignores the task-specificity of informed consent. Work on the TM focuses first on the differences between research and care in general and assumes that most (or all) potential subjects should understand these differences. In effect, this approach leads to the implicit assumption that subjects are patients, and standard clinical care is a relevant option for them. A task-specific analysis of informed consent suggests, in contrast, that differences in methods between research and care are relevant to the risks and benefits of only a subset of clinical trials; specifically, the differences are relevant to valid consent only for studies that satisfy at least the following conditions:[24] (a) the potential subjects have an illness or condition, (b) standard interventions exist for the illness or condition, (c) standard interventions are available to potential subjects outside of research, (d) the methods of the research study in question differ from the methods used in the clinical setting to provide the interventions, (e) these differences in methods appreciably change the risks and/or potential benefits of enrolling in a study.

Even when these conditions obtain, the most effective approach may simply be to explain the specific things that potential subjects should understand. In the previous example of a study that involves three extra blood draws purely for research, potential subjects could be told that they will get three extra blood draws that will not benefit them, which they would not get if they simply obtained clinical care. Many potential subjects will be able to understand this without having to understand that clinical research is designed to collect generalizable knowledge and the blood draws provide a way for investigators to do so. This suggests that emphasis on the TM will be useful only when a sixth condition obtains as well: (f) explaining general differences in methods is useful for helping potential subjects to understand the essential elements of consent.

There may be some research subjects, like those in the original TM article, who are so focused on receiving clinical care that they assume that all of the blood draws they undergo must be for their own benefit. In this subset of individuals, it may be necessary to provide a fairly in-depth explanation of the differences between research and care, to get them to understand the essential elements of consent. While empirical research will be needed to be certain, it seems likely that this will be true for only some individuals, suggesting that all six conditions will be satisfied for only a subset of clinical trials, and only for a subset of the potential subjects for those trials. This conclusion suggests that most subjects of most trials do not need to understand the fundamental differences between research and care in order to understand their risks and benefits.

The Defining Purpose of Research

The previous section argued that understanding the differences in the methods used in research and care often is not relevant to understanding the risks and potential benefits involved in research participation. Proponents of the TM might grant this conclusion, but argue that research subjects should nonetheless understand that clinical care is devoted to individual patients, while clinical research attempts to benefit future patients. There are several closely related ways to characterize this difference, all of which begin with the claim that clinical care is focused on helping present patients and providing individualized treatment. In contrast, research is designed to benefit future patients; researchers intend to benefit future patients; researchers provide protocolized

rather than individualized treatment; and/or the purpose of research is to benefit future patients. A recent consensus group argues the most fundamental difference between clinical research and clinical care is a *difference in purpose.* Clinical trials have the primary or defining purpose of obtaining generalizable knowledge; clinical care has the primary or defining purpose of promoting the health and well-being of individual patients. This group concludes that the TM occurs when "individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge."[25]

Proponents of the TM might argue that subjects should understand the *defining purpose of research* (and/or its use of protocolized treatment) because these features are so central to research that they constitute an independent essential element of consent: subjects cannot give valid consent unless they understand these things. The first challenge for proponents of the TM based on differences in purpose is to avoid relying on a caricature of clinical care; that is, there are many ways in which clinical medicine also relies on protocolized treatment, and, in many ways, clinical medicine is not intended or designed solely to benefit present patients.[26] For example, clinical medicine is designed to train physicians and to save money that can be used to help future patients.

Second, such defenses of the TM tend to exaggerate the differences between clinical research and clinical care. There are many ways in which research is designed and intended to benefit current subjects. Moreover, investigators often try to help present subjects and often provide individualized treatment. Consider a few examples. Almost all research regulations include a stipulation that the risks to subjects are to be minimized. Minimizing at least significant risks is considered important, even when doing so might reduce the value of the study for future patients. In these cases, studies are designed in part to protect present subjects. Furthermore, it is widely agreed that research should be designed to enhance the benefits to present subjects. Investigators and review committees routinely alter the design of research studies, changing the number and timing of drug doses, for example, to achieve this end. Investigators often enroll individuals in research with the intention of providing them with clinical benefit, even in Phase I studies.[27] Investigators frequently provide individualized care to research subjects that is not needed for scientific purposes. These examples underscore that almost all research studies involve a mix of elements, some of which are intended, or designed, or individualized to benefit subjects, and others to collect information to benefit future patients. While work on the TM attempts to identify the most fundamental or defining difference(s) that most or all subjects need to understand, a task-specific analysis suggests that the differences, if any, that subjects should understand depends on the study in question and their circumstances.

Another problem for such defenses of the TM is that many (perhaps most) clinical trials are funded by for-profit companies. Often the primary goal of for-profit companies is to make a profit; when companies attempt to gather generalizable knowledge that can benefit future patients and also earn a profit, it is not clear whether the *defining purpos*e of the research is to gather generalizable knowledge or to make a profit. Or, the defining purpose may be to obtain approval for a drug from the U.S. Food and Drug Administration (FDA). Imagine that while a company is conducting a trial, it learns the trial will not generate valuable generalizable knowledge, but may lead to the FDA's approving the drug and the company's earning a profit. The possibility that the company may continue the trial suggests that the purpose, at least as far as the investigators and funder are concerned, is to make a profit, not to gather valuable generalizable to benefit future patients.

This conclusion is supported when companies, at least sometimes, conduct so-called "me-too" studies: studies of drugs that are no better than currently existing treatments. While these studies do not have the potential to benefit future patients, they do have the potential to produce a profit for the company (if patients using a competitor's product can be convinced to use the company's product instead). In these cases, at least, and perhaps more generally, the primary purpose of studies conducted by for-profit companies seems to be to make a profit, not to

benefit future patients. The general point here is that when one evaluates research in general, as proponents of the TM do, one focuses on the point that research collects generalizable information. That is the one feature that research studies share, hence, plausibly, it is the defining purpose of clinical research. However, when one turns to specific research studies, conducted by specific individuals in specific contexts, there may be other purposes that add to, and perhaps even supplant, that defining purpose.

For the sake of argument, let us set aside for-profit studies and focus on the subset of studies conducted by non-profits. Arguably, the defining purpose of these studies is to collect generalizable knowledge, hopefully to benefit future patients. Do subjects need to understand this to give valid consent? Why? In other contexts, it is not clear individuals need to understand the defining purpose of a joint activity to give valid consent to participate. Presumably, volunteers can give valid consent to help with a carwash for charity without knowing the defining purpose of the activity or the charity in general. Similarly, I work for the U.S. federal government, and I think I gave valid consent to do so. Yet I have no idea what the defining purpose of the U.S. government is, or of governments in general (I am not alone in this regard; philosophers have been debating for thousands of years regarding the purpose of government).

These considerations suggest that the defining purpose of research is not itself an essential element of informed consent. Recognizing this, proponents of the TM might argue that understanding the defining purpose of research is important for understanding the essential elements of consent. One option would be to argue that understanding the defining purpose of research is important for understanding the risks and potential benefits of research.[28] This view is suggested by commentators who define the TM as "the belief that a study will provide a therapeutic benefit to individual participants, rather than to future patients."[29] Similarly, commentators on the TM often cite, with concern, data that cancer patients who enroll in Phase I studies have "as a major motivating factor in their decision the possibilities of medical benefit and not having a better option."[30]

The view that, in order to understand the risks and potential benefits of research, subjects should understand the difference in the purposes between research and care, or the differences in design, and/or that research treatment is protocolized rather than individualized, is subject to the same objections considered above with respect to differences in methods (for example, differences in methods are irrelevant to risks and potential benefits of some studies; many subjects will be able to understand the risks and potential benefits of research without understanding the differences). Rather than repeat that discussion, let us consider a specific example of the problems that can arise when one ignores the task-specific nature of informed consent and focuses on the general differences between research and care.

Focus on the general differences between research and care can lead to an assumption that individuals will not benefit from participating in Phase I studies because their purpose is not to benefit patients. But this does not necessarily follow. To determine whether cancer patients will benefit from participation in Phase I studies, one needs to collect empirical data on the impact of participation in such studies. One analysis found that some individuals do benefit from participation in Phase I cancer trials.[31] These data indicate that understanding the purpose of research often is not needed to understand the *risks and potential benefits* it poses; indeed, explaining the purpose of research might serve to undermine potential subjects' understanding if it leads to their assuming that they cannot benefit from studies that are designed to collect generalizable information.

To consider a second possibility, a widely endorsed essential element of informed consent is that subjects should understand that studies "involve research." Proponents might argue that part of understanding that a study involves research is to understand that it has the purpose of collecting generalizable information. Or they might argue that understanding that the purpose of a study is to collect generalizable information is helpful for understanding this essential element of informed consent. To evaluate these possibilities, it is necessary to consider what is required to understand that a study "involves

research." What does this involve, and why do potential subjects need to understand that a study involves research, in addition to understanding the other essential elements of informed consent? If potential subjects understand the procedures, risks, potential benefits, and alternatives, why do they also need to understand that the study involves research?

One way to determine what potential subjects need to understand to give informed consent is to evaluate what they need to know to appreciate how enrollment in research will affect their primary rights and interests. It has been argued that individuals have a right, based in their right to autonomy, to control the projects to which they contribute. In addition, it is in individuals' interests to understand the nature of their relationships. This analysis suggests that, in order to understand that the study in question "involves research," potential subjects should understand that they are being invited to participate in a project to help others, and that the investigators with whom they will interact are trying to benefit others.[32]

Many potential research subjects will be able to understand that they are being invited to contribute to a project to help others, and that investigators are working to benefit others, without understanding that the fundamental purpose of research is to collect generalizable knowledge to benefit future patients. Some subjects might understand these things without thinking about the defining purpose of research at all; others might understand these things but think that the defining purpose of *all* research is to make a profit. If this is correct, it follows that understanding the fundamental purpose of research is relevant to valid informed consent for only some subset of potential subjects.

Because the defining purpose of research is to collect generalizable knowledge to help future patients, subjects who choose to participate in research contribute to helping others. Explaining the defining purpose of research might help some potential subjects to understand that the study in question involves research. Granting this possibility, emphasis on the TM seems to distort what potential subjects need to understand. The present version of the TM argues that research subjects need to understand that research involves collecting generalizable knowledge to benefit future patients because this is the defining purpose of research. The present analysis, in contrast, suggests that research subjects need to understand only that a purpose of research is to collect generalizable knowledge, and they need to understand this only when it is necessary to understand that enrollment will involve contributing to a project to help others.[33]

ENHANCING SUBJECTS' APPRECIATION OF WHAT THEY ARE BEING ASKED TO DO

We have considered two ways in which the differences between research and care might be relevant to consent for research: the differences might themselves be one of the essential elements of informed consent, or understanding the differences may be useful or important for understanding one or more of the essential elements of informed consent, for example, the risks of the study in question. A final possibility to consider is that understanding the differences between research and care, while not strictly necessary to valid informed consent, may be valuable to the extent that it increases potential subjects' appreciation of what they are being asked to do:

> If TM is important largely because a failure to recognize the differences between research and ordinary care negates the ability of a potential participant to provide a meaningful informed consent—which we believe it is—and if we continue to be reluctant to use human subjects for research without their knowledgeable consent—which we believe we should—then a strong priority should be given to developing and testing interventions to avoid the consequences of TM.[34]

One way to understand the reference to *meaningful* informed consent in this quotation is in terms of a claim regarding ethically *valid* informed consent. On this reading, individuals who do not understand the differences between research and care are not able to give valid consent. We have considered, and questioned, two ways of supporting this view: the differences

between research and care are themselves essential elements of informed consent, or understanding these differences is necessary to understand one or more of the essential elements of informed consent.

A third option would be to understand this reference to *meaningful* informed consent not in terms of a claim regarding *valid* consent, but in terms of a claim regarding *ethically preferable* consent. Typically, a greater understanding of the activities in which one is involved is better than less understanding. This suggests that, in addition to the essential elements of informed consent, it also is valuable for potential subjects to understand prominent aspects of clinical research. Such an understanding provides potential subjects with a richer understanding of what research involves and a richer understanding of what they are being asked to do. Arguably, the methods used to collect generalizable knowledge, as well as the defining purpose of research, represent important aspects of clinical research. Potential subjects who understand these aspects will have a greater appreciation for research and, therefore, will be in a position to provide more meaningful consent. This view seems right. However, before proponents of the TM endorse this argument, it will be important to recognize its implications.

Many research subjects do not understand the essential elements of informed consent—the things they should understand to give valid consent. Thus, before much effort is put into making research subjects' consent more meaningful, it will be important to make sure that potential subjects at least reach the threshold of providing ethically valid consent. This suggests that, even if we should not forget the TM entirely, we should forget it for the time being, until we figure out how to get potential subjects to understand the essential elements of consent. At that point, research would be needed to determine whether there are ways to get potential subjects to understand even more about research, including the differences between research and care. Of course, it will also be important to make sure that such steps do not significantly reduce potential subjects' understanding of the essential elements of informed consent.

With this caveat in mind, one way to support the claim that it would be better for potential subjects to understand the differences between research and care is to argue that potential subjects *want* to understand these differences: "Very few people with the capacity to choose are indifferent to whether an experienced clinician will select and monitor the treatment they receive."[35] Imagine a survey that provided potential subjects with a checklist of a thousand aspects of a given study and asked which aspects they would like to know. Imagine further that the vast majority of potential subjects indicated the same three things. In this case, respect for the subjects suggests that investigators should explain these three things. If this happened and the subjects did understand these three things, the subjects would have a richer understanding about research. It would not follow, however, that potential subjects would have to understand those three things to give valid or even meaningful consent; the potential subjects might simply be interested in knowing things that they do not need to know. For example, imagine that many potential subjects checked off that they would like to know where the investigator goes to church, or whether the investigator rides a motorcycle. A finding that the potential subjects failed to understand those things would not imply that the subjects had failed to give valid or meaningful informed consent. Potential subjects who are given a checklist may check hundreds of items. People tend to be curious, and they may want to know any number of things. One problem is that explaining everything potential subjects might want to know may undermine their understanding of important aspects of the study, such as its risks and that participation is voluntary. To identify what it is that potential subjects need to understand, there needs to be a way to identify, among all the things potential subjects might want to know, what things they *should* understand to give meaningful consent.

It could be argued that potential subjects should understand the things that they most want to know, and they could be asked to rank order the items that they choose from a list. Or it could be that potential subjects should understand those things that are most likely to in-

fluence their decision regarding whether to enroll in research; if so, then empirical data will be needed to determine whether the differences between the methods of research and care are among the things that potential subjects especially want to know, or whether they are among those things most likely to influence potential subjects' decisions regarding whether to enroll.

Let us assume that potential subjects are very interested in the methods and/or purpose of clinical research. For example, even in the setting of clinical equipoise, it seems plausible that many individuals would want to know that they might receive a placebo, and that whether they receive a placebo will not be determined by what the investigators think is best for them personally. Granting this, there are many other aspects of clinical research that seem important and relevant to potential research subjects' enrollment decisions. They may be very interested in knowing that a study was reviewed by a committee charged with determining whether it satisfied ethical and regulatory standards. Potential subjects may be very interested in knowing the level of experience and expertise of the members of the committee. They may want to know what the committee (for example, an IRB) thought of the study and what the vote regarding its approval was. Potential subjects may especially want to know the reasons and arguments endorsed by committee members who had concerns with the study or voted against its approval. Similarly, potential subjects may want to know what alternative studies could be conducted instead. For studies conducted by for-profit companies, potential subjects may want to know what the companies are likely to do with their profits. Those who strongly support efforts to protect the environment may want to know how the use of the profits will affect the environment.

The present point is not to determine how long this list of salient aspects of clinical research might be. Instead, the point is that there are likely to be a number of aspects that—while not essential—are things that individuals very much want to know; before one argues on the present grounds that the TM is especially important, one would need to develop an argument for its importance relative to these other aspects. This defense of the TM is further complicated because different individuals are likely to prioritize their final list of significant items differently. Assuming that it is not possible to personalize the consent process for every individual, a method would be needed to determine which, among the items that are considered significant, subjects should know in order to give meaningful consent.

For the sake of argument, let us further assume that the differences in methods and/or differences in purposes between research and care are something that many (or most) potential subjects really want to know, and/or that this consideration is likely to have a particularly strong influence on the decision of many or most potential subjects. Even granting this assumption, it will be important to determine why potential subjects want to know these things. The most plausible assumption is that potential subjects believe these differences influence the risks and potential benefits of clinical research. In particular, it seems likely that many will want to know that the investigators will not be choosing which treatment is best for them personally in a randomized trial, because they assume that this approach will lead to less desirable medical outcomes, compared to clinical care. When this is not the case, informing potential subjects of the use of randomization may undermine their understanding of the risks and potential benefits of research enrollment. This possibility poses a dilemma.

Potential subjects may very much want to know about the methods of the proposed study, such as the use of randomization. Yet, potential subjects who know this may assume that randomized treatment is worse for them than clinical care would be. Contrary to the standard defense of the TM, potential subjects who are informed about randomization may end up with a *worse* understanding of the risks and potential benefits of research in the setting of clinical equipoise. Presumably, it is more important for potential subjects to understand the risks and potential benefits of research participation than it is for them to understand the methods of research that they want to know, but which do not influence the risks and potential benefits.[36] If this is right, it suggests that potential subjects

do not need to understand (and perhaps should not even be told) the methods of research when those methods do not influence the risks and potential benefits of their participation.

An alternative approach would be to inform potential subjects of the methods of research, but to also explain how clinicians determine which treatments to prescribe in the setting of equipoise.[37] Presumably, many, perhaps most clinicians are influenced by factors that are irrelevant to the interests of individual patients. For example, in the setting of clinical equipoise, clinicians' choices regarding treatment might be strongly influenced by pharmaceutical industry advertisements. In this case, potential subjects may prefer being in research to receiving clinical care. They may prefer a situation in which the treatment they receive is determined by a random process, rather than being determined by biasing influences.

Or, in the setting of clinical equipoise, clinicians might (unconsciously) prescribe the treatment they were taught in residency, because they are more comfortable with it. If potential subjects very much want to understand the differences between research and care, they will need to understand these aspects of clinical care. These considerations provide further reason to think that it will be difficult to explain the fundamental differences between research and care in ways that do not confuse potential subjects.

FUTURE RESEARCH

Attempting to determine what potential subjects need to understand through the lens of the TM tends to downplay or ignore the task-specificity of informed consent (what potential subjects should understand depends on the study.) As a result, this approach misses the point that the fundamental differences between research and care—differences in methods and in purpose—are relevant to only a subset of clinical trials. This conclusion suggests that directing investigators to focus on the TM ultimately may do more to undermine than to promote informed consent for clinical research. Future empirical research could test this conclusion.

One option would be to randomize potential subjects to two different consent processes. The first arm of the study would (1) explain the fundamental differences in methods and differences in purpose between research and care, (2) explain what potential subjects should understand, (3) answer any questions, (4) test potential subjects' understanding of what they should understand. The second arm would (1) explain what potential subjects should understand, (2) answer any questions, (3) test potential subjects' understanding of what they should understand. Comparison of how well subjects understand what they should understand, across a range of studies, would provide an empirical estimate of the impact of focusing on the TM.[38]

Explanation of differences in methods may help some subjects to appreciate the risks and potential benefits of research participation. Explanation of the purpose of research may help some subjects to understand that the study in question involves research. One might conclude that addressing the TM "up front" will help some subjects to understand. If one adds in the assumption that this approach will not do any harm, it seems to follow that subjects' understanding in the first arm is likely to be better.

While it will take empirical evaluation to be sure, there are several problems with this conclusion. First, the differences in methods between research and care are irrelevant to informed consent for many studies. For these studies, explanation of the differences in methods is at best irrelevant, and, at worst, may confuse potential subjects and undermine their understanding. In addition, there are many reasons that potential subjects may fail to understand what they need to understand, and there is limited time during the informed consent process to explain these things. Spending time explaining considerations that are irrelevant may reduce the amount of time devoted to explaining things that are relevant. Applied to a broad range of studies, then, subjects' understanding in the first arm may in fact be worse. This possibility supports the claim that focusing on the TM may, overall, undermine—rather than enhance—informed consent for clinical research.

Proponents could respond that this conclusion shows only that problems arise if one makes more of the TM than one should, and tries to apply it indiscriminately. The original

work on the TM was not intended to be applied to many studies, such as research with healthy volunteers or with patients who have no standard treatment options, suggesting that a more accurate test of the TM would be to limit it to the subset of studies for which it is relevant.

Even when the fundamental differences between research and care are relevant to a given study, it does not follow that explaining these differences will help potential subjects understand or appreciate what they need to understand. Many subjects are likely to understand the essential elements of informed consent, say, once they are explained to them without any explanation of the fundamental differences between research and care. For example, as mentioned, existing data suggest that randomization in the setting of clinical equipoise does not undermine subjects' interests. Of course there may be cases, perhaps many cases, in which individualized treatment is better able to identify the treatments that are more likely to promote the clinical interests of individual patients. In addition, some randomized studies may be conducted when there is no equipoise between the two interventions being tested.[39] In these cases, the use of randomization poses a real chance of undermining potential subjects' interests. Yet, it seems likely that some potential subjects will be able to understand this without having randomization explained to them. Investigators could explain to subjects that if they enroll in the trial, they may receive a treatment that is not the best one that is available for them. Investigators could further explain the important differences between the best treatment and the second-best treatment, including the differences in risks and/or potential benefits. This seems relatively simple, and many potential subjects are likely to understand it.

As the literature on the TM indicates, some potential subjects might understand randomization, but assume that it applies to others, not to themselves. That is, they may understand it without appreciating its implications. A plausible response would be to make clear that this possibility applies to them personally, rather than try to explain the fundamental differences between research and care. This approach is plausible because the essential elements of consent are relatively straightforward, whereas the methods of clinical research, such as randomization and double-blinding, are complex. Similarly, it seems likely that some potential subjects will be able to understand that if they enroll in a study, they will help others, and that the investigators are attempting to further this goal. At this point, it may be that many, perhaps most, potential subjects will understand what they need to understand, even in the context of studies for which the fundamental differences between research and care are relevant.

Undoubtedly, there will be some potential subjects who are not able to appreciate the essential elements of informed consent without understanding the differences between research and care. For example, without explanation, some may continue to assume that the treatment they receive will be chosen based on clinical judgment. For these individuals, an explanation of the fundamental differences between research and care may help. Notice, though, that which fundamental differences will need to be explained will likely vary. Some subjects may need to understand differences in methods to understand the risks; others may need to understand the purpose of research to understand that they will be contributing to a project to help others. Thus, the need to address the TM is now limited to a small subset of potential subjects in the context of a small subset of all clinical trials. Furthermore, it is possible that a significant portion of this subset may be simply unable to understand the essential elements of consent for a study, even with a thorough explanation of the fundamental differences between research and care.

In the future study we are imagining, investigators working in the first arm of the study explain the differences in methods and the differences in purpose between research and care to all potential subjects. As a result, the investigators will end up explaining these differences to potential subjects who can understand what they should understand without having these differences explained. In contrast, investigators working in the second arm of the study explain these differences only to those individuals who are having difficulty understanding what they should understand without this explanation.

The important point is that investigators working in the second arm are not precluded from explaining the differences between research and care to potential subjects. Rather, they explain these differences when doing so is useful for helping potential subjects to understand what they should understand.

Potential subjects fail to understand different things, and for different reasons. Some may fail to understand the risks or potential benefits of the study in question for reasons unrelated to the TM. For example, they might not have been paying attention and may need the information repeated. Or they may be anxious and need time to relax. Other individuals may fail to understand other essential elements, such as the fact that participation is voluntary. The advantage of the second arm is that it allows investigators to tailor the consent process to the specific study and subjects in front of them.

Undoubtedly, some potential subjects will not understand what they should understand because they confuse research with care. Proponents of the TM seem to conclude that these individuals will not be able to understand what they should understand until they appreciate the differences between research and care. The problem with this analysis is that it fails to distinguish between sources of misunderstanding and necessary obstacles to understanding. A person may fail to understand a particular fact because of some other beliefs they hold. However, it does not follow that one must first address these other beliefs before the person can understand the fact in question.

Imagine that a British man playing baseball for the first time assumes he will get six runs if he hits a home run. He believes this because he confuses baseball with cricket. It does not follow that one must explain the fundamental differences between baseball and cricket before the man will be able to understand this. Instead, one might be able to simply explain: "In this game, hitting the ball off the field gives you one run." The general lesson, here, is that focusing on what individuals should understand is likely a more effective and efficient method for getting them to understand these things, as opposed to first eliminating potential obstacles to their understanding these things.

CONCLUSIONS

To give valid informed consent, potential subjects need to understand the essential elements of informed consent as they pertain to the study in question. What potential subjects need to appreciate to understand the essential elements of informed consent can vary significantly, depending on the study in question, their own circumstances, and the available alternatives. Attempting to ensure valid consent by first identifying the fundamental differences between research and care and then explaining these differences to potential subjects ignores the task-specificity of informed consent.

Work on the TM focuses on one potential source for failing to understanding several of the essential elements of informed consent. Failure to understand differences in methods may cause potential subjects to not understand the risks or potential benefits; failure to understand the purpose of research may cause potential subjects to not understand that a study involves research.

In effect, work on the TM focuses on surrogate (or proxy) markers for several of the essential elements of informed consent. Reliance on surrogate markers can be effective when it is not feasible to measure directly the item that is of interest. For example, surrogate markers can be important for evaluating the progression of gastrointestinal tumors, which are difficult to evaluate directly. In contrast, it is relatively easy to evaluate whether potential subjects understand the essential elements of informed consent. This suggests that we should stop worrying about the TM and focus instead on identifying what potential subjects should understand to enroll in specific studies, and ensure that they understand these things.

Finally, it might be possible to defend the TM on the grounds that understanding the fundamental differences between research and care, while not necessary to valid consent, leads to ethically preferable consent. To make this argument, proponents will have to provide reasons to think that understanding the fundamental differences between research and care is more important than understanding other prominent aspects of research. Even if success-

ful, this argument suggests we should stop worrying about the TM until we identify methods to ensure subjects understand the essential elements of consent.

CONFLICTS OF INTEREST

The author reports no conflicts of interest.

NOTES

1. Important, but much less discussed in the bioethics literature, is the possibility that individuals receiving clinical care will think they are involved in research.

2. J. Kimmelman, "The therapeutic misconception at 25: treatment, research, and confusion," *Hastings Center Report* 37 (2007): 36-42.

3. K.P. Weinfurt et al., "The correlation between patient characteristics and expectations of benefit from Phase I clinical trials," *Cancer* 98 (2003): 166-75; G.E. Henderson et al., "Therapeutic misconception in early phase gene transfer trials," *Social Science and Medicine* 62 (2006): 239-53.

4. C.M. Simon, L.A. Siminoff, E.D. Kodish, and C. Burant, "Comparison of the informed consent process for randomized clinical trials in pediatric and adult oncology," *Journal of Clinical Oncology* 22 (2004): 2708-18; P. Hietanen, A.R. Aro, K. Holli, and P. Absetz, "Information and communication in the context of a clinical trial," *European Journal of Cancer* 36 (2000): 2096-104.

5. R. Dresser, "The ubiquity and utility of the therapeutic misconception," *Social Philosophy and Policy* 19 (2002): 271-94.

6. F.G. Miller and S. Joffe, "Evaluating the therapeutic misconception," *Kennedy Institute of Ethics Journal* 16 (2006): 353-66.

7. See note 1 above.

8. P.S. Appelbaum, L.H. Roth, and C. Lidz, "The therapeutic misconception: Informed consent in psychiatric research," *International Journal of Law and Psychiatry* 5 (1982): 319-29; P.S. Appelbaum et al., "False hopes and best data: Consent to research and the therapeutic misconception," *Hastings Center Report* 17 (1987): 20-4.

9. Appelbaum et al., see note 8 above.

10. Ibid.

11. P.S. Appelbaum, C.W. Lidz, and T. Grisso, "Therapeutic misconception in clinical research: Frequency and risk factors," *IRB* 26 (2004): 1-8.

12. G.E. Henderson et al., "Therapeutic misconception in early phase gene transfer trials," *Social Science and Medicine* 62 (2006): 239-53.

13. C.W. Lidz, P.S. Appelbaum, T. Grisso, and M. Renaud, "Therapeutic misconception and the appreciation of risks in clinical trials," *Social Science and Medicine* 58 (2004): 1689-97.

14. NBAC, "Ethical and Policy Issues in International Research," 2001, *http://bioethics.georgetown.edu/nbac/human/oversumm.pdf,* accessed 23 August 2012.

15. See note 12 above.

16. M. Hadskis et al., "The therapeutic misconception: a threat to valid parental consent for pediatric neuroimaging research," *Accountability in Research* 15 (2008): 133-51; I.S. Durand-Zaleski et al., "Informed consent in clinical research in France: assessment and factors associated with therapeutic misconception," *Journal of Medical Ethics* 34 (2008): e16.

17. International Conference on Harmonization (ICH), "Good Clinical Practices" (1996, E6 4.8.10.), *http://www.ich.org/cache/compo/276-254-1.html,* accessed 22 December 2010; R.J. Levine, *Ethics and regulation of clinical research,* 2nd ed. (New Haven, Conn.: Yale University Press, 1986), 98-118.

18. L.B. Dunn, "Assessment of Therapeutic Misconception in Older Schizophrenia Patients with a Brief Instrument," *American Journal of Psychiatry* 163 (2006): 500-6.

19. Appelbaum, Roth, and Lidz, see note 8 above.

20. The possibility of beneficial incidental findings indicates that, strictly speaking, essentially all research procedures offer some potential for clinical benefit. For example, a blood draw that is done purely for research purposes may reveal information that ultimately benefits subjects, such as the presence of a treatable condition of which they were previously unaware. This possibility reveals that an accurate explanation regarding the potential benefits of purely research procedures is complicated.

21. See for example the U.S. National Institute of Allergy and Infectious Diseases Primary Immune Deficiency Clinic webpage, *http://www.niaid.nih.gov/topics/immunedeficiency/pidclinic/Pages/Default.aspx,* accessed 29 December 2010. Many individuals with rare diseases will receive unproven methods whether they obtain care from a physician or enroll in a research study. Determining what these individuals need to understand through the lens of the TM, that is, by evaluating the differences between research and care, seems to suggest that they do not need to appreciate that the research study involves unproven treatments (since this does not represent a difference between research and clinical care). Evaluation of the study itself, in contrast, reveals that individuals should appreciate this, since it is a central feature of the study.

22. Se note 13 above.

23. C.P. Gross et al., "Does random treatment assignment cause harm to research participants?" *PLoS Medicine* 3 (2006): e188.

24. For simplicity, I have worded these conditions so that they apply to individuals with a condition. This is the standard case. A comprehensive account would have to apply these conditions to individuals without a condition who are candidates for clinical care, for example, healthy individuals who are candidates to receive a vaccine in clinical care or in a research study.

25. G.E. Henderson et al., "Clinical Trials and Medical Care: Defining the Therapeutic Misconception," *PLoS Medicine* 4 (2007): e324.

26. D. Wendler, "Are physicians obligated always to act in the patient's best interests?" *Journal of Medical Ethics* 36 (2010): 66-70.

27. M.B. Lipsett, "On the nature and ethics of phase I clinical trials," *Journal of the American Medical Association* 248 (1982): 941-2.

28. F.G. Miller and S. Joffe, "Benefit in phase 1 oncology trials: therapeutic misconception or reasonable treatment option?" *Clinical Trials* 5 (2008): 617-23.

29. S.J. Cico, E. Vogeley, and W.J. Doyle, :Informed consent language and parents' willingness to enroll their children in research," *IRB: Ethics and Human Researc*h 33 (2011): 6-13.

30. C. Daugherty et al., "Perceptions of Cancer Patients and Their Physicians Involved in Phase I Trials," *Journal of Clinical Oncology* 13 (2005): 1062-72.

31. E. Horstmann et al., "Risks and benefits of phase 1 oncology trials, 1991 through 2002," *New England Journal of Medicine* 352 (2005): 895-904.

32. D. Wendler and C. Grady, "What should research participants understand to understand they are participants in research?" *Bioethics* 22 (2008): 203-8.

33. A different response on the part of proponents of the TM would be to argue that the fundamental difference between research and care is that involvement in research involves contributing to a project to help others. Hence, the present analysis is consistent with a focus on the TM. The analysis under consideration argues that subjects need to understand this because it is relevant to their rights and interests. The version of the TM being considered here instead claims that research subjects need to understand this because it represents the fundamental difference between research and care. Some commentators have proposed collecting data for research purposes as part of standard clinical care. In that case, emphasis on the TM would imply that subjects no longer need to understand this, since it no longer represents a difference between research and care. Or this possibility reveals that proponents of the TM are unlikely to regard this as the fundamental difference between research and care.

34. P.S. Appelbaum and C.W. Lidz, "Re-Evaluating the Therapeutic Misconception: Response to Miller and Joffe," *Kennedy Institute of Ethics Journal* 16 (2006): 367-73.

35. Ibid.

36. The present approach could test this possibility by asking potential subjects something along the lines of: "What if there were some aspect of the study that you wanted to know, but knowing this would confuse you about the risks and potential benefits. Would you want to know this?"

37. Even in the setting of equipoise, some potential subjects may have preferences for one treatment over another. Consider a study that is evaluating a surgical procedure compared to a medical treatment. Even when the evidence suggests that the risks and potential benefits of the two interventions are equivalent overall, some potential subjects might prefer the medical treatment because they want to avoid a surgery scar. Or potential subjects may prefer the surgery because they are going on vacation soon and want the treatment to be over as quickly as possible. While a number of potential subjects may have these preferences, they do not provide a reason why potential subjects need to understand randomization. Rather, potential subjects who have these preferences should understand that if they enroll in the study they might get surgery and they might get medical treatment. Thus, if they have a strong preference for one treatment over the other they should seek that treatment from their doctor rather than enroll in the study (assuming the preferred treatment is available outside of the research context). This possibility seems relatively easy to understand without understanding the mechanism by which treatments will be assigned in the study.

38. This test could be used to assess the adequacy of subjects' understanding, under the assumption that adequate understanding requires understanding only the essential elements of informed consent or understanding the essential elements of informed consent and other factors. For present purposes, I will not distinguish these two.

39. For example, when a treatment that is known to be inferior is much less expensive, it may be worth doing a clinical trial to evaluate whether the increased potential benefits of the more expensive treatment justify its increased costs.