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Problems with the Consensus Definition of the Therapeutic Misconception

David S. Wendler

ABSTRACT

In a previous article,[1] I attempted to assess the likely impact of the most prominent versions of the therapeutic misconception (TM) on research subjects' informed consent. I concluded that the TM is not nearly as significant a concern as is commonly thought, and that focusing on it is more likely to undermine than promote research subjects' informed consent.

A recent commentary rejects these conclusions, as least as they pertain to the "consensus" definition of the TM.[2] The authors of the commentary argue that work on the TM remains central to ensuring the appropriateness of research subjects' consent and, by implication, the ethical acceptability of clinical research.

The present work evaluates the arguments offered in support of these claims. This analysis reveals that the authors offer few substantive responses to my arguments, and the responses they do offer fail to undermine my prior conclusions. Furthermore, consideration of an additional issue—the emergence of learning healthcare systems—suggests that the TM is likely to be even less significant in the future, hence, focusing on it may be even more problematic than I argued previously.

David S. Wendler, PhD, is Head of the Unit on Vulnerable Populations in the Department of Bioethics, NIH Clinical Center, Bethesda, Maryland, *dwendler@nih.gov.* The views expressed in this article are the author's own. They do not represent the position or policy of the National Institutes of Health or the Department of Health and Human Services.

INTRODUCTION

Many commentators have argued that, in order to ensure the ethical acceptability of clinical research, the therapeutic misconception (TM) must be reduced, and hopefully eliminated. Over the past 20 years, an enormous literature has attempted to explicate and defend this view. In contrast, there have been almost no analyses of all this work on the TM: What impact is this focus on the TM likely to have on the ethical acceptability of clinical research?

To address this gap in the literature, I attempted to evaluate the significance of the TM, and the likely impact of its most prominent versions on research subjects' informed consent.[3] I concluded that the TM is not nearly as significant a concern as is commonly thought, and that "emphasis on the TM is more likely to undermine than promote research subjects' informed consent." Unfortunately, Churchill, King, and Henderson (CKH) found my analysis fragmentary, often illogical, and ultimately reducing to the critique of a straw man.[4] The present work attempts to clarify my position and consider CKH's primary arguments against it. This analysis suggests that CKH do not offer any compelling reasons to question my prior conclusions regarding the significance of the TM. Moreover, consideration of an additional issue, the emergence of learning healthcare systems, suggests that focusing on the TM may be even more problematic than I argued previously.

BACKGROUND

Work on the TM is based on two central claims: (1) clinical research differs from clinical care in fundamental ways, and (2) it is vital for individuals involved in clinical research to understand these differences. To defend the two claims and establish the significance of the TM three questions need to be answered. Which fundamental differences between research and care need to be understood? Who needs to understand the differences? Why do the individuals in question need to understand the differences?

Those concerned with the TM answer these questions in different ways, leading to versions of the TM that differ in subtle and sometimes significant ways.[5] The existence of numerous versions brings us to the first puzzling aspect of work on the TM. There is widespread agreement that addressing the TM is vital to ensuring the ethical acceptability of clinical research, yet there is no agreement on what the TM amounts to in the first place. The present analysis attempts to avoid the confusion engendered by so many different versions of the TM by focusing on the version that is endorsed by CKH, what has been called the "consensus" definition of TM. The consensus definition holds that the TM occurs when "individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge."[6] The present analysis assesses the consensus definition of the TM as it pertains to research subjects. This focus will allow us to concentrate on the third, and most important question for establishing the significance of the TM: Why do research subjects need to understand the fundamental differences between research and care?[7]

A TASK-SPECIFIC APPROACH TO INFORMED CONSENT

It is widely agreed that research subjects' consent to participate in clinical research must be informed.[8] That is, to give informed consent, research subjects need to understand certain facts about the study in question, typically including its risks and potential benefits, the fact that participation is voluntary, and the alternatives. My previous article in *JCE* began with what seems the most straightforward way to ensure that research subjects understand these things. Specifically, I argued that investigators (and others) should identify which facts research subjects need to understand, disclose these facts, assess whether subjects understand them, and re-explain any facts that a particular individual did not understand the first time.

When determining what potential subjects need to understand, it is important to recognize that frequently they are choosing between participating in research and receiving clinical care. To make this choice, potential subjects often need to understand the relevant differences between the two options. This analysis suggests, consistent with work on the TM, that research subjects sometimes need to understand differences between research and standard clinical care. However, which facts potential subjects need to understand will vary from study to study. Consider a study that provides subjects with standard-of-care treatment for their condition, and takes two extra blood draws for research purposes. In this case, potential subjects should understand that, if they enroll, they will undergo two blood draws purely for research purposes that they would not undergo if they instead sought care in a clinical setting. In other instances, subjects might need to understand that enrollment in research involves receiving two doses of a drug rather than the standard one dose. And for some research studies, such as research with healthy volunteers, the differences between research and clinical care are irrelevant to informed consent.

An important virtue of such a "task-specific" approach to informed consent is that it recognizes that what subjects need to understand depends on the study in question. This contrasts with work on the TM, which tends to assume that most or all research subjects need to understand the same differences between research and clinical care. For example, according to the consensus definition, most or all research subjects need to understand the difference in purposes between research and clinical care.

A task-specific approach to informed consent also has the potential to address failures of understanding that arise from other sources. In the previous example, some subjects might not understand that research enrollment involves two "non-beneficial" blood draws because they are anxious; others might not understand this fact because they were not paying attention; still others because the investigator explained it using overly technical language. Given that there are many possible sources of misunderstanding, a task-specific approach first explains to subjects the facts they need to understand and then re-explains any facts that were not understood the first time. A task-specific approach attempts to identify and eliminate possible sources of misunderstanding only when a given subject does not understand one or more of the facts she or he needs to understand, following re-explanation. Many subjects who are anxious or who were not paying

attention will be able to understand the two non-beneficial blood draws following an explanation of this specific fact. The few who continue to misunderstand following re-explanation could be excluded, or the investigators could take steps to identify and address the source of the misunderstanding (for example, give the individuals some time to relax).

In effect, those concerned about the TM argue that investigators should reverse this order of explanation with respect to the TM. Investigators first should assess whether potential subjects have the TM. For potential subjects who do, investigators should explain the fundamental differences between research and care, and then make sure that the potential subjects understand these differences before explaining the study in question. For example, to implement this approach using the consensus definition, investigators would first explain that the defining purpose of clinical research is to collect generalizable knowledge, whereas the defining purpose of clinical care is to promote the health of the present patient. The investigators would evaluate whether the potential subjects understand these differences sufficiently and, once they do, then explain the facts about the study that the potential subjects need to understand to give informed consent. As far as I can tell, those concerned with the TM never explain why the TM should be treated differently than the many other possible sources of misunderstanding. The implicit assumption seems to be that the TM is more prevalent and that it is more likely to confuse research subjects than other potential source of misunderstanding.

The defining purpose of a joint activity is not a simple concept. The same is true for generalizable knowledge, and the possibility that one might obtain it by sticking a needle in the arm of research subjects. This complexity suggests that identifying and dispelling the TM in potential research subjects might consume a fair amount of time and resources.[9] CKH defend the use of these resources on the grounds that the fundamental differences between research and care are relevant to consent for most or all subjects. Thus, to evaluate their view, we need to consider whether most or all research subjects need to understand that the defining purpose of clinical research—but not of clinical care—is to produce generalizable knowledge.

WHAT IS THE PURPOSE OF RESEARCH?

Current U.S. regulations define research as a systematic investigation that is "designed to develop or contribute to generalizable knowledge."[10] On the assumption that the design of a given project is based on the purpose for which it is conducted, this definition suggests, consistent with the consensus definition of the TM, that the defining purpose of clinical research is to collect generalizable knowledge. At the same time, the collection of generalizable knowledge is not the only important purpose of many studies. To see this, imagine that the researcher in our previous example is the founder and owner of the biotech company that is sponsoring the study and his primary goal is to make a profit. When designing the study, he may prioritize earning a profit over collecting generalizable knowledge. For example, when deciding which individuals will be eligible for the study, he may choose inclusion criteria based on what will be most effective for marketing future products, not based on what will best yield generalizable knowledge. In this case, the primary goal of the investigator and the sponsor is to make a profit, suggesting that the primary purpose of the study is to make a profit, not to collect generalizable knowledge. And, given that the majority of clinical trials are sponsored by for-profit entities, this conclusion suggests that the consensus definition of the TM may not apply to many clinical trials.

CKH respond to this line of argument as follows: "What Wendler overlooks is that research has for a very long time been sanctioned and endorsed . . . as the pursuit of socially valuable . . . knowledge." As far as the history of clinical research goes, this seems right. However, it is not clear what this fact about the history of clinical research has to do with determining the purpose of clinical trials that are sponsored by for-profit entities. One possibility is that the authors are appealing to a distinction between the primary purpose of a study and the defining purpose. The primary purpose, meaning the purpose or goal that explains why the activity is being conducted, may be to earn a profit. However, the defining purpose, meaning the purpose or goal that defines the activity as research, is to collect generalizable knowledge.

While this response may seem appealing, it runs the risk of begging the question. The conclusion that the defining purpose of the blood draws is to collect generalizable knowledge traces to our having categorized the blood draws as part of a research study. For many purposes, this categorization makes sense. For example, it makes sense for U.S. research regulations to categorize the two blood draws as research, since their goal is to mandate guidelines for the conduct of research. However, there is nothing about the blood draws themselves that implies that they

must be categorized in this way. If we were instead interested in who owes taxes, we might categorize the blood draws as part of a for-profit venture. In this case, the defining purpose of the blood draws, categorized as part of a for-profit endeavor, would be to earn a profit for the sponsor.

This analysis reveals that the blood draws can be categorized in different ways, and these different categorizations are associated with different defining purposes. This conclusion becomes important once we realize that the investigator's and sponsor's goal of earning a profit may have as much, or even more of an impact on the design of the study than the goal of collecting generalizable knowledge. Moreover, the former goal may be more salient for potential participants who are less inclined to undergo extra blood draws to help others earn a profit, than to help others collect data that might benefit the health of future patients. These possibilities underscore the need for proponents of the consensus definition of the TM to explain why, for the purposes of respecting and protecting research subjects, it is more important to disclose that the blood draws involve research than it is to disclose that the blood draws involve a money-making venture. As far as I can tell, CKH do not offer such an explanation.

A further problem, that I did not consider in my previous work, concerns the recent development of learning healthcare systems. Specifically, there have been calls to redesign clinical care to systematically collect data on patients' outcomes.[11] In a learning healthcare system (LHC), encounters between clinician and patient are designed to both provide care to the patient and collect information that can be used to improve care for future patients. For present purposes, the important point is that learning healthcare systems are designed, in part, to collect generalizable knowledge.[12] This development seems to undermine the claim that research and care are fundamentally different because research, but not care, is designed to collect generalizable knowledge.

One way to defend the consensus definition of the TM in the face of this development would be to argue that collecting generalizable knowledge is a secondary goal of learning healthcare systems, whereas collecting generalizable knowledge is the primary goal of clinical research. Alternatively, proponents might argue that, in the context of LHC systems, some interventions will be designed primarily to benefit the present patient, while others will be designed primarily to collect data that might benefit future patients. The pill that patients take for hypertension will be designed primarily to improve their cardiovascular health, while the quality of life surveys they complete and the blood draws they undergo will be designed primarily to collect information to identify better ways to treat hypertension in the future. For present purposes, let us assume that proponents of the TM can effectively argue that, despite the blending of research and care that occurs in LHC systems, it will still be possible to categorize activities and interventions into those that are (primarily) clinical research and those that are (primarily) clinical care. At that point, the TM would be claiming that the ethical acceptability of clinical research depends on subjects understanding that the primary purpose of the procedures that fall into the category of research is to collect generalizable knowledge, whereas the collection of generalizable knowledge is only a secondary purpose of the procedures that are categorized as clinical care.

At first glance, it is not entirely clear why this distinction might be central to the ethical acceptability of clinical research. For example, imagine that the goal of earning a profit for the healthcare system has a significant impact on the design of an intervention. In that case, it seems important for individuals to be informed of this fact, whether or not the intervention ultimately falls on the research or care side of the divide. Similarly, the possibility that some individuals may be less willing to help others earn a profit, as opposed to helping investigators improve the health of future patients, would provide reason to regard the profit-earning motivation as something that individuals should understand, independent of whether the intervention is primarily research or care. The next section considers how proponents of the consensus definition of the TM might accept these conclusions, but nonetheless argue that most or all research subjects need to understand the (presumed) difference in defining purposes between research and care.

IS THE PURPOSE OF RESEARCH ITSELF AN ESSENTIAL ELEMENT OF CONSENT?

A plausible view holds that what individuals need to understand to give informed consent for a given study depends on how the decision whether to enroll in the study, rather than pursue one of the available alternatives, might affect the individuals' important rights and interests. For example, potential subjects should understand the risks of a study, because being harmed would set back their interests. In contrast, the purpose of research concerns the reasons why investigators and funders conduct it. They conduct it in order to collect generalizable knowledge. This raises the question of why, to the

extent that they are concerned with protecting research subjects' rights and interests, proponents of the TM are so interested in the goals or motivations or intentions of investigators and funders.

Perhaps the most obvious answer is that potential subjects need to understand that the study in question (or a given procedure within a learning healthcare system) involves research. And, to understand this, potential subjects need to understand that the goal of investigators is to collect generalizable knowledge. In an end note, CKH suggest this response when they claim that it is hard to imagine research subjects understanding that they are participating in research unless they understand that "research is, by definition, driven by the pursuit of generalizable knowledge."

In my original article I argued that, to understand that they are being invited to participate in 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." This analysis is supported by the fact that individuals have non-welfare interests in contributing to projects that are consistent with their moral beliefs. Knowing that they are being invited to contribute to helping others allows individuals to decide whether they want to make this contribution. Notice that this is important even in the context of activities whose defining purpose is something other than collecting generalizable knowledge. For example, even in the context of learning healthcare systems, there is a reason to inform patients that they will be contributing to a project to help others.

I suspect that this disagreement may be central to the debate over the significance of the TM. Yet, CKH do not mention, much less provide any reasons to question, my analysis regarding what research subjects need to understand in order to understand that they are participating in research.

IS UNDERSTANDING THE PURPOSE OF RESEARCH NECESSARY FOR OTHER REASONS?

The previous analysis undermines the claim that, in order to give informed consent, most or all research subjects need to understand the fundamental differences between research and care. A different defense of the consensus definition of the TM would be to argue that understanding the fundamental difference between research and care is not, itself, something that research subjects need to understand. Instead, understanding the fundamental differences between research and care is a necessary prelude to understanding the things that research subjects need to understand. For example, to understand the risks of research, subjects need to understand the fundamental differences between research and care. The possibility that this might be the basis for CKH's endorsement of the consensus definition of the TM is suggested by the following claim: "it is hard to see how understanding the other key elements would be intelligible unless subjects were clear on the central difference of purpose, which then provides context for all the particulars that need to be disclosed."

The most plausible version of this view holds that potential subjects need to understand the purpose of research in order to understand its risks and potential benefits. To evaluate this view, I considered the possibility of a subject being asked to undergo extra blood draws for research purposes. I speculated that many subjects will be able to understand the risks of the blood draws and the fact that the blood draws wouldn't help them, without necessarily understanding the defining purpose of research. CKH respond to this example by arguing, "Wendler's argument is difficult to follow, since an adequate explanation to subjects of the need for extra blood draws would entail an explanation that they are necessary to fulfill the larger aims of research and are not needed for this patient's care."

The claim here seems to be that subjects will not understand the risks of the blood draws and that the blood draws do not offer any potential benefit, unless the subjects understand their purpose. Yet, in many cases, it seems that individuals are able to understand a request to undergo two blood draws without understanding their purpose. Imagine that someone asks to obtain two vials of your blood through a needle for his or her own purposes. Presumably you could understand the risks and lack of personal benefits, even if you do not understand the individual's purpose for obtaining the blood. In particular, the risks of the blood draws are determined by the nature of the procedure, not its purpose. Likewise, many individuals likely will be able to understand the lack of benefit to them of a blood draw without understanding its purpose. They will be able to understand the negative—these blood draws will not benefit me—without understanding who or what might benefit from them. You might readily grasp that the blood draws offer you no potential benefit without knowing, and perhaps without caring, whether they are being done for research, to collect blood for an art project, or for a blood transfusion.

Proponents of the TM might respond that many or most potential subjects will inevitably assume that

the blood draws are being done for clinical care. Thus, without an explanation of the actual purpose, these individuals will assume that the blood draws offer them some potential for clinical benefit. Undoubtedly, there will be some individuals for whom this is the case. The research context includes aspects that tend to encourage this confusion. In particular, requests for research blood draws are often made by clinicians who wear white coats and work in hospitals. As a result, potential subjects may assume that the blood draws are being done for their clinical care.

One way to try to address this concern would be to explain to potential subjects the defining purpose of research and how the blood draws help to promote that purpose. A more straightforward approach that I endorsed in my previous article would be simply to ask potential subjects, after the disclosure process, whether the blood draws offer them any chance for medical benefit. For those who think they do, the investigators could emphasize that they are not being done for clinical care and they do not offer any chance of benefit to subjects. I speculated that many subjects will understand this the first time it is explained to them, and many of those who do not understand it the first time will understand it following a targeted explanation. CHK disagree. They believe that many potential subjects will suffer from the TM and many, perhaps most, of these individuals will fail to understand the risks and potential benefits of research participation.

At this point, debate over the significance of the TM becomes an empirical one. To defend the significance of the TM, its proponents need to show that many, perhaps most, potential research subjects have the TM, and that the presence of the TM makes it very difficult or impossible for many individuals to understand the things they need to understand to give consent. Imagine that there are 100 potential subjects for a study that involves two extra research blood draws. Proponents of the TM assume that many individuals, perhaps 60, will have the TM and that, as a result, many of them, say 40, will continue to believe the blood draw is for their benefit, even after an investigator explains to them, and then re-explains, that this is not the case. My suspicion is this will be true for, at most, a handful of the 100 potential subjects. As far as I am aware, no one has collected the data needed to resolve this disagreement. Hence, in my previous article, I described a study that could be used to collect the relevant data.

Briefly, the study would randomize potential subjects to either a task-specific or TM-endorsed consent process. The task-specific approach would explain the facts that subjects need to understand, and then re-explain any facts that were not understood the first time. The TM-endorsed approach would first identify which subjects have the TM and then try to eliminate it. This approach would then explain the facts that subjects need to understand. The study would evaluate how long the two processes take and what percentage of individuals in the two arms understand the facts that they need to understand to give consent. Surprisingly, CKH do not mention this proposal in their commentary on my article, nor do they provide any reason to think that the results will support their view. Hence, to determine whether it is time to stop worrying about the TM, an important step will be to start collecting the relevant data.

THE RESEARCH RELATIONSHIP

Work on the TM is rightly concerned with protecting the rights and interests of research subjects. To promote this goal, proponents of the consensus definition of the TM argue that it is important for research subjects to understand the differences in defining purposes between research and clinical care. Bracketing for the moment the specific problems we have been considering with the consensus definition of the TM, this focus may seem puzzling. What do the goals or motivations of investigators and funders have to do with protecting subjects? The answer is suggested by a passage in which CKH argue that my analysis regarding the relative unimportance of the TM fails because I neglected a critical feature that distinguishes clinical care from clinical research. I quote them at length because their claim may point to the fundamental concern that underlies work on the TM:

> The idea that the people I am relating to in a clinic or hospital setting are all here to help me, that they have my welfare primarily in mind, is the default assumption of our relationships with doctors and nurses. In research this assumption is false; this is the central phenomenon of the TM. . . . As patients we are often comfortable with much that is left unsaid about procedures and interventions, precisely because we are secure in an understanding that our benefit is the primary professional motivation. Research interactions require a great deal more in terms of negotiation and consent precisely because this core fiduciary value cannot be taken for granted. That our trust in physicians may at times be misplaced—perhaps because of the parallel influences on the treatment relationship that arise

from the larger context of healthcare delivery, that Wendler discusses only in reference to research—does not alter the need to attend most carefully to the research relationship.

The basic idea here seems to be that confusing research with clinical care is troubling because clinicians are motivated primarily to help their patients, whereas researchers are motivated primarily to collect data. As a result, participation in research is much more risky overall than receiving clinical care. Clinicians are focused on protecting us; the concerns of researchers lie elsewhere. On this view, identifying and eliminating the TM is important as a way to put overly trusting subjects on their guard. This suggests a possible reason that proponents of the TM focus so much on the goals or motivations of investigators and funders. Even if, as I have argued, many subjects will be able to understand the risks of research procedures, it is nonetheless important for subjects to understand the fundamental differences between the purposes of research and care; this understanding alerts subjects that they largely have to protect themselves.

While the claim that clinical research is much riskier than clinical care makes sense, there are good reasons to think it is mistaken. First, as I argued previously, many investigators are motivated to help their subjects. I have personally interacted with hundreds of researchers who are very concerned for the welfare of their subjects. This concern likely provides important protection for research subjects. And, although I am not aware of any data to this effect, I suspect that some clinicians are not primarily motivated to benefit the patient in front of them. Instead, they are motivated to have a career or make a living, and the treatment of patients is a means to achieve their goals.

Of course, many clinicians are concerned with the welfare of their patients. However, the goals of having a career and making money can put patients at risk to a greater extent than the goal of collecting data places research subjects at risk. For example, the motivation to have a career can lead surgeons to accept cases for which they are less prepared or equipped to perform than a colleague may be, thus posing increased risk to patients that may be greater than the levels of net risk that are permitted in clinical research.

Second, as mentioned previously, the development of learning healthcare systems that are designed to provide clinical care and simultaneously collect data has the potential to undermine the presumed difference between research and care. Physicians who are trained within a learning healthcare system will be motivated both to help the present patient and to collect data to help future patients. Third, even if we grant that there is a difference in the primary motivations between physicians and researchers, it does not necessarily follow that research participation is always riskier. There are many other differences between research and care that can affect their respective risks. Investigators are subject to significantly more oversight than personal physicians, including oversight by institutional review boards (IRBs) that must review their studies every year. And oversight may be more important in terms of protection than the motivations of clinicians and investigators. In addition, investigators tend to be relatively expert with respect to the condition under study. This level of expertise almost certainly protects and benefits subjects compared to patients, many of whom are seen by clinicians whose knowledge and skills are below average.

Finally, significant harms to research subjects typically have greater negative consequences for researchers than harms to patients have for clinicians. For example, the development of a new treatment can cost hundreds of millions of dollars and take a decade. Significant harm to even a few subjects can undermine and even derail an entire research program. In this case, because researchers are motivated to develop new treatments, and because many of them are motivated to make money, they may be very protective of research subjects.

CONCLUSIONS

To give informed consent, research subjects typically should understand the central features of the study in question as they relate to their rights and interests (for example, that enrollment involves research, the risks, the potential benefits). CKH's defense of the TM, and their rejection of my prior arguments, seems to be based on the claim that it is difficult or impossible for many individuals to understand these things unless they understand that the purpose of research, but not the purpose of clinical care, is to collect generalizable knowledge. I have argued that CKH do not provide a compelling defense for this view. In particular, the emergence of learning healthcare systems undermines the claim that clinical care is not designed to collect generalizable knowledge. In addition, even when this difference exists, it is irrelevant to informed consent in some cases (for example, research with healthy

volunteers) and may be less relevant than other considerations (whether a study is for-profit or not). Finally, I have argued that the TM is only one source of possible misunderstanding, that it may not be the most important source, and that most potential subjects will be able to understand what they need to understand to give informed consent without understanding that research and care have different defining purposes. This analysis suggests that identifying and eliminating the TM will be important for, at most, a small subset of research subjects. To support the consensus definition of the TM at this point, its proponents need to provide reasons to think that it accurately characterizes the fundamental difference between research and care, including learning healthcare systems, and reason to think that a significant percentage of potential subjects will not be able to understand what they need to understand unless they understand this difference.

NOTES

1. D.S. Wendler, "Time to Stop Worrying about the Therapeutic Misconception," *The Journal of Clinical Ethics* 23, no. 3 (Fall 2012): 272-87.

2. L.R. Churchill, N.M.P. King, and G.E. Henderson, "Why We Should Continue to Worry about the Therapeutic Misconception," in this issue of *JCE.*

3. Wendler, see note 1 above.

4. Churchill, King, and Henderson, see note 2 above.

5. As a result, grappling with the TM can feel like grappling with Proteus, who, in his attempts to escape Menelaus, changes into a "lion with a great mane; then all of a sudden he became a dragon, a leopard, a wild boar; the next moment he was running water, and then again directly he was a tree." Homer, *The Odyssey,* 800 B.C.E, translated by Samuel Butler, *http://classics.mit.edu/Homer/odyssey.4.iv.html,* accessed 10 May 2013.

6. G. Henderson et al., "Clinical Trials and Medical Care: Defining the Therapeutic Misconception," *PLOS Medicine* 11, e324 (2007): 1735-8. Although not stated explicitly, the consensus definition of the TM includes a suppressed clause that the defining purpose of research, but not of clinical care, is to collect generalizable knowledge.

7. This limitation, which is consistent with my previous article, allows us to evaluate the original, as well as the most prominent versions of the TM. However, in response to my arguments, CKH suggest that the TM may be more important to the extent that it affects "investigators, the media, the general public, and the institutions and organizations that oversee and sponsor research." To support this claim, CKH point out that IRBs around the world approve trials in order to have something to offer patients for whom all else has failed. As stated, this practice does not strike me as necessarily problematic, much less a claim on which to base one's defense of the TM. Depending on the circumstances, this might be just the right thing for IRBs to do. With respect to investigators, the authors' concern seems to be that investigators do not always act in ways that are consistent with the goal of developing generalizable knowledge. For example, they point out that investigators sometimes deviate from the goal of collecting data in order to help subjects, and, there is "considerable evidence that physicians not infrequently refer patients to trials with the intent and expectation that a trial is the best treatment." This version of the TM seems to be more about the behavior of investigators and funders than the understanding of research subjects. If that is right, this version will require a new consensus definition of the TM. In addition, this version has the potential to lead proponents into ironic waters. As I argue below, the primary motivator of work on the TM seems to be protection of subjects from the risks associated with collecting data. In the present case, the concern seems to involve actions that deviate from the collection of data in order to benefit subjects. See the authors' statement: "Yet because benefiting patients who are subjects seems virtuous, the risks of harm arising from investigator TM may be far less visible and thus potentially more damaging." The risks they have in mind here seem to concern the validity of the scientific results of research studies, rather than the well-being of its subjects.

8. This agreement is widespread, but not unanimous. For example, some commentators argue that subjects need not understand the study in question; all that is required is adequate disclosure on the part of investigators.

9. In a recent work, Appelbaum and colleagues propose an instrument that might be used to identify the TM among research subjects: P. Appelbaum et al., "Therapeutic misconception in research subjects: development and validation of a measure," *Clinical Trials* 9 (December 2012): 748-61. In an accompanying commentary, I attempted to estimate the practical impact of their approach, including the time that would be required to implement it: D. Wendler, "Taking the measure of the therapeutic misconception," *Clinical Trials* 9 (December 2012): 762-4. In their response to my comments, Appelbaum and Lidz claim that their endorsed approach may not be as time-intensive as I suggest. P.S. Appelbaum and C.W. Lidz, "The mismeasure of therapeutic misconception," *Clinical Trials* 9 (December 2012): 765.

10. "Code of Federal Regulations, Title 45, Public Welfare, Department of Health and Human Services, Part 46, Protection of Human Subjects," 45 *CFR* 46, 2009, *http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html,* accessed 5 November 2013.

11. L.A. Olsen, D.R. Aisner, and J.M. McGinnis, *The Learning Healthcare System: Workshop Summary,* Institute of Medicine of the National Academies Roundtable on Evidence-Based Medicine (Washington, D.C.: National Academies Press, 2007), *http://books.nap.edu/openbook.php?record_id=11903,* accessed 5 November 2013.

12. R.R. Faden et al., "An ethics framework for a learning health care system: a departure from traditional research ethics and clinical ethics," *Hastings Center Report* 43 (2013): S16-27.