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Commentary

Why We Should Continue to Worry about the Therapeutic Misconception

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ABSTRACT

In a recent article in *The Journal of Clinical Ethics,* David Wendler argues that worries about the therapeutic misconception (TM) are not only misconceived, but detract from the larger agenda of a proper informed consent for subjects involved in clinical research.[1] By contrast, we argue that Wendler mischaracterizes those who support TM research, and that his arguments are fragmentary, often illogical, and neglect a critical difference between clinical care and clinical research. A clear explanation about the chief aim of research is, in fact, what gives the other elements in a consent process their meaning. We argue that informed consent must be both trial-specific and context-sensitive, and that concern about the TM is needed now more than ever.

CAN WE RELAX ABOUT THE TM? INTERROGATING THE ARGUMENTS

David Wendler has argued recently that concerns about the therapeutic misconception are misguided, overblown, not applicable in many instances of clinical research, and actually counterproductive, in that they divert attention away from the "essential elements of informed consent."[2] His effort to make good on these assertions fails, we will argue, because his analysis is fragmentary and in places illogical, and most importantly because he neglects a critical feature that distinguishes clinical care from clinical research. Not only should we continue to worry about the TM, but the case for continued vigilance on the part of investigators, institutional review boards (IRBs), and research sponsors is compelling.

One of Wendler's central claims is that the empirical work on the TM and its prevalence is based on "mistaken methods for determining what things research subjects should understand," because these studies largely assume that all research subjects need to understand the same differences between research and routine care.[3] His position is that not all patient-subjects need to understand that research and treatment are not the same thing; he proposes that the need for such understanding is context dependent, what he terms "task-specific."[4]

We might all concede some version of this. For example, understanding the essential differences be-

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tween research and treatment can be far more important in Phase I trials than in Phase III trials. But Wendler's critique is more radical. He asserts that there often is little or no "fundamental or enduring difference" between research and treatment, and that to insist that there is a difference, and to focus on efforts to communicate it, "distorts what subjects should understand."[5] He also cites the potential for "commentators to exaggerate" the differences, as, for example, when a given research protocol is arguably less risky than a standard treatment using unproven methods, because, he asserts, commentators feel the need "to identify some way in which most (or all) research studies differ from clinical care."[6]

Of course, Wendler is correct that exaggeration is possible, in the consent form, the consent process, and scholarly discussion. Furthermore, it is clear that researchers have obligations to subjects in research, as Carl Coleman has argued.[7] Yet the framework of understanding that establishes how a researcher and a subject interact is fundamentally different from the framing assumptions of doctor-patient relationships. We address this difference in relationships in the next section.

Wendler does not address this relational difference at all. Instead he claims that empirical studies and conceptual analyses of the TM to date have focused on two sorts of differences: differences in methods and differences in purposes. With regard to methods, he points to practices of randomization, double-blinding, fixed treatments, and other features often necessary in investigations that aim for generalizable knowledge. Yet these features of research methods, Wendler contends, are mostly relevant to the extent that they alter the balance of risks of harm and potential benefits, and that otherwise these differences in methods between research and clinical care may be irrelevant to valid consent. He concludes that the best remedy when there is an increase in risk is simply to state this detail, without what he considers the more difficult task of explaining the relevant differences between research and clinical care, despite the fact that this is why the differences exist. "Many potential subjects will be able to understand this [extra blood draws of no direct benefit to the subject] without having to understand that clinical research is designed to collect generalizable knowledge and that the blood draws provide a way for investigators to do so."[8] Here 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. Wendler summarizes his view on methods by saying that "TM will be useful only when . . . explaining general differences in methods is useful for helping potential subjects to understand the essential elements of consent."[9] This conclusion only makes sense if we assume that knowing whether an intervention is research or clinical care is not always essential.

When Wendler turns from differences in methods to differences in purpose, the argument becomes even more strained. Here, as with the examination of methods, he stresses that too much emphasis on "the *defining purpose of research*" as the search for generalizable knowledge can lead us in the wrong direction. He rightly states that much clinical research does aim to benefit those enrolled in research, but he fails to note that this is necessarily a secondary aim, a felicitous by-product of the major research purpose, and not the chief agenda. Along the same lines, he also appears to equate the investigator's intent to benefit patient-subjects with the certainty of a beneficial effect.[10] Moreover, he seems to consider the investigator's duty to protect subjects through risk minimization, which is a requirement of all clinical trials governed by the "Common Rule,"[11] as evidence that the investigator is behaving as a clinician, thus somehow blurring the research-treatment distinction.[12]

Wendler rightly suggests that a great deal of commercially based research is aimed at profit, but here he seems to confuse the larger aims of the sponsors of the research with the primary purpose of research as discussed between investigators and research participants. Investigators can of course also be motivated by profit, as well as fame, tenure, and a range of other things. But surely listing the multiplicity of purposes of the various actors in the research enterprise is beside the point. Indeed, in his portrayal of differences in purpose, Wendler argues that understanding the large purposes of organizations and activities is often unimportant to legitimate participation. He cites as examples (1) consent to help with a car wash for charity, and questions whether in volunteering for car washing one really understands the larger aims of that charity; and (2) his own case of working for the U.S. federal government and how well he understands governmental aims.[13] The first example trivializes his case; there is usually little or no moral burden assumed by either party in a car wash. The second example seems to obfuscate the primary purpose of clinical research by suggesting it is similar to the many and varied purposes of the federal government. If we pursue this analogy, it leads in a direction that undercuts Wendler's claim.[14]

The existence of multiple and often conflicting aims among the actors in research is commonplace, and certainly is the reason for a range of disclosure requirements and conflict-of-interest management plans. What Wendler overlooks is that research has for a very long time been sanctioned and endorsed—whatever the mixed motivations of particular actors—as the pursuit of socially valuable, generalizable knowledge. This understanding is not only its definition in the federal "Common Rule," but a definition with wide professional and social acceptance. We can think of no quicker way to undermine public support for medical research than to suggest that whether or not research subjects are clearly informed that they are involved in research is somehow unimportant. This is, of course, not the only thing important to a valid informed consent, but 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. Wendler suggests that a preoccupation with the TM will dislodge other important features of a research enrollment discussion, such as disclosures of the risks of harm and potential benefits. It seems far more likely that an overall effort to eliminate or reduce the TM will lead naturally to a more accurate disclosure of the essential elements as applicable to the research study under consideration, such as risk/benefit expectations, inconvenience, randomization, and the rest.

THE CRITICAL FEATURE OVERLOOKED

Most people do not begin their interaction with healthcare professionals with a critical, structural analysis of the purposes, far less the methods, that justify the interventions they will undergo. Indeed, these things are all mediated through an important, prior feature of the activity, established at the beginning, namely, the relationship, including assumptions about what that relationship is or should be like. The TM involves a misunderstanding of purposes and methods only because it is first a misunderstanding of relationships, of the kind of relationship in which the health professional and the other party are engaged.[15] One obvious but important clue to the character of the relationships is that we typically use different names for the actors—physician or investigator, and patient or subject. So in its most obvious form, the TM is when I think I am a patient in a therapeutic alliance with a doctor, but in fact I am in a research protocol in which the physician may in fact be a doctor, may even be "my doctor," but is not acting primarily as a doctor, or my doctor, in the current set of interactions. And of course here, "not acting primarily as a doctor" means that there is a different primary purpose for at least some of the interventions at hand. There are a variety of reasons why this happens, some obvious and some more subtle. As most commentators have noted, and Dresser has written about in great detail, research is susceptible to being misunderstood as routine clinical care because the context of the clinic—white coats, doctors and nurses with name badges, sometimes a previous relationship, et cetera—looks and smells therapeutic.[16] 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. Without this, misunderstandings of methods and purposes would not arise, or would be far less frequent. It is precisely this linchpin differentiation about the qualitatively divergent kinds of relationships in research and clinical care that is overlooked in Wendler's essay, and which seems to blind him to just how serious misunderstandings of purpose and methods can be.

Yet whether the TM on the part of the research subject always has adverse consequences for the subject's ongoing decision making during research participation is not the point. Even in this age of high autonomy, relationships between physicians and patients depend upon trust, and the interaction is necessarily a fiduciary one. 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.

MORE WORRIES: THE TM AS CHARACTERISTIC OF RESEARCHERS AS WELL AS PATIENT-SUBJECTS

Everything we have said here takes on a deeper importance when we factor in the reality that it isn't patient-subjects alone who are susceptible to the TM,

but also investigators, the media, the general public, and the institutions and organizations that oversee and sponsor research as well.[17] Wendler is correct that most of the scholarly literature on the TM focuses on the perceptions and beliefs of subjects and potential subjects. Yet there is considerable evidence that physicians not infrequently refer patients to trials with the intent and expectation that a trial is the best treatment.[18] IRBs around the world approve trials in order to have something to offer patients for whom all else has failed,[19] and study sponsors and disease advocacy organizations often express the same concerns.[20] There is, moreover, ample evidence that consent forms, when not using treatment language almost exclusively, at best use conflicting and confusing terminology that conveys decidedly mixed messages to potential subjects.[21] This terminological confusion is rarely avoided well by investigators (though there are notable exceptions), and rarely corrected well by IRBs (again with some notable exceptions). Perhaps more important, in a multi-method study of consent forms and the consent process in early phase gene transfer research, we found that when investigators took seriously the limited potential for direct benefit described in their consent forms, and mirrored that in the consent process and in their own understanding, subjects were least likely to express the TM.[22]

Addressing the problem of the TM among investigators and others is especially important because it has ramifications far beyond those of the TM in research subjects and potential subjects. It is worthy of note that the definition of research in the "Common Rule" is not among the basic elements of consent that must be included in the consent form. Instead, it appears in the regulations for the benefit of investigators and IRBs, so that they can better understand the tasks before them. The first two items on the seven-item list of what makes clinical research ethical are validity and value, which together are critical for the production of generalizable knowledge.[23] The failure to conduct research according to its primary purpose is just as likely to lead to bending of inclusion/exclusion criteria, protocol deviations, and other serious compromises of data when those problems arise from a focus on benefiting patient-subjects as when they arise from the pressure to publish positive results to increase the sponsor's profits. Yet because benefiting patients who are subjects seems virtuous, the risks of harm arising from the TM on the part of investigators may be far less visible, and thus potentially more damaging.

If nothing else, attending to the TM serves as an important tool of critical self-reflection for the physician-investigator.[24] There are few substitutes for the value of a thoughtful consent process, for the purposes of information sharing, decision making, and relationship building in clinical research as well as in patient care.

THE CONSENSUS AND THE WORK THAT NEEDS TO BE DONE

Following from Appelbaum and colleagues' first empirical documentation of the TM in 1982, there have been subsequent attempts to develop scales for the TM[25] or measures of informed consent more broadly[26] that might be used to document misunderstandings and as educational tools during the enrolling of research subjects. In response, many concerns have been raised about what was being measured. Were TM researchers trying to eradicate hope, which no one should want to do? Were they confusing fundamental misconceptions of the research enterprise with less troubling mis-estimations of the potential for direct medical benefit, and how much should we care about the latter?[27]

Because efforts to measure the TM inevitably raise thorny definitional debates, we convened an interdisciplinary group of clinical investigators, social science researchers, and bioethicists to develop both an agreed-upon definition of TM and a road map for empirical measurement. This is set out in our 2007 publication, which defines the TM as existing when "individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge, regardless of whether the subjects enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the clinical trial."[28] It is this definition that Wendler finds so troubling and that we defend in this rebuttal. Equally important, however, are the more specific recommendations we set forth in this consensus report, which we identify as the logical extensions of this definition and propose as guides for assessing what potential patient-subjects should understand. These six dimensions include assessing understanding of the scientific purpose; the procedures; the inherent uncertainty (clinical equipoise) regarding safety and efficacy of the intervention under study; the fact that studies typically adhere to protocols; and that, in a clinical trial setting, clinicians who are investigators are, in this setting, investigating the safety and efficacy of an intervention. We further argue that while these dimensions should be applicable across populations and studies, assessments of the TM "should be tailored to the experiences of particular groups . . . [and to pa-

tient-subjects] participating in trials with different designs."[29]

There is an ever-present tension between developing scales or measures that are universally applicable and also relevant to the particulars of individual trial contexts. There are also robust and legitimate critiques of measurement approaches that have been suggested in the literature for both misconception and misestimation. Most noteworthy is a recent publication by Weinfurt and colleagues, who (reasonably) argue that estimation of benefit in early phase oncology trials depends upon the way the question is asked. They compare benefit assessment using two different approaches ("How confident are you that the experimental therapy will control your cancer?" versus "If 100 people were to participate in this study, how many could be expected to have their cancer controlled as a result of the experimental therapy?").[30] While the "belief" type question elicits a higher mean expectation of benefit than the "frequency" type, leading the authors to recommend frequency type questions to assess subjects' expectations, the study still demonstrates significant therapeutic mis-estimation, even when the frequency question is used. Methodological challenges in empirical assessment of the TM present exciting opportunities to improve its measurement and that of research understanding generally. They do not imply, however, that the fundamental task is not worth attempting.

CONCLUSION

In his portrayal of the researchers and scholars whose work addresses the TM, Wendler offers up for critique a straw man. The approach adopted by researchers who have studied the TM does not "effectively ignore" the idea that what potential subjects should understand "depends on the study in question and the circumstances of potential subjects in that study."[31] Rather, these researchers simply disagree with Wendler when he asserts that making the research/treatment distinction is not a crucial feature of consent. Wendler calls his own approach "task-specific." Of course consent should be quite "trial-specific" regarding risks, benefits, and aspects of the protocol that would diverge from ordinary clinical care. What Wendler overlooks is that consent is also highly sensitive to context, and must account for circumstantial features of the interaction with potential subjects. One of the most important circumstantial features of enrolling most patient-subjects is that they can easily think that treatment is the primary aim of the interventions. With this in mind, it is hard to see why a trial-specific, context-sensitive discussion of the different primary aims of research and treatment could be unimportant. Indeed, just how potential subjects might the weigh risks and benefits and understand the requirements of a protocol depends on what they think the larger agenda is. We have heard many stories—most investigators can tell them—about how patients who are potential research subjects brush aside the need for a full consent process with responses that beg for a research/treatment discussion: "I'm sure you wouldn't be offering this if it wasn't good for me." Or "I have always received excellent care here, so I trust you to do what you think I need." This is common fare for research done in clinics and medical centers. In addition to a "trial-specific" consent process, we also need a context sensitive consent process, in which the possibility of the TM is always a part of the investigator's awareness.

In contrast to what Wendler seems to assume, this mindfulness does not at all require a consent process that attempts to elicit, or a consent monitoring process that would test, potential subjects' understanding of the definition of research or the conceptual foundations of the TM. He implies that the scholars engaged in TM research would require similarly unwieldy and abstract disclosures; instead, we maintain that those interested in the TM would much prefer to endorse a process designed to assist potential subjects in understanding the research study they are considering joining and what will happen to them if they do.[32] Especially in the current climate of increased attention to research, including not only pressures to produce generalizable knowledge but also pressures for medical progress and early access to innovations,[33] as well as the development of new models like "learning healthcare systems,"[34] we believe that it is possible and highly desirable both to continue thinking productively about how to recognize and minimize the TM, and how best to educate and inform patients who are also research subjects.

NOTES

1. D. Wendler, "Time to Stop Worrying about the Therapeutic Misconception," *The Journal of Clinical Ethics* 23, no. 3 (Fall 2012): 272-89.

2. Ibid. Wendler indicates what he means by the "essential elements of informed consent" on page 275, and it includes four elements, the first of which is "that enrollment involves participation in research." We argue later in this essay that it is hard to imagine fulfilling the requirement of this first element of consent without disclosing that research is, by definition, driven by the pursuit of

generalizable knowledge.

3. Ibid., 273.

4. Ibid.

5. Ibid.

6. Ibid.

7. C. Coleman, "Duties to Subjects in Clinical Research," *Vanderbilt Law Review* 58 (2005): 387-449.

8. See note 1 above, p. 277.

9. Ibid.

10. On page 278 Wendler says, "Investigators often enroll individuals in research with the intent of providing them with clinical benefit, even in Phase I studies." He makes this assertion despite the voluminous literature pointing out the uncertainty of benefit in early phase research, and despite the possibility that the investigator who wishes to benefit subjects may also be exhibiting the TM, as we will argue below. See note 1 above.

11. See 45 *CFR* 46.111(a) (1).

12. See note 1 above, p. 278.

13. Ibid., 279.

14. Assuming that federal employees have a contract for services that will sustain or further some governmental aims, and that these aims would have to be specified before employment in order to legitimate the contract, this seems quite similar to volunteering for medical research. In both cases, learning that the guiding purpose of the activity in which one is engaged has not been disclosed would be a serious breach.

15. See L. Churchill, "Physician-Investigator/Patient-Subject: Exploring the Logic and the Tension," *Journal of Medicine and Philosophy* 5, no. 3 (1980): 215-24. See also N. King, G. Henderson, and J. Stein, ed., *Beyond Regulations: Ethics in Human Subjects Research* (Chapel Hill: University of North Carolina Press, 1999); and N. King and L. Churchill, "Clinical Research and the Physician-Patient Relationship: The Dual Roles of Physician and Researcher," in *The Cambridge Textbook of Bioethics* (Cambridge, U.K.: Cambridge University Press, 2007), 710-38. See also M. Easter et al., "The Many Meanings of 'Care' in Clinical Research," in *The View From Here: Social Science and Bioethics* (Oxford, U.K.: Blackwell, 2007), 30-47.

16. See R. Dresser, "The Ubiquity and Utility of the Therapeutic Misconception," *Social Philosophy and Policy* 19, no. 2 (July 2002), 271-94. See also M. Miller, "Phase 1 Cancer Trials: A Collusion of Misunderstanding," *Hastings Center Report* 30, no. 4 (July-August 2000): 34-43.

17. See A. Harmon, *http://topics.nytimes.com/top/news/health/series/target_cancer/index.html,* accessed 18 April 2013. See also the suggestions of therapeutic effects within the NIH website's information to patients: *http://www.nih.gov/health/whyparticipate/htm,* accessed 18 April 2013, which states that participants will "possibly receive the newest treatment."

18. S. Joffe and J. Weeks, "Views of American oncologists about the purposes of clinical trials," *Journal of the National Cancer Institute* 94, no. 24 (2002): 1847-53.

19. L. Churchill et al., "Assessing Benefits in Clinical Research: Why Diversity in Benefit Assessment Can Be Risky," *IRB: Ethics and Human Research* 25 (2003): 1-7.

20. R. Dresser, *When Science Offers Salvation: Patient Advocacy and Research Ethics* (New York: Oxford University Press, 2001). Also, Pamala Sankar notes that some principal investigators change their description of Phase I participation depending upon which cohort the patient-subject would enter, emphasizing safety in early dosing cohorts and potential benefit when enrollment would place a potential subject in a cohort receiving a higher dose. See P. Sankar, "Communication and Miscommunication in Informed Consent to Research," *Medical Anthropology Quarterly* 18 (2004): 429-44.

21. N. King et al., "Consent Forms and the Therapeutic Misconception: The Example of Gene Transfer Research," *IRB: Ethics and Human Research* 27, no. 1 (2005): 1-8; and N. King, "Describing and Defining Benefit Appropriately in Clinical trials," *Journal of Law, Medicine and Ethics* 28 (2000): 332-43.

22. G. Henderson et al., "Therapeutic Misconception in Early Phase Gene Transfer Trials," *Social Science and Medicine* 62 (2006) :239-53.

23. E. Emanuel, D. Wendler, and C. Grady, "What Makes Clinical Research Ethical?" *Journal of the American Medical Association* 283 (2000): 2701-11.

24. This valuable feature of informed consent is often overlooked. For a classic statement of its importance see A. Capron, "Informed Consent in Catastrophic Disease Research and Treatment," *University of Pennsylvania Law Review* 138 (1974): 341-429, see especially 669-72.

25. P. Appelbaum et al., "Therapeutic Misconception in Research Subjects: Development and Validation of a Measure," *Clinical Trials* 9 (December 2012): 748-61.

26. S. Joffe, "Quality of Informed Consent in Cancer Clinical trials: A Cross-sectional Survey," *Lancet* 358 (2001): 1772-7.

27. S. Horng and C. Grady, "Misunderstanding in Clinical Research: Distinguishing Therapeutic Misconception, Therapeutic Misestimation and Therapeutic Optimism," *IRB: Ethics and Human Research* 25 (2003): 11-16.

28. G. Henderson et al. "Clinical Trials and Medical Care: Defining the Therapeutic Misconception," *PLOS Medicine* 11, e324 (2007): 1735-8.

29. Ibid., 1737.

30. K. Weinfurt et al., "Research Participants High Expectations of Benefit in Early-Phase Oncology Trials: Are We Asking the Right Question?" *Journal of Clinical Oncology* 30 (2012): 4396-4400.

31. See note 1 above, p. 273.

32. See, for a good example, S. Koyfman, M. McCabe, E. Emanuel, and C. Grady, "A Consent Form Template for Phase I Oncology trials," *IRB: Ethics and Human Research* 31 (2009): 1-8.

33. R. Dresser, "Alive and Well: The Research Imperative," *Journal of Law, Medicine and Ethics* 40 (2012): 915-21.

34. See "Report, Ethical Oversight of Learning Health Care Systems," *Hastings Center Report* 43 (2013): S1-45.