Franklin G. Miller and Jonathan D. Moreno, "Informed Consent and the Ethics of Clinical Research: Reply to Commentaries," *The Journal of Clinical Ethics* 16, no. 4 (Winter 2005): 376-9.

Informed Consent and the Ethics of Clinical Research: Reply to Commentaries

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We appreciate the thoughtful commentaries by Sreenivasan, Evans, and Truog, both for their positive remarks about our article, "The State of Research Ethics: A Tribute to John C. Fletcher," and their constructive criticisms, which appear in this issue of *The Journal of Clinical Ethics.* They raise several important issues that deserve much more systematic treatment than is possible in a brief reply. All three rightly criticize us for being dogmatic about informed consent to research in a way that runs contrary to the spirit of our tribute to John Fletcher; accordingly, we are grateful for being awakened from our own "dogmatic slumber."

Sreenivasan argues that the comprehension of research participants is not a necessary condition of valid informed consent to clinical trials and suggests that our assertion to the contrary is question-begging. On reflection, we think that he is correct about both of these points. Nevertheless, it is very important to recognize the limitations of his account of informed consent to clinical trials, as spelled out more thoroughly in his *Lancet* article.[1] There, the claim that comprehension — specifically, the absence of a therapeutic misconception about research participation — is not necessary for valid consent to randomized controlled trials (RCTs) was premised on the condition that such RCTs have a *personally* favorable risk-benefit ratio for the research participants. An example would be a trial comparing two or more medically indicated treatments for a given disorder, as in the important, recently reported research comparing newer antipsychotic medications to an older antipsychotic medication in patients with schizophrenia — an example that is also relevant to Truog's commentary.[2]

We agree that with respect to a trial of this sort, Sreenivasan makes a persuasive case that defective comprehension — for example, in the form of a belief by a participant that she will be receiving antipsychotic medication based on a personalized medical judgment of what is best for her — would not invalidate her consent to participate. But it is essential to recognize that RCTs are heterogeneous in their ethically relevant features. Whether, for example, a therapeutic misconception is compatible with informed consent for RCTs that have a personally favorable risk-benefit ratio for all participants but include a placebo control is open to question. Moreover, consider placebo-controlled trials that withhold proven effective treatment. One of us (FGM) has argued elsewhere that such trials can be justified.[3] Although this is a controversial stance, assume for the sake of argument that it is correct. We would dispute that a strong therapeutic miscon-

ception about such a trial — for example, an RCT comparing a novel antidepressant agent to a placebo control — would be compatible with valid informed consent. When participants are placed at a predictable prospect of disadvantage in a given RCT, as compared with standard medical care, then some minimal level of comprehension of key features of trial design (such as randomization and the use of placebo controls) is necessary for valid informed consent. Defense of this claim would require detailed discussion. The point of making it here, however, is simply to show that because comprehension is not a necessary condition of valid consent for *all* RCTs, it doesn't follow that comprehension is never required for valid consent. We suggest that an adequate account of valid consent to clinical research requires the type of careful and systematic contextual analysis exemplified by Alan Wertheimer in his *Consent to Sexual Relations*.[4]

Evans's commentary raises some deep issues, especially how to think about voluntariness as it relates to enrolling in clinical research. He correctly notes that his argument would not elide voluntary participation to equipoise-satisfying RCTs, but would make nonparticipation come at "an unusually high price." This seems to us to be a price too high to pay; however, a critique of Evans's position, and other recent comparable arguments,[5] would merit a paper of its own. We confine our reply to only a couple points.

Evans describes the way we distinguish between clinical research and medical care solely as one of different aims of the two activities. And he is right to suggest that different aims, by themselves, don't entail different ethical standards. However, as our discussion indicated, the distinction is also a matter of characteristic methods — RCTs contain procedures such as randomization, placebo controls, and masking of treatment, which are foreign to medical care — and, most importantly, the justification of risks; RCTs, unlike medical care, typically contain procedures that pose some risk or burden to participants that are not justified by the compensating prospect of medical benefit to them. This trio of differences calls for different ethical principles governing clinical research as compared with medical care.[6]

Evans is mistaken in his belief that whenever clinical equipoise obtains, there is no ethically significant difference between research participation and receiving standard medical care, that enrollment in RCTs "*aligns with* medical therapy." Here it is sufficient to point out a counter-example. Consider the following case of an RCT of antibiotic treatment for chronic Lyme disease.[7] Prior to the trial, patients with chronic Lyme disease often were being treated with prolonged parenteral antibiotic therapy without any rigorous evidence to support its efficacy. Given the lack of evidence-based treatment for this condition, a placebo-controlled trial of antibiotic treatment would be consistent with clinical equipoise. The trial involved randomizing patients either to intravenous antibiotic therapy for 30 days, followed by 60 days of oral antibiotic treatment, or to intravenous dextrose followed by pill placebo. All the participants received a lumbar puncture to satisfy eligibility criteria for the trial and to characterize the study population. Placement of intravenous placebo is not without risk or burden. (Patients were monitored by home visits from study nurses every two days during the intravenous treatment phase.) Similarly, lumbar puncture is an invasive procedure that carries a risk of prolonged headache. Although clinical equipoise was satisfied and maintained during the trial, the participants all received lumbar punctures that were not justified on medical grounds, and those in the placebo arm got a sham invasive intervention without medical justification. Accordingly, equipoise-satisfying trials can present participants with significant risks and burdens that they would not undergo in receiving standard medical care. The same point can be made about trials comparing two cancer chemotherapy regimens when the research requires a biopsy, which is not medically indicated, to measure study outcomes. We have described the Lyme disease trial at some length to reinforce the thesis in our article that careful attention to methodological and contextual features of clinical research is vital to ethical analysis in this domain.

Truog accuses us of being dogmatic about the *priority* of informed consent. We made clear at the outset of our all-too-brief discussion of informed consent that this norm is only one of several ethical requirements; that it is not the "cornerstone" of research ethics, and not necessarily the most important ethical requirement. We would add that informed consent is neither necessary nor sufficient for ethical clinical research.[8] There is a range of legitimate situations in which informed consent to clinical trials can be waived, including emergency research. When specifying this range, however (as in bioethics in general), the devil is in the details.

We have no qualms with waiving informed consent for the example that Truog develops in his commentary. How could it really matter to patients which of two standard soaps is used to scrub their surgical wound when it is not known whether one might be more effective than another? It gets more tricky in the case of RCTs evaluating two or more medically indicated treatments. Consider, here, the recent RCT, mentioned above, comparing newer antipsychotic drugs to an older-line drug.[9] Would this satisfy the conditions that Truog specifies, such that informed consent to research participation, arguably, is not required? The key condition in question would be item number 4 in Truog's article — that no reasonable person would have a preference for one arm over the other. It is not clear whether this would apply to the antipsychotic RCT. None of the drugs under investigation previously had been shown to be superior in efficacy to any of the others. All the drugs have disturbing side-effects and are difficult to tolerate; however, the side-effects are different. Perhaps, then, reasonable persons informed about the known side-effect profiles of these drugs might prefer one arm of the trial over another. But let's assume for the sake of argument that this trial meets all of the requisite conditions. Nevertheless, why should we waive informed consent? Might reasonable persons want to know that they are participating in an experiment rather than merely receiving standard medical care, and that the drug they are getting is being selected, not because it is thought that it might be best for them? (We suggest that the reasonable person is more likely to care about being enrolled in an RCT comparing two pharmacologic treatments than one comparing two types of soap.) If conducting a valuable RCT with informed consent would not be feasible, as Truog indicates in his two-soap case, then this might be a valid reason to weigh in the balance in judging whether this sort of treatment trial should go forward without informed consent. But, certainly, obtaining informed consent for head-to-head trials of medically indicated treatments is not impossible or generally unfeasible, although it does add some burden of time and expense. We believe that the informed consent waiver advocated by Truog and his colleagues, which we do regard as a salutary challenge to thinking about the value of informed consent in clinical research, would only justifiably apply to a narrow range of cases. There remains to be considered, moreover, a slippery-slope risk that making an exception for these legitimate cases will lead to an erosion of standards of informed consent for a wider range of trials.

Finally, we would like to endorse the sentiments about John Fletcher expressed by Truog at the beginning of his commentary. We imagine that Fletcher would have enjoyed this colloquy about informed consent and the ethics of clinical research and would have urged all of us to get to work to do a better job in thinking through these issues.

DISCLAIMER

The opinions expressed are those of the second author (FGM) and do not necessarily reflect the position or policy of the National Institutes of Health, the Public Health Service, or the Department of Health and Human Services.

NOTES

1. G. Sreenivasan, "Does Informed Consent to Research Require Comprehension?" *Lancet* 362 (2003): 2016-8.

2. J.A. Lieberman et al., "Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia," *New England Journal of Medicine* 353 (2005): 1209-23.

3. F.G. Miller, "Placebo-controlled Trials in Psychiatric Research: An Ethical Perspective," *Biological Psychiatry* 47 (2000): 707-16; E.J. Emanuel and F.G. Miller, "The Ethics of Placebo-controlled Trials — a Middle Ground," *New England Journal of Medicine* 345 (2001): 915-9; F.G. Miller and H. Brody, "What Makes Placebo-controlled Trials Unethical?" *American Journal of Bioethics* 2, no. 2 (2002): 3-9.

4. A. Wertheimer, *Consent to Sexual Relations* (New York: Cambridge University Press, 2003).

5. D. Orentlicher, "Making Research a Requirement of Treatment: Why We Should Sometimes Let Doctors Pressure Patients to Participate in Research," *Hastings Center Report* 35, no. 5 (2005): 20-8.

6. F.G. Miller and D.L. Rosenstein, "The Therapeutic Orientation to Clinical Trials," *New England Journal of Medicine* 348 (2003): 1383-6; F.G. Miller and H. Brody, "A Critique of Clinical Equipoise: Therapeutic Misconception in the Ethics of Clinical Trials," *Hastings Center Report* 33, no. 3 (2003): 19-28.

7. M.S. Klempner et al., "Two Controlled Trials of Antibiotic Treatment in Patients with Persistent Symptoms and a History of Lyme Disease," *New England Journal of Medicine* 345 (2001): 85-92.

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

9. See note 2 above.