Virtual Mentor
American Medical Association Journal of Ethics
April 2014, Volume 16, Number 4: 289-294.

MEDICINE AND SOCIETY

Consent and Rights in Comparative Effectiveness Trials

Collin O'Neil, PhD

Since the FDA usually requires only that a new treatment be proven superior to placebo for approval, physicians must often choose between two or more approved therapies for a given condition without good evidence to guide them. Comparative effectiveness research on existing treatments has the potential to rectify this situation, and randomized controlled trials are often the most reliable method of determining the relative merits of different treatments. Although nothing experimental is administered to the patients in a randomized controlled trial comparing approved therapies, such a trial still counts as human subjects research and is covered by the federal regulations governing such research. These regulations, known as the "Common Rule," require that institutional review boards (IRBs) review these trials to ensure that the rights and interests of the subjects are adequately protected. In particular, IRBs are charged with ensuring that the researchers obtain consent to participation in research from the subjects [1].

Some commentators have identified these trials as an area of low-risk research that is overburdened by the current regulations. The most provocative recommendation they have made is that, in at least the most innocuous of these trials, the regulations should no longer require researchers to obtain explicit consent for research from the patients [2-5]. Underlying this recommendation is a moral claim, namely, that even though the subjects are involved in research, the consent obtained in ordinary clinical practice suffices for respecting the rights of the subjects against the interventions in these trials. On one interpretation these commentators are merely claiming that, so long as the health care system adequately publicizes the fact that treatment within the system will be offered in the context of randomized controlled trials, the physicians themselves need not disclose to patients that they are involved in research. My criticism will be directed against the more radical interpretation of the recommendation, namely, that in at least some of these trials the research purpose need not be disclosed to the patients at all [6-8].

I will begin by examining two rights-based reasons for disclosing the research purpose in these trials. The first is that, unless the patients are made aware of the research purpose, they are liable to be mistaken about the risks and benefits of the interventions because they differ from what one would expect to receive in clinical care. The second, more broadly applicable reason is that, even when there is no difference between the risks and benefits of the trial interventions and those of clinical care, unless the research purpose is disclosed, the trial may enroll some patients who have objections to serving particular research purposes or to

participating in research altogether. Both rationales for disclosing the research purpose are concerned with avoiding the same danger, namely, that patients may be accepting interventions they would not have accepted had they been more fully informed and that, consequently, their rights are infringed despite their consent. But there may be RCTs that avoid this danger without disclosing the research purpose, and neither of these two rationales would apply in such cases. I will sketch a new rights-based argument that requires disclosing the research purpose in all RCTs, even when there is no danger that the patients would not have accepted the interventions had they been informed of the research purpose [9].

Consent Based on Ignorance or Mistake about the Risks and Benefits

The kind of trial at issue is a randomized controlled trial (RCT) designed to evaluate the relative merits of two FDA-approved treatments, X and Y. In such a trial the physician recommends X to the patient, not because he or she believes it is better than Y for the patient, but because this is what the randomizing device instructs. The physician follows this instruction for the purpose of generating information of benefit to future patients.

Treatment X is an intervention, and it is widely acknowledged that people have a moral right against being intervened upon, a right against physical interference. This does not mean of course that physicians may never administer interventions. The patient may waive his or her right against being intervened upon by giving consent: the function of consent is to waive rights. But it is a familiar point that consent is not always successful in waiving whatever right needs to be waived—i.e., that consent is not always "valid." One reason consent may be invalid is that it is *based* on ignorance or mistake about the intervention; if the patient had been better informed, he or she would not have consented to it. One argument for disclosing the research purpose in at least certain RCTs is that, unless it is disclosed, there is a danger that the patients' consent to the interventions will be based on a mistaken assessment of the relevant risks and benefits.

Patients have different expectations of clinical care than of research participation. Among other things, a patient expects of clinical care that (a) any interventions the physician proposes will be necessary for her care, and (b) if there is more than one proven treatment for her condition and the physician believes one would be better for her than the other, the physician will recommend the treatment she believes to be superior. Clinical trials sometimes disappoint these expectations. They may, unlike standard clinical care, include nontherapeutic interventions, such as blood draws conducted for purely research purposes, disappointing (a). And a trial may assign a patient a treatment at random even when the physician believes one treatment would be better for the patient, disappointing (b). Although, in the kind of trial under consideration, X and Y are both approved treatments and neither has been proven superior to the other, a physician might still have reason to believe that one would be more effective for a patient or that a patient might find the side-effect profile of one more acceptable. If the patient is to contribute meaningful data to the study,

however, the treatment cannot be assigned on the basis of what the physician or the patient might prefer, but must be assigned randomly [10].

If a patient consents to a nontherapeutic blood draw under the false impression that it is necessary for her care, she is significantly mistaken about its risks and benefits and, insofar as her consent is based on this mistake, her consent is invalid. Since X is, unlike the blood draw, a proven treatment, she may not be mistaken about its risks and benefits. But her consent to X may be based on the mistaken belief that, since the physician only recommended X, there must not be any alternative treatment available that in the physician's judgment would be better for her or might be more acceptable to her. In theory, a patient could understand how these clinical care expectations are disappointed without knowing why. But it would be far easier for her to comprehend these deviations if the research purpose underlying them were disclosed.

Consent Based on Ignorance or Mistake about the Purpose Underlying the Intervention

The reason just given for disclosing the research purpose applies only when the trial violates the clinical care expectations mentioned above. But some RCTs will not violate those expectations. Consider a trial that involves no nontherapeutic interventions and that enrolls patients only with the physician's assent, so that patients are randomized only when the physician is truly indifferent between X and Y. Assume as well that X and Y do not differ along any dimensions, such as side-effect profiles, that might give a patient reason to prefer one or the other. In this case, ignorance of the underlying research purpose would not lead to mistakes about the risks and benefits of the interventions relative to clinical care. Is there still a danger of invalid consent if the research purpose is not disclosed?

The fact that in accepting the treatment the patient would thereby be contributing to a research goal is in itself a departure from clinical care. The research purpose may not cause the risks and benefits to differ from those of clinical care, but some patients might have conscientious objections to playing a role in promoting particular types of research goals. Other patients might be inclined to refuse to consent to the treatment if they knew there was a research purpose underlying the assignment just because they are suspicious of research and fear that their interests will be compromised. Even if these fears are unwarranted and they would in no respect be better off receiving standard clinical care, it would still be true of these patients that, had they been informed of the research purpose, they would not have consented.

Certainly the most reliable way to ensure that no patients who would refuse to participate if they were informed that it was research are enrolled in the trial is to disclose the research purpose to everyone. But when the goal of the research is uncontroversial, as it is in these RCTs comparing two FDA-approved drugs, conscientious objections would be unlikely. Mistrust of research may be more common, but there might, at least in principle, be other means adequate to ensure that patients who mistrust research are not enrolled in the trial, e.g., careful subject

selection. Let's suppose, for the sake of argument, that the researchers can somehow be sure that none of the patients enrolled in the trial would have refused the interventions had they been made aware of the research purpose. Although such patients are ignorant of the research purpose, their consent to the interventions is not *due* to this ignorance. In such an idealized situation, would there still be any rights-based reason to disclose the research purpose to the patients?

Consent In Ignorance of the Right that Needs to be Waived

To successfully waive a right against an intervention, the consent to the intervention must not be based on ignorance or mistake. But more is required. To waive a particular right via consent, it must be waived intentionally. This means that one must know which right or rights one needs to waive. Even if one would have attempted to waive a certain right had one known it was the right one needed to waive, so that one's consent is not *based* on ignorance of which right one needs to waive, that right is not waived unless one actually attempts to waive it and not some other right.

So it is important to ask: which right or rights does a participant in an RCT need to waive? The patient knows that X is a bodily intervention, and so knows that the right against physical interference is the general kind of right she needs to waive. But we possess a variety of distinct rights against bodily interventions, such as a right against unintended interventions and (much stronger) rights against intended interventions. Within the class of rights against intended interventions, there is another significant division. We have rights against interventions that are intended for our own benefit and rights against interventions intended for the benefit of others. These are not merely different specifications of one general right against physical interference. These are distinct rights, with distinct (though partly overlapping) rationales. We mark the infringement of the distinct right against interventions intended for the benefit of others by saying that the person subject to the intervention was "used" or "exploited," not merely that they were interfered with.

When a physician proposes to administer a blood draw for purely research purposes to a patient, this is an especially clear case in which the right against interventions intended for the benefit of others needs to be waived. But even when an intervention is a treatment, as X is, this same right needs to be waived when the reason one treatment is administered rather than another is in order to achieve a research purpose, as in RCTs. To waive this right via consent, patients must know that this is the right they need to waive, something they can know only if they know that there is a research purpose behind the choice of intervention. Thus, on pain of failing to respect the patients' rights, research consent must be obtained even in those RCTs in which there is no reason to believe that, if patients were made aware of the underlying research purpose, they would not have consented to the intervention [11]. Explicit consent to treatment plus merely presumed consent to research does not suffice to waive the right against being intervened upon for the benefit of others, because successfully waiving this distinct right requires actually knowing that it is the right one needs to waive.

References

1. General requirements for informed consent. 45 CFR section 46.116.
2. Truog RD, Robinson W, Randolph A, Morris A. Is informed consent always necessary for randomized, controlled trials? *New Engl J Med.* 1999;340(10):804-807.
3. Largent EA, Joffe S, Miller FG. Can research and care be ethically integrated? *Hastings Cent Rep.* 2011;41(4):37-46.
4. Faden R, Kass NE, Goodman SN, Pronovost P, Tunis S, Beauchamp TL. An ethics framework for a learning health care system: a departure from traditional research ethics and clinical ethics. ethical oversight of learning health care systems. *Hastings Cent Rep*. 2013;43(1):S16-S27.
5. Faden R, Kass N, Whicher D, Stewart W, Tunis S. Ethics and informed consent for comparative effectiveness research with prospective electronic clinical data. *Med Care.* 2013;51(8 Suppl 3):S53-S57.
6. For some other criticisms, see Fried C. *Medical Experimentation: Personal Integrity and Social Policy.* New York, NY: Elsevier; 1974.
7. Menikoff J. The unbelievable rightness of being in clinical trials. ethical oversight of learning health care systems. *Hastings Cent Rep.* 2013;43(1):S30-S31.
8. Brody H, Miller FG. The research-clinical practice distinction, learning health systems, and relationships. *Hastings Cent Rep.* 2013;43(5):41-47.
9. I will not be arguing that randomization must be understood. See Wendler D. Must research participants understand randomization? *Am J Bioethics.* 2009;9(2):3-8.
10. Even when an individual investigator has reason to believe X or Y would be better for a particular patient or even patients in general, randomization will still satisfy Benjamin Freedman's version of the clinical equipoise requirement provided there is a lack of consensus within the expert community regarding the relative merits of X and Y. See Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med*. 1987;317(3):141-145.
11. It is important to note that this argument for obtaining research consent in RCTs does not extend to all research. Consider research that merely collects data on the outcomes of clinical care that is not itself motivated by a research purpose. Although the patients are contributing to research, their right against being intervened upon for the benefit of others does not need to be waived, since the only interventions that are performed on them are for their own benefit, not for the benefit of others. The same is true of research on samples or specimens that were originally extracted for therapeutic purposes. Again, the subjects are contributing to research, but it is only their samples that are being used, not the patients themselves. If patients had a right not to contribute to research purposes, even indirectly, then research consent would be required in these cases as well. But I do not believe they possess such a right, although I will not argue for this here. (This is not to say that there are no other rights that might need to be waived in research on medical records and stored samples.)

Collin O'Neil, PhD, is an assistant professor and faculty fellow at the New York University Center for Bioethics. He was previously a bioethicist at the National Institutes of Health (NIH) Division of AIDS and a postdoctoral fellow in the Department of Bioethics at the NIH Clinical Center.

Related in VM

The AMA *Code of Medical Ethics*' Opinions on Physicians' Participation in Clinical Research, April 2014

Should Participation in Vaccine Clinical Trials be Mandated? January 2012

Conducting Clinical Research during Disasters, September 2010

Helping Patients Decide Whether to Participate in Clinical Trials, January 2007