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1. Lahita R, Kluger J, Drayer DE, Koffler D, Reidenberg MM. Antibodies to nuclear antigens in patients treated with procainamide or acetylprocainamide. *N Engl J Med* 1979;301:1382-5.

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## Correspondence



### Is Informed Consent Always Necessary for Randomized, Controlled Trials?

*To the Editor:* Truog et al. (March 11 issue)<sup>1</sup> propose expanding the categories of research for which institutional review boards could waive the requirement for obtaining informed consent beyond the categories currently allowed under applicable federal regulations. Such a proposal would allow investigators to ignore the central bioethical principle of respect for persons on which informed consent is grounded. The authors fail to marshal a persuasive argument for violating this basic tenet of research ethics with regard to human subjects.

Truog et al. begin their argument by observing that many physicians rely on "general" informed consent, rather than "specific" informed consent, when using innovative approaches to the clinical care of individual patients. By inference, they argue that general informed consent should also suffice for certain randomized, controlled trials comparing treatments that do "not involve more than minimal additional risk in comparison with any of the alternatives." Their reasoning has two major flaws.

First, in many cases, general informed consent is inadequate for innovative clinical interventions. In such cases, physicians should provide (and most conscientious physicians do provide) the patient or the patient's representative with additional information, including a description of the proposed innovative intervention, the reasonably foreseeable risks and discomforts associated with the intervention, its expected benefits, and available alternative therapies, thus obtaining specific informed consent. Second,

whereas general informed consent establishes a fiduciary relationship between an individual patient and a physician, this fiduciary relationship does not extend to the relationship between a researcher and a subject.

One of the authors' proposed new criteria for allowing the waiver of informed consent is that "no reasonable person should have a preference for one treatment over another, regardless of the differences between the treatments being compared." Truog et al. appear to ignore the assumption that most reasonable people would insist on specific informed consent for research and would view a waiver of their consent as a violation of their basic rights, except in a limited number of circumstances. In addition, the principle of respect for persons does not rely on a reasonable-person standard, but instead refers the decision about whether to participate to the individual prospective subject.

In support of their argument, Truog et al. state, "Studies have shown that patients rarely demonstrate an adequate understanding of consent forms and often do not even understand the meaning or implications of randomization." These observations merely emphasize the need to improve the procedures for obtaining informed consent to ensure that subjects understand all pertinent aspects of a research protocol before enrollment.

For many of the types of research described by the authors, obtaining informed consent from each of the subjects would not appear to be a major impediment to conducting the research. Indeed, in accordance with the authors' own criteria, most people would not have a preference for one treatment over any others being studied. Therefore, most prospective subjects approached during the consent process would probably agree to participate in such trials. For those who did not agree to participate, the consent process would have respected and protected their rights.

Under the Common Rule in the Code of Federal Regulations,<sup>2</sup> institutional review boards can waive or alter the requirement for obtaining informed consent when the following criteria are met: "(1) the research involves no more than minimal risk to the subjects; (2) the waiver or alteration will not adversely affect the rights and welfare of the

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subjects; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation." Truog et al. have failed to present a sound argument for changing these criteria.

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1. Truog RD, Robinson W, Randolph A, Morris A. Is informed consent always necessary for randomized, controlled trials? *N Engl J Med* 1999; 340:804-7.
2. 45 C.F.R. §46 (Protection of Human Subjects). (Rev. June 18, 1991.)

*To the Editor:* The article by Truog et al. is based on a false premise. The authors claim that there is a distinction between "general" and "specific" informed consent and between informed consent for "therapeutic" innovations and informed consent for "research." These dichotomies are both false and dangerous. Modern informed consent is meant to safeguard the patient's interest in decision-making autonomy (liberty) and respect for persons and their dignity.<sup>1</sup> There is only one standard for informed consent: consent that is voluntary, competent, informed, and based on understanding.<sup>2</sup> The doctrine is meant to empower patients to make decisions and has nothing to do with making things easier for physicians and researchers.

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1. Annas GJ. Questing for grails: duplicity, betrayal and self-deception in postmodern medical research. *J Contemp Health Law Policy* 1996;12:297-324.
2. Katz J. The consent principle of the Nuremberg Code: its significance then and now. In: Annas GJ, Grodin MA, eds. *The Nazi doctors and the Nuremberg Code: human rights in human experimentation*. New York: Oxford University Press, 1992:227-39.

*To the Editor:* Truog et al. rely on the reasonable-person standard to determine whether persons should be informed about becoming subjects in a randomized, controlled trial. This standard would require informing prospective subjects whenever enrollment in the trial would lead to additional tests, clinic visits, or other inconveniences beyond those associated with ordinary treatment. It would also support informing prospective subjects if the investigators planned to collect and maintain records of confidential information apart from the standard medical record.

Both these criteria are related to the broader issue of how the reasonable-person standard should be interpreted in the context of research. In the context of the law, the standard is usually interpreted by a jury of one's peers. Truog et al. suggest that an institutional review board can apply the standard to determine whether informed consent may be waived. But most boards are composed primarily of employees of the research institution, together with one or two members of the community. This group is not sufficiently representative to judge when a reason-

able person would want to be consulted about participation in a clinical trial. At a minimum, the decision about whether to waive informed consent should be made by a group that more closely resembles the population of prospective subjects.

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*To the Editor:* The argument by Truog et al. that informed consent should be waived for participants in certain types of randomized clinical trials is at striking variance with the current trend toward increasing the requirements for informed consent, even to obtain retrospective access to medical records for epidemiologic studies that have no influence whatsoever on the patient's medical care.

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*To the Editor:* Truog et al. suggest that institutional review boards be responsible for applying the criteria for a waiver of informed consent. At a time when the adequacy of the institutional-review-board system as a means of protecting the rights and welfare of subjects is being questioned,<sup>1</sup> proposing criteria that allow more discretion to institutional review boards and place more burdens on them may not be prudent. In an effort to provide public notice, the authors suggest that institutions tell patients of their intention to use their standards governing the waiver of informed consent. Patients would then "have the opportunity to seek care elsewhere." But such an opportunity may not exist for many patients, either because of economic constraints or because their choice of care is restricted by their managed-care plans.

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1. Office of Inspector General. *Institutional review boards: a time for reform*. Washington, D.C.: Department of Health and Human Services, June 11, 1998.

*To the Editor:* The reasoning by Truog et al. recalls the beneficent paternalism that was common decades ago, when many physicians argued that informed consent did not apply to the research they did that involved their patients. Unfortunately, this reasoning survives, because as the authors note, informed consent is often neglected in treatment. Compounding this wrong fails to correct it.

An important purpose of informed consent, which the authors ignore, is to let subjects know they are subjects. In the proposed scenario, everyone knows but the subjects. How can this be justifiable? Even if there is no reason to prefer one intervention over another and even if there is only minimal risk, potential subjects may have valid reasons to want to decide whether they become subjects.

Another purpose of informed consent that Truog et al. ignore is "to encourage self-scrutiny by the physician-investigator."<sup>1</sup> If a researcher cannot adequately explain to potential subjects what the research is about and why it is important, why should patients or the public be satisfied with skipping the explanation? Justifying research to the institutional review board is not the same as, and cannot substitute for, informed decision making by patients about their participation in research.

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1. Capron AM. Informed consent in catastrophic disease research and treatment. *U Penn Law Rev* 1974;123:341-438.

*To the Editor:* The Council on Ethical and Judicial Affairs of the American Medical Association takes issue with the statement by Truog et al. that "physicians can do almost anything they want in the name of therapeutic innovation." Physicians must inform patients about the experimental nature of the treatments they propose, whether or not these treatments are used as part of a research protocol. The council has issued a policy on this matter, titled "Opinion 2.07: Clinical Investigation," which reads, in part:

In clinical investigation primarily for treatment . . . voluntary written consent must be obtained from the patient, or from the patient's legally authorized representative if the patient lacks the capacity to consent, following (a) disclosure that the physician intends to use an investigational drug or experimental procedure, (b) a reasonable explanation of the nature of the drug or procedure to be used, risks to be expected, and possible therapeutic benefits, (c) an offer to answer any inquiries concerning the drug or procedure, and (d) a disclosure of alternative drugs or procedures that may be available.<sup>1</sup>

Research trials raise issues not found in the treatment setting. Whereas patients who are given one of two drugs as part of a treatment regimen can easily have their physicians alter the dosage or switch to an alternative treatment, these options are unlikely to be available to patients participating in controlled research trials. Moreover, the public's distrust of research is likely to be exacerbated if patients believe that physicians can enroll them in studies without obtaining their consent. The only situation for which a waiver of informed consent is permissible in research (i.e., emergency conditions) is markedly different from the situation described by the authors, since informed consent can be obtained in the situation they describe.

Making research easier to conduct is laudable, but this goal should not be pursued at the expense of other important goals. We do not agree that the authors have made a strong enough argument for a waiver of informed consent. We believe that physicians have an ethical obligation to inform patients about enrollment in clinical trials.

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1. AMA Council on Ethical and Judicial Affairs. Code of medical ethics: current opinions with annotations. Chicago: American Medical Association, 1998:17-9.

The authors reply:

*To the Editor:* Most of the observations about our article are based on the assumption that a clear line can be drawn between clinical treatment and research. That such an assumption is widespread is not surprising, since an entire bureaucracy, from local institutional review boards to the Office for Protection from Research Risks at the National Institutes of Health, depends on the truth of the premise. We question this orthodoxy and suggest that there is instead a spectrum that extends from established, evidence-based interventions through unproved therapeutic innovations to formal, randomized clinical trials. Our point is that much of clinical practice defies an easy dichotomy between "treatment" and "research."

An analogy to our position is the story of the man who loses his watch on a dark street but chooses to look for it under the lamppost because the light is better there. The current approach is to insist on the most rigorous requirements for informed consent in randomized, controlled trials — not because these trials consistently pose the greatest threat to respect for the patient's autonomy but rather because this type of activity can easily be identified as "research" and thus subjected to institutional scrutiny.

Dresser expresses concern about the adequacy of a reasonable-person standard, since most institutional review boards have only one or two members from the community. We share this concern and strongly support her suggestion of greater community involvement, precisely because the purpose of having members from the community is to be sure that the interests of the community are adequately represented.

Carome argues that we ignore the central principle of respect for persons. We propose not to ignore this principle but to balance its influence against other forces shaping our decisions. He does acknowledge that there are "a limited number of circumstances" in which patients would be willing to waive their consent. We agree.

Grodin differs from the other critics by agreeing with us that the requirements for informed consent are not linked to whether the interventions are labeled as "research" or "therapy." Unless he is implying that specific and detailed informed consent be obtained for every intervention, from routine laboratory testing to each medication prescribed, however, we interpret his letter as implying that the nature of the consent required is linked to the nature of the interventions under consideration. This is exactly our point, and it leads to the recommendations that we outlined.

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