Sounding Board

IS INFORMED CONSENT ALWAYS NECESSARY FOR RANDOMIZED, CONTROLLED TRIALS?

CONSIDER this paradox: if a physician reads a case report about a novel method of ventilation for critically ill patients and wants to try it in the next several patients with respiratory failure he or she treats, the physician may do so provided the patients have given general consent for treatment. On the other hand, if a physician is interested in performing a randomized, controlled trial to determine rigorously which of two widely used antibiotics is more effective at treating bronchitis, he or she must prepare a formal protocol, obtain approval from the institutional review board, and seek written informed consent from potential participants. In each case, the physician is performing an experiment. In each case, there is uncertainty about the best way to treat the patient. Yet in the context of clinical care, the experiment can be done with virtually no external scrutiny, whereas in the context of a clinical trial, the experiment is prohibited unless substantial hurdles are overcome. This is true even when the experimental therapy (e.g., a promising but risky method of ventilation) involves risks that are unknown or substantially different from those of the alternatives.

To put it another way, physicians can do almost anything they want in the name of therapeutic innovation, but only if there is no attempt to gain systematic knowledge from the intervention. Or, to paraphrase Smithells, "I need permission to give a new drug to half my patients but not to give it to all of them."[1] In this article we argue that the current approach to informed consent is at least partially off target, in that patients are often "protected" from clinical trials under circumstances in which the risks associated with participation in the trial are virtually nil, but they receive no protection from physicians who want to experiment with new treatments in the name of therapeutic innovation.

The reasons for the current approach are not mysterious. In a simplistic sense, all medical interventions may be characterized as either therapy or research. Research differs from therapy in many important ways. The goal of research is to gain new knowledge, and any benefits from the research are reaped primarily by future patients. The aim of therapy is to benefit the patient at hand. These differences have predictably led to an elaborate process designed to protect patients involved in clinical trials, whereas minimal constraints are placed on physicians providing clinical care.

This emphasis on protecting subjects during research should not be surprising. Since the Nuremberg trials, society has been wary of the conflict of interest that is present in all research — that the interests of the current patient may be sacrificed to other interests, such as those of future patients or even those of the investigators. Indeed, the distrust of society seems justified, because even after the adoption of the Nuremberg Code[2] and the Declaration of Helsinki,[3,4] examples of abuse in the conduct of research have been documented throughout the world.[5]

An analysis of the goals of informed consent can provide insight into the paradox described above. Informed consent is either general or specific. A patient gives general informed consent for treatment as part of the process of establishing a fiduciary relationship with a physician. Specific informed consent is necessary whenever the proposed intervention involves a high risk–benefit ratio, either in an absolute sense or in comparison with the alternatives, or whenever the preferences or values of the patient are relevant to the decision at hand. The distinction between these two tiers of informed consent is illustrated by the fact that physicians typically order routine tests and prescribe standard medications under the general consent for treatment but obtain specific consent before undertaking a major diagnostic or therapeutic procedure, before prescribing a potentially toxic medication, or whenever a patient's values and preferences would be expected to have a substantial influence on the clinical course chosen.

We suggest that the obligation to seek specific consent for research should likewise depend on the risk–benefit ratios of the intervention and the alternatives as well as the degree to which the patient would be expected to have preferences about the various options for diagnosis or treatment that are under investigation. We believe that as with clinical care, in the case of many randomized, controlled trials, the patient's participation can and should be considered to be authorized by his or her general consent for treatment and that specific consent should not be required.

Consider, for example, a hypothetical trial comparing two similar cephalosporins for preoperative prophylaxis. Both are widely used, but they differ markedly in cost, and their comparative efficacy in preventing wound infections is unknown. If both drugs have been in use long enough that their side-effect profiles are known to be similar, patients are unlikely to prefer one medication over another; it is also unlikely that the process of obtaining specific consent would serve the patient in any meaningful way. Other examples of this type of study are a randomized trial to assess whether low-dose heparin increases the longevity of intraarterial catheters in the intensive care unit, a randomized trial of two brands of antacid to control gastric acidity, and a randomized comparison of two methods of mechanical ventilation to determine which method results in more rapid resumption of spontaneous, unassisted breathing. These hypothetical trials share several characteristics, which we have integrated into the following proposed criteria for determining whether the requirement of informed consent for a randomized, controlled trial can be waived.

First, informed consent should not be waived unless all the treatments offered in the trial could be offered outside the trial without the specific informed consent of the patient. This is often the case when a trial is comparing two therapies that are already in use or when an existing therapy or drug is being used for a new indication. In the hypothetical trials described above, the specific informed consent of the patient would thus not be required for any of the options being offered.

Second, the treatments should not involve more than minimal additional risk in comparison with any of the alternatives.[6] When the risks associated with each of the options are assumed to be similar, the patient could be treated outside the trial with any one of the interventions under study. Again, the examples we cited could meet this requirement. Of course, physicians would exclude a patient for a justifiable medical reason — for example, if the patient were known to be allergic to one of the medications being studied.

Third, genuine clinical equipoise must exist among the treatments. This state of balance is, of course, a general ethical requirement before a randomized, controlled study can be undertaken. There should be honest uncertainty about which treatment is superior.[7] If the informed consent of the patient is judged unnecessary, investigators have an even greater burden of proof to ensure clinical equipoise.

Fourth, no reasonable person should have a preference for one treatment over any other, regardless of the differences between the treatments being compared. This standard would cover not only the direct effects of the intervention being studied but also the indirect effects associated with research, such as whether the study would require extra visits to the clinic or other inconveniences.

Although the reasonable-person standard is widely used in the law, it is far from perfect.[8] For example, there is always the possibility that a patient may be unusual in ways that cannot be anticipated and that would lead the patient to have an unanticipated preference for one treatment over another. This problem arises with both general and specific informed consent, however, and cannot be addressed solely by demanding more rigorous standards for research.

The validity of the reasonable-person standard depends in large part on how it is implemented. We propose that studies for which a waiver of informed consent is requested should, like all other studies, be submitted to an institutional review board for review and approval. The institutional review board would therefore assume responsibility for applying the standard. Because an important function of the institutional review board is to ensure the involvement of the community through the representation of people without medical backgrounds, the board would be in the best position to apply the reasonable-person standard and to determine whether the informed-consent requirement could be waived.

How should the reasonable-person standard be applied with reference to the community in which the research is being performed? Since the abuses of the Tuskegee syphilis study, members of racial minority groups have been particularly sensitive to the implications of being involved in research without their consent.[9] Although we believe that exemptions to informed consent should be considered only when potential subjects would have no reason to decline participation, we recognize that for some the refusal to participate in research may not be related to the pertinent facts of a particular study but, rather, may be based on important historical and cultural issues of concern. Depending on the community and the context of the research, these issues may be grounds for insisting on specific informed consent for participation in the research.

Fifth, patients should be informed that the institution or clinical setting in which they are being treated uses the standards that we have described as guidelines for determining the need for specific instead of general informed consent. Thus, patients would have the opportunity to obtain additional information about the policy or to seek care elsewhere.

These criteria for the waiver of informed consent should be interpreted narrowly and applied conservatively. For example, a trial comparing a beta-blocker with an angiotensin-converting–enzyme inhibitor for treatment of hypertension should not be approved for a waiver of informed consent, because of the substantially different side effects of the two classes of drugs. Similarly, comparisons of medical treatments and surgical interventions should always require specific informed consent, even if the outcomes are presumed to be similar, because of the probable relevance of patients' preferences to the decision. Finally, specific informed consent should be required whenever a study compares therapies that involve a trade-off between efficacy and safety, as would be the case in a trial of the use of an anticoagulant to reduce the morbidity associated with strokes. This decision requires the balancing of benefits against qualitatively dissimilar risks, necessitating the involvement and specific consent of the patient.

Our arguments may also have important implications for studies that fall under the heading of quality improvement.[10] Consider, for example, a study that seeks to identify the more effective disinfectant hand soap by using one brand for patients in one hospital ward and a different brand for patients in another, with nosocomial infection rates as the outcome measure. The patients are to be randomly assigned to the wards. Should specific informed consent be sought from the patients enrolled in the study? If so, then what should be done if a patient chooses not to participate? (Should he or she be transferred to another ward, or should data not be collected on that patient?) Our criteria may be useful in determining the need for specific informed consent in a context such as this one.

Our arguments pull in two different directions. Greater respect for the autonomy of patients means that many experiments that are currently undertaken in the context of clinical care under the guise of therapeutic innovation should be subject to much greater scrutiny. Such a shift in thinking would have far-reaching consequences, from changing the way that surgeons approach consent for the use of new techniques in the operating room to altering the way that physicians prescribe drugs for indications for which they have not been approved by the Food and Drug Administration (FDA).

Yet we have argued that specific informed consent should not be mandatory for all randomized, controlled trials. Although this idea has been proposed before,[11-14] many will nevertheless find it objectionable. They may argue that it backtracks from crucial elements of human rights at a time when we need to be as vigilant as possible and that essential principles enunciated at Nuremberg and Helsinki must not be compromised under any circumstances. Furthermore, they may claim that informed consent is an essential protection against the exploitation of patients by research investigators. These are important objections.

In response, our proposal should serve as a reminder that the process of informed consent is not a goal or ideal in itself. Rather, informed consent is important because it is frequently essential for ensuring that the patient's right to self-determination is respected. Our proposal not only supports this important objective but also provides grounds for criticizing the inappropriate use of what are termed therapeutic innovations without the specific informed consent of the patient.

There is little evidence to support the claim that informed consent, as currently practiced, provides protection against the exploitation of patients in research. Studies have shown that patients rarely demonstrate an adequate understanding of consent forms[15-17] and often do not even understand the meaning or implications of randomization.[18,19] The most effective protection against exploitation comes not from the process of informed consent but, rather, from the careful oversight and scrutiny of conscientious institutional review boards. Boards that approve questionable studies on the assumption that the informed-consent process will protect research subjects against abuse abrogate their responsibility to defend patients against unethical research. Our proposal recognizes and emphasizes the essential role of institutional review boards in this regard.

In addition, there is a price that is paid when one insists on specific informed consent for all randomized, controlled trials. Many worthwhile studies will not be conducted if investigators are required to obtain specific informed consent. Many small but meaningful improvements in the quality of care will not occur if clinicians are forced to engage every patient in a dialogue about informed consent, especially when there is no reason to believe that the patient would have any preference regarding participation in the research. When unnecessary roadblocks prevent the easy evaluation of the comparative efficacy of new forms of technology and new interventions, these innovations tend to be adopted uncritically into practice.[20] And this result is unfortunate, given that many of them would probably be found worthless or even harmful if subjected to formal evaluation in a clinical trial.

These clinical and practical realities were recently acknowledged in the United States with regard to research under emergency conditions. For many years, research on emergency treatments was virtually paralyzed by the impossibility of obtaining informed consent from the subjects. For new therapies, such as the administration of hemoglobin substitutes in severe trauma and of thrombolytic agents in acute myocardial infarction, or new methods of performing cardiopulmonary resuscitation, systematic clinical trials could not be undertaken. In 1996, the FDA and the Department of Health and Human Services endorsed a waiver of informed consent for this type of research under certain clearly defined conditions. Although they acknowledged the importance of informed consent to medical practice, these agencies endorsed the waiver on the grounds that it would allow desperately ill patients access to new therapies and would result in important benefits to future patients.[21] The agencies recognized that without the waiver, this important work would never be done.[22]

We believe that the same rationale supports our proposal against the anticipated objections of those who prefer to see no exceptions made to the doctrine of informed consent. When benefits to society and to future patients can be gained without meaningfully compromising respect for patients' autonomy and without any serious increase in risk to those involved, blind insistence on informed consent is not only unnecessary, but also harmful.

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