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Problems of the Randomized Clinical Trial

As medicine has become increasingly scientific and less accepting of unsupported opinion or proof by anecdote, the randomized controlled clinical trial has become the standard technique for changing diagnostic or therapeutic methods. The use of this technique creates an ethical dilemma.^{1,2} Researchers participating in such studies are required to modify their ethical commitments to individual patients and do serious damage to the concept of the physician as a practicing, empathetic professional who is primarily concerned with each patient as an individual. Researchers using a randomized clinical trial can be described as physician-scientists, a term that expresses the tension between the two roles. The physician, by entering into a relationship with an individual patient, assumes certain obligations, including the commitment always to act in the patient's best interests. As Leon Kass has rightly maintained, "the physician must produce unswervingly the virtues of loyalty and fidelity to his patient."³ Though the ethical requirements of this relationship have been modified by legal obligations to report wounds of a suspicious nature and certain infectious diseases, these obligations in no way conflict with the central ethical obligation to act in the best interests of the patient medically. Instead, certain nonmedical interests of the patient are preempted by other social concerns.

The role of the scientist is quite different. The clinical scientist is concerned with answering questions — i.e., determining the validity of formally constructed hypotheses. Such scientific information, it is presumed, will benefit humanity in general. The clinical scientist's role has been well described by Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, who states the goals of the randomized clinical trial in these words: "It's not to deliver therapy. It's to answer a scientific question so

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that the drug can be available for everybody once you've established safety and efficacy."⁴ The demands of such a study can conflict in a number of ways with the physician's duty to minister to patients. The study may create a false dichotomy in the physician's opinions: according to the premise of the randomized clinical trial, the physician may only know or not know whether a proposed course of treatment represents an improvement; no middle position is permitted. What the physician thinks, suspects, believes, or has a hunch about is assigned to the "not knowing" category, because knowing is defined on the basis of an arbitrary but accepted statistical test performed in a randomized clinical trial. Thus, little credence is given to information accrued beforehand in other ways or to information accrued during the trial but without the required statistical degree of assurance that a difference is not due to chance. The randomized clinical trial also prevents the treatment technique from being modified on the basis of the growing knowledge of the physicians during their participation in the trial. Moreover, it limits access to the data as they are collected until specific milestones are achieved. This prevents physicians from profiting not only from their individual experience, but also from the collective experience of the other participants.

The randomized clinical trial requires doctors to act simultaneously as physicians and as scientists. This puts them in a difficult and sometimes untenable ethical position. The conflicting moral demands arising from the use of the randomized clinical trial reflect the classic conflict between rights-based moral theories and utilitarian ones. The first of these, which depend on the moral theory of Immanuel Kant (and seen more recently in neo-Kantian philosophers, such as John Rawls⁵), asserts that human beings, by virtue of their unique capacity for rational thought, are bearers of dignity. As such, they ought not to be treated merely as means to an end; rather, they must always be treated as ends in themselves. Utilitarianism, by contrast, defines what is right as the greatest good for the greatest number — that is, as social utility. This view, articulated by Jeremy Bentham and John Stuart Mill, requires that pleasures (understood broadly, to include such pleasures as health and well-being) and pains be added together. The morally correct act is the act that produces the most pleasure and the least pain overall.

A classic objection to the utilitarian position is that according to that theory, the distribution of pleasures and pains is of no moral consequence. This element of the theory severely restricts physicians from being utilitarians, or at least from following the theory's dictates. Physicians must care very deeply about the distribution of pain and pleasure, for they have entered into a relationship with one or a number of individual patients. They cannot be indifferent to whether it is these patients or others that suffer for the general benefit of society. Even though society might gain

from the suffering of a few, and even though the doctor might believe that such a benefit is worth a given patient's suffering (i.e., that utilitarianism is right in the particular case), the ethical obligation created by the covenant between doctor and patient requires the doctor to see the interests of the individual patient as primary and compelling. In essence, the doctor-patient relationship requires doctors to see their patients as bearers of rights who cannot be merely used for the greater good of humanity.

As Fauci has suggested,⁴ the randomized clinical trial routinely asks physicians to sacrifice the interests of their particular patients for the sake of the study and that of the information that it will make available for the benefit of society. This practice is ethically problematic. Consider first the initial formulation of a trial. In particular, consider the case of a disease for which there is no satisfactory therapy — for example, advanced cancer or the acquired immunodeficiency syndrome (AIDS). A new agent that promises more effectiveness is the subject of the study. The control group must be given either an unsatisfactory treatment or a placebo. Even though the therapeutic value of the new agent is unproved, if physicians think that it has promise, are they acting in the best interests of their patients in allowing them to be randomly assigned to the control group? Is persisting in such an assignment consistent with the specific commitments taken on in the doctor-patient relationship? As a result of interactions with patients with AIDS and their advocates, Merigan⁶ recently suggested modifications in the design of clinical trials that attempt to deal with the unsatisfactory treatment given to the control group. The view of such activists has been expressed by Rebecca Pringle Smith of Community Research Initiative in New York: "Even if you have a supply of compliant martyrs, trials must have some ethical validity."⁴

If the physician has no opinion about whether the new treatment is acceptable, then random assignment is ethically acceptable, but such lack of enthusiasm for the new treatment does not augur well for either the patient or the study. Alternatively, the treatment may show promise of beneficial results but also present a risk of undesirable complications. When the physician believes that the severity and likelihood of harm and good are evenly balanced, randomization may be ethically acceptable. If the physician has no preference for either treatment (is in a state of equipoise^{7,8}), then randomization is acceptable. If, however, he or she believes that the new treatment may be either more or less successful or more or less toxic, the use of randomization is not consistent with fidelity to the patient.

The argument usually used to justify randomization is that it provides, in essence, a critique of the usefulness of the physician's beliefs and opinions, those that have not yet been validated by a randomized clinical trial. As the argument goes, these not-yet-validated

beliefs are as likely to be wrong as right. Although physicians are ethically required to provide their patients with the best available treatment, there simply is no best treatment yet known.

The reply to this argument takes two forms. First, and most important, even if this view of the reliability of a physician's opinions is accurate, the ethical constraints of an individual doctor's relationship with a particular patient require the doctor to provide individual care. Although physicians must take pains to make clear the speculative nature of their views, they cannot withhold these views from the patient. The patient asks from the doctor both knowledge and judgment. The relationship established between them rightfully allows patients to ask for the judgment of their particular physicians, not merely that of the medical profession in general. Second, it may not be true, in fact, that the not-yet-validated beliefs of physicians are as likely to be wrong as right. The greater certainty obtained with a randomized clinical trial is beneficial, but that does not mean that a lesser degree of certainty is without value. Physicians can acquire knowledge through methods other than the randomized clinical trial. Such knowledge, acquired over time and less formally than is required in a randomized clinical trial, may be of great value to a patient.

Even if it is ethically acceptable to begin a study, one often forms an opinion during its course — especially in studies that are impossible to conduct in a truly double-blinded fashion — that makes it ethically problematic to continue. The inability to remain blinded usually occurs in studies of cancer or AIDS, for example, because the therapy is associated by nature with serious side effects. Trials attempt to restrict the physician's access to the data in order to prevent such unblinding. Such restrictions should make physicians eschew the trial, since their ability to act in the patient's best interests will be limited. Even supporters of randomized clinical trials, such as Merigan, agree that interim findings should be presented to patients to ensure that no one receives what seems an inferior treatment.⁶ Once physicians have formed a view about the new treatment, can they continue randomization? If random assignment is stopped, the study may be lost and the participation of the previous patients wasted. However, if physicians continue the randomization when they have a definite opinion about the efficacy of the experimental drug, they are not acting in accordance with the requirements of the doctor-patient relationship. Furthermore, as their opinion becomes more firm, stopping the randomization may not be enough. Physicians may be ethically required to treat the patients formerly placed in the control group with the therapy that now seems probably effective. To do so would be faithful to the obligations created by the doctor-patient relationship, but it would destroy the study.

To resolve this dilemma, one might suggest that the patient has abrogated the rights implicit in a doctor-

patient relationship by signing an informed-consent form. We argue that such rights cannot be waived or abrogated. They are inalienable. The right to be treated as an individual deserving the physician's best judgment and care, rather than to be used as a means to determine the best treatment for others, is inherent in every person. This right, based on the concept of dignity, cannot be waived. What of altruism, then? Is it not the patient's right to make a sacrifice for the general good? This question must be considered from both positions — that of the patient and that of the physician. Although patients may decide to waive this right, it is not consistent with the role of a physician to ask that they do so. In asking, the doctor acts as a scientist instead. The physician's role here is to propose what he or she believes is best medically for the specific patient, not to suggest participation in a study from which the patient cannot gain. Because the opportunity to help future patients is of potential value to a patient, some would say physicians should not deny it. Although this point has merit, it offers so many opportunities for abuse that we are extremely uncomfortable about accepting it. The responsibilities of physicians are much clearer; they are to minister to the current patient.

Moreover, even if patients could waive this right, it is questionable whether those with terminal illness would be truly able to give voluntary informed consent. Such patients are extremely dependent on both their physicians and the health care system. Aware of this dependence, physicians must not ask for consent, for in such cases the very asking breaches the doctor-patient relationship. Anxious to please their physicians, patients may have difficulty refusing to participate in the trial the physicians describe. The patients may perceive their refusal as damaging to the relationship, whether or not it is so. Such perceptions of coercion affect the decision. Informed-consent forms are difficult to understand, especially for patients under the stress of serious illness for which there is no satisfactory treatment. The forms are usually lengthy, somewhat legalistic, complicated, and confusing, and they hardly bespeak the compassion expected of the medical profession. It is important to remember that those who have studied the doctor-patient relationship have emphasized its empathetic nature.

[The] relationship between doctor and patient partakes of a peculiar intimacy. It presupposes on the part of the physician not only knowledge of his fellow men but sympathy. . . . This aspect of the practice of medicine has been designated as the art; yet I wonder whether it should not, most properly, be called the essence.⁹

How is such a view of the relationship consonant with random assignment and informed consent? The Physician's Oath of the World Medical Association affirms the primacy of the deontologic view of patients' rights: "Concern for the interests of the subject must always prevail over the interests of science and society."¹⁰

Furthermore, a single study is often not considered sufficient. Before a new form of therapy is generally accepted, confirmatory trials must be conducted. How can one conduct such trials ethically unless one is convinced that the first trial was in error? The ethical problems we have discussed are only exacerbated when a completed randomized clinical trial indicates that a given treatment is preferable. Even if the physician believes the initial trial was in error, the physician must indicate to the patient the full results of that trial.

The most common reply to the ethical arguments has been that the alternative is to return to the physician's intuition, to anecdotes, or to both as the basis of medical opinion. We all accept the dangers of such a practice. The argument states that we must therefore accept randomized, controlled clinical trials regardless of their ethical problems because of the great social benefit they make possible, and we salve our conscience with the knowledge that informed consent has been given. This returns us to the conflict between patients' rights and social utility. Some would argue that this tension can be resolved by placing a relative value on each. If the patient's right that is being compromised is not a fundamental right and the social gain is very great, then the study might be justified. When the right is fundamental, however, no amount of social gain, or almost none, will justify its sacrifice. Consider, for example, the experiments on humans done by physicians under the Nazi regime. All would agree that these are unacceptable regardless of the value of the scientific information gained. Some people go so far as to say that no use should be made of the results of those experiments because of the clearly unethical manner in which the data were collected. This extreme example may not seem relevant, but we believe that in its hyperbole it clarifies the fallacy of a utilitarian approach to the physician's relationship with the patient. To consider the utilitarian gain is consistent neither with the physician's role nor with the patient's rights.

It is fallacious to suggest that only the randomized clinical trial can provide valid information or that all information acquired by this technique is valid. Such experimental methods are intended to reduce error and bias and therefore reduce the uncertainty of the result. Uncertainty cannot be eliminated, however. The scientific method is based on increasing probabilities and increasingly refined approximations of truth.¹¹ Although the randomized clinical trial contributes to these ends, it is neither unique nor perfect. Other techniques may also be useful.¹²

Randomized trials often place physicians in the ethically intolerable position of choosing between the good of the patient and that of society. We urge that such situations be avoided and that other techniques of acquiring clinical information be adopted. For example, concerning trials of treatments for AIDS, Byar

et al.¹³ have said that "some traditional approaches to the clinical-trials process may be unnecessarily rigid and unsuitable for this disease." In this case, AIDS is not what is so different; rather, the difference is in the presence of AIDS activists, articulate spokespersons for the ethical problems created by the application of the randomized clinical trial to terminal illnesses. Such arguments are equally applicable to advanced cancer and other serious illnesses. Byar et al. agree that there are even circumstances in which uncontrolled clinical trials may be justified: when there is no effective treatment to use as a control, when the prognosis is uniformly poor, and when there is a reasonable expectation of benefit without excessive toxicity. These conditions are usually found in clinical trials of advanced cancer.

The purpose of the randomized clinical trial is to avoid the problems of observer bias and patient selection. It seems to us that techniques might be developed to deal with these issues in other ways. Randomized clinical trials deal with them in a cumbersome and heavy-handed manner, by requiring large numbers of patients in the hope that random assignment will balance the heterogeneous distribution of patients into the different groups. By observing known characteristics of patients, such as age and sex, and distributing them equally between groups, it is thought that unknown factors important in determining outcomes will also be distributed equally. Surely, other techniques can be developed to deal with both observer bias and patient selection. Prospective studies without randomization, but with the evaluation of patients by uninvolved third parties, should remove observer bias. Similar methods have been suggested by Royall.¹² Prospective matched-pair analysis, in which patients are treated in a manner consistent with their physician's views, ought to help ensure equivalence between the groups and thus mitigate the effect of patient selection, at least with regard to known covariates. With regard to unknown covariates, the security would rest, as in randomized trials, in the enrollment of large numbers of patients and in confirmatory studies. This method would not pose ethical difficulties, since patients would receive the treatment recommended by their physician. They would be included in the study by independent observers matching patients with respect to known characteristics, a process that would not affect patient care and that could be performed independently any number of times.

This brief discussion of alternatives to randomized clinical trials is sketchy and incomplete. We wish only to point out that there may be satisfactory alternatives, not to describe and evaluate them completely. Even if randomized clinical trials were much better than any alternative, however, the ethical dilemmas they present may put their use at variance with the primary obligations of the physician. In this regard,

Angell cautions, "If this commitment to the patient is attenuated, even for so good a cause as benefits to future patients, the implicit assumptions of the doctor-patient relationship are violated."¹⁴ The risk of such attenuation by the randomized trial is great. The AIDS activists have brought this dramatically to the attention of the academic medical community. Techniques appropriate to the laboratory may not be applicable to humans. We must develop and use alternative methods for acquiring clinical knowledge.

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CLINICAL TRIALS — ARE THEY ETHICAL?

BIOMEDICAL research leads to better understanding of biology and ultimately to improved health. Physicians have for millenniums attempted to understand disease, to use this knowledge to cure or palliate, and to relieve attendant suffering. Improving strategies for prevention and treatment remains an ethical imperative for medicine. Until very recently, progress depended largely on a process of carefully observing groups of patients given a new and promising therapy; outcome was then compared with that previously observed in groups undergoing a standard treatment. Outcome in a series of case patients as compared with that in nonrandomized controls can be used to assess the treatment of disorders in which therapeutic effects are dramatic and the pathophysiologic

features are relatively uncomplicated, such as vitamin deficiency or some infectious diseases. Observational methods are not very useful, however, in the detection of small treatment effects in disorders in which there is substantial variability in expected outcome and imperfect knowledge of complicated pathophysiologic features (many vascular disorders and most cancers, for example). The effect of a treatment cannot easily be extracted from variations in disease severity and the effects of concomitant treatments. Clinical trials have thus become a preferred means of evaluating an ever increasing flow of innovative diagnostic and therapeutic maneuvers. The randomized, double-blind clinical trial is a powerful technique because of the efficiency and credibility associated with treatment comparisons involving randomized concurrent controls.

The modern era of randomized trials began in the early 1950s with the evaluation of streptomycin in patients with tuberculosis.¹ Since that time trial techniques and methods have continuously been refined.² In addition, the ethical aspects of these experiments in patients have been actively discussed.³⁻⁷

In what follows I argue that randomized trials are in fact the most scientifically sound and ethically correct means of evaluating new therapies. There is potential conflict between the roles of physician and physician-scientist, and for this reason society has created mechanisms to ensure that the interests of individual patients are served should they elect to participate in a clinical trial.⁶

CLINICAL RESEARCH

The history of medicine is richly endowed with therapies that were widely used and then shown to be ineffective or frankly toxic. Relatively recent examples of such therapeutic maneuvers include gastric freezing for peptic ulcer disease, radiation therapy for acne, MER-29 (triparanol) for cholesterol reduction, and thalidomide for sedation in pregnant women. The 19th century was even more gruesome, with purging and bloodletting. The reasons for this march of folly are many and include, perhaps most importantly, the lack of complete understanding of human biology and pathophysiology, the use of observational methods coupled with the failure to appreciate substantial variability between patients in their response to illness and to therapy, and the shared desire of physicians and their patients for cure or palliation.

Chance or bias can result in the selection of patients for innovative treatment who are either the least diseased or the most severely affected. Depending on the case mix, a treatment that has no effect can appear to be effective or toxic when historical controls are used. With the improvement in diagnostic accuracy and the understanding of disease that has occurred with the passage of time, today's patients are identified earlier in the natural history of their disease: Recently select-