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Making Research a Requirement of Treatment

Why We Should Sometimes Let Doctors Pressure Patients to Participate in Research

by DAVID ORENTLICHER

When a patient could be offered one of multiple established treatments, doctors should be able to offer treatment only if the patient agrees to participate in research aimed at determining which of the treatments is most effective. Making treatment conditional on research participation will help researchers complete badly needed studies.

In recent years, a number of events have raised concerns about the adequacy of safeguards to protect people who volunteer for medical research. Individuals without a serious illness, like Jesse Gelsinger and Ellen Roche, have died unexpectedly while participating in clinical trials.¹ The federal Office for Human Research Protections temporarily halted studies at several major academic centers for their failure to observe research guidelines.² Overseas trials of HIV-therapy during pregnancy have been criticized for including a placebo control arm.³ For some studies, we must worry whether research subjects are placed at too great a risk by physicians seeking to advance medical knowledge.

At the same time, we must also question whether research safeguards are sometimes overly protective of people who might enter clinical trials. Progress in treating trauma patients, for example, was hampered for many years by the requirements of informed consent—seriously injured patients often lack the decision-making capacity necessary to agree to enrollment in a research trial, and family members may not be available to consent to the trial on their behalf. These difficulties in enrolling patients slowed the development of promising therapies—including more effective methods for cardiac resuscitation and substitutes for blood to transfuse patients who have suffered major blood loss.⁴ To address this problem, federal guidelines for informed consent were modified in 1996 to permit valuable research in the emergency setting.⁵

This article argues that just as there was a need to relax the requirements of informed consent for trauma research, there is a need to relax the precautions taken to ensure voluntary participation of subjects in

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another kind of research trial—studies involving the comparison of two or more established therapies to see whether one is superior to the alternative(s). For many medical problems, physicians can choose among multiple therapeutic options, and the choice is typically based more on hunch than on data. Patients would benefit greatly from studies that clarify the relative benefits and risks of different options for their illnesses.

However, these studies can be delayed—and medical progress impeded—by difficulties in securing the participation of enough individuals.⁶ In the AFFIRM study comparing the two leading therapies for chronic atrial fibrillation, for example, only fifty-five percent of patients invited to enroll in the study chose to do so.⁷ In a study of alternative therapies for some chronic lung diseases (including asthma and emphysema), more than half

Researchers and trial sponsors have employed a number of approaches to address the difficulties in recruiting patients for clinical trials. Some have employed more intensive recruitment practices, including notices on radio and television.¹² Others have taken their trials overseas, where recruitment is often easier.¹³ But these alternatives are either insufficiently effective¹⁴ or raise their own ethical concerns.¹⁵

This article argues on behalf of another way to increase patient enrollment in clinical trials: It should be permissible for a physician to condition a patient's access to treatment on the patient's willingness to enter a clinical trial when the trial compares two or more accepted therapies to find out whether they are equivalent or whether one is better than the others. That is, the physician should be able to offer treatment to the patient

Hypothetical Case Study

As an illustration of the concern with current standards for informed consent in research, consider the following hypothetical case study, which is based on an important, federally funded clinical trial.

The clinical trial was the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial.¹⁶ Sponsored by the National Heart, Lung, and Blood Institute, AFFIRM compared two established treatment strategies for persistent or recurrent atrial fibrillation to see if one offered either better outcomes or less adverse effects.¹⁷ In one strategy, physicians try to restore and maintain the atrium's normal sinus rhythm with cardioversion (the application of an electrical shock to jolt an abnormal heartbeat into a normal one) and antiarrhythmic drugs.¹⁸ This method is known as "rhythm control." Alternatively, physicians can try to control the response of the heart's ventricles to the atrial fibrillation by maintaining a good ventricular heart rate—a method known as "rate control." With this second strategy, physicians employ both drug and nonpharmacologic therapies.¹⁹ In the AFFIRM study, patients were randomized to receive one of the two treatment strategies, and the patients received their care from their current physician according to the study protocol's guidelines. Thus, while the patients were participating in a research trial, there was nothing experimental about their treatment. The only experimental part of the trial was the fact that a patient's own treatment strategy was chosen randomly. (Results from AFFIRM were published in December 2002, and they suggested that rate control has important advantages over rhythm control as a therapeutic option.²⁰)

Now assume one change in the trial. In the actual study, cardiologists invited patients with atrial fibrillation to enter the AFFIRM trial. Patients who chose to enroll were assigned to one of the treatment strategies ran-

If a patient did not want to participate, the cardiologist would decline to accept the patient for care or would end the patient-physician relationship and instruct the patient to obtain care from another cardiologist.

of the patients invited to participate in the study declined the invitation, with total recruitment taking twice as long as expected (sixteen months instead of eight months).⁸

Patients decline invitations to enroll for a number of reasons. Some people are uncomfortable with the idea of being part of a testing process, or with the possibility that which treatment they will receive will be decided randomly.⁹ Many of these patients are concerned that the physicians are more interested in the research study than in the patient's care.¹⁰ Patients also cite concerns about the burden of extra tests and appointments and the uncertainty of the consequences for their health from participation.¹¹

only in the setting of the clinical trial. Patients who declined to participate in the study would have to receive care from another physician.

Concerns about ensuring that patients participate in research truly voluntarily discourage or prevent physicians from employing such a measure. Conditioning treatment on a patient's willingness to enroll in a trial is thought to constitute unacceptable coercion. But in fact, linking treatment to participation in research could be a valuable and ethically sound way to increase patient participation, as long as the clinical trial involves a comparison of alternative, established therapies.

domly. If a patient declined enrollment, then the cardiologist provided one of the two treatment strategies according to the cardiologist's usual practice. But suppose instead that some cardiologists told their patients that they would treat the atrial fibrillation only if the patients enrolled in the study. If a patient did not want to participate in AFFIRM, the cardiologist would decline to accept the patient for care or would end the patient-physician relationship and instruct the patient to obtain care from another cardiologist. Participation in AFFIRM would have been a condition of receiving care from these cardiologists.

Before discussing the propriety of such a condition, a couple of explanatory points are in order. First, in the hypothetical trial, the informed consent process would remain generally unchanged. The patients would be given all of the information that normally is given before enrolling in a clinical trial, and the patient would have the freedom to give or withhold consent. The one difference with current practice is that a decision not to enroll in the trial would entail the need to find another physician for care.

Second, the point of using AFFIRM as an example is to present a clinical trial in which patients are randomized between or among alternative treatments, when (1) each of the therapies is well accepted for treating patients (that is, none of the alternatives is considered "experimental" or substandard therapy)²¹ and (2) data are lacking as to how the therapies compare in their ability to treat the patients' disease. As a corollary, there should be genuine uncertainty as to whether any of the treatments is superior or inferior to the others (a condition known as "clinical equipoise"²²). Many trials would meet these criteria. For example, a study comparing two or more established drugs for arthritis might be conducted. Similarly, researchers might want to compare different drugs used to lower cholesterol,

reduce blood pressure, ameliorate depression, or limit the damage from a heart attack.

The condition that none of the alternatives be "experimental" makes the proposal in this article more cautious than a new policy of the Centers for Medicare & Medicaid Services. That policy links Medicare coverage to patient participation in research trials. CMS designed the policy to systematically determine when Medicare should cover new and expensive treatments or diagnostic tests. For example, coverage for new uses of approved anticancer drugs has been conditioned on the willingness of patients to enroll in a clinical trial sponsored by the National Cancer Institute. But the CMS policy affects research on tests or treatments whose efficacy has not been established for the patients being studied.²³

Today's Research Guidelines

Under current practice, it is highly unlikely that approval would be given to a study in which physicians made participation in the study a condition for receiving treatment. Studies that involve testing or observation of people must be authorized by an institutional review board (IRB), a committee that reviews the proposed study and considers whether it meets ethical standards for medical research. For example, an IRB would analyze the proposal to ensure that participation in the study is voluntary and that the health of the volunteers is not placed at too great a risk.²⁴ For a study conditioning treatment on participation in research, IRBs would be concerned that potential subjects would be coerced into enrolling in the trial—that a decision to enroll would not be truly voluntary.

Whether IRBs would be *required* to reject the hypothetical protocol is uncertain. According to the federal rules governing research on human subjects, the informed consent process must include "a statement

that participation is voluntary, [that] refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and [that] the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled."²⁵

One could argue that enrollment would satisfy the federal requirement of voluntary participation—a patient could enter the trial or seek care from another cardiologist. Moreover, the patients would not be deprived of any benefits to which they were "otherwise entitled"—after all, a patient is not entitled to obtain treatment from any particular cardiologist. Rather, the patient-physician relationship is a contractual one, based on the mutual consent of patient and physician.²⁶

Alternatively, one might concede that physicians have no duty to take on a particular patient—that they need not have a good reason for denying care. However, physicians cannot deny care for bad reasons, and conditioning treatment on a willingness to participate in research might be considered a bad reason, just as denying care because of a patient's race or sex constitutes a bad, and therefore unacceptable, reason. Moreover, if a patient already was receiving care from a cardiologist, a refusal to continue treatment outside of the study would apparently constitute a penalty—a termination of care by the physician.

Still, even if a cardiologist ended an existing patient-physician relationship, one could say that no violation of federal research rules had occurred. Since physicians can end a patient-physician relationship with proper notice,²⁷ patients are not "otherwise entitled" to a particular physician's care.

International standards for research are also ambiguous but give more reason to reject the hypothetical protocol. According to the World Medical Association's Declaration of Helsinki, "the refusal of a patient to participate in a study must never interfere with the patient-physician re-

lationship.”²⁸ It might be said that if physicians are not obligated to enter into particular patient-physician relationships, then there is no “interference” when a physician declines to provide care. Yet withholding care if a patient refuses to enter a study appears to constitute interference.

The ethical guidelines of the Council for International Organizations of Medical Sciences (CIOMS) also suggest that the hypothetical protocol would be unacceptable. In the commentary to the guideline on obtaining informed consent, the CIOMS guidelines state:

Intimidation in any form invalidates informed consent. Prospects

would enroll in a clinical trial to avoid having health services withheld.

Whether or not the hypothetical version of AFFIRM would violate existing standards for medical research, physicians and IRBs currently would be very reluctant to make enrollment in a research trial a condition for receiving care. There would have to be a significant change in prevailing attitudes before the hypothetical version of AFFIRM could take place.

To be sure, one can point to a common example in which IRBs already permit researchers to link participation in a clinical trial to access to treatment: Many patients with cancer must agree to participate in a

Making a Change

Although current practices discourage conditioning treatment on participation in research, physicians could make a strong case for having the freedom to treat patients only in the setting of a clinical trial, when a study is comparing well-established therapies.

Eliminating unnecessary impediments to medical progress. When a physician chooses between multiple therapies without knowing which therapy offers the greatest benefit, the physician may be subjecting many patients to inferior treatment. The physician could use the different alternatives equally to ensure that at least some patients receive the best treatment, or the physician could make a best guess as to the most appropriate treatment, knowing that either all or none of the patients will receive the optimal therapy. (To be sure, with some conditions, one treatment might work best for some patients, while another treatment might work best for others. But there will still be uncertainty as to which patients do better with which treatments.)

The only way to ensure that all patients receive optimal therapy is to run a clinical trial comparing the alternatives. Moreover, the number who receive inferior treatment can be minimized by completing the trial rapidly. Physicians might therefore want to enroll all of their patients in a definitive study. If patients have the option of declining participation, the study could take much longer,³¹ as in the study of treatment for chronic lung disease for which recruitment took twice as long as expected.³²

Related to the interest in practicing medicine optimally is the interest in professional autonomy. Just as it is important for patients to have control over the decision of whether to accept health care, it is important for physicians to have control over whom they treat and how they treat them. Thus, it is well recognized by the law that the patient-physician re-

We might want to say that patients should be willing to participate in new trials. To put it another way, if people want to share in the benefits of their society, they arguably should share in its burdens, too.

tive subjects who are patients often depend for medical care upon the physician/researcher, who consequently has a certain credibility in their eyes, and whose influence over them may be considerable, particularly if the study protocol has a therapeutic component. They may fear, for example, that refusal to participate would damage the therapeutic relationship *or result in the withholding of health services*. The physician/investigator must assure them that their decision on whether to participate will not affect the therapeutic relationship or other benefits to which they are entitled²⁹

On the one hand, the guidelines speak of maintaining “benefits to which [patients] are entitled,” and patients are not entitled to care from any particular cardiologist. On the other hand, the commentary explicitly discusses the concern that patients

clinical trial as a condition of receiving care. A patient may be referred to a specialized cancer center for treatment and find that treatment at the center would entail enrollment in a research study. Indeed, about 70 percent of children with cancer receive at least some of their treatment through a clinical trial sponsored by the National Cancer Institute,³⁰ and in order to receive treatment at the National Institutes of Health Clinical Center, patients must agree to participate in medical research. An unwillingness to enroll would result in the patient returning for care to the patient’s treating physician. But the existence of this practice in oncology and other specialized areas does not change the fact that physicians typically would not decline to treat a patient outside of a research protocol if the patient refused to enroll in the physician’s clinical trial.

lationship is created only with the voluntary consent of both patient and physician,³³ and that physicians can choose the methods of surgery or the types of drugs they will employ.

Note that the kinds of studies this article suggests have a kinship with the practices of hospitals at academic medical centers.³⁴ Patients can choose care at a teaching hospital and accept the condition that medical students and residents will participate in their care, or they can decide to go elsewhere for their care and avoid treatment by students and residents. In other words, society already accepts the idea that patient participation in the achievement of an important social goal can sometimes be made a condition of patient access to medical care.

Encouraging more of a social sentiment in favor of participation in medical research. Today's patients benefit greatly from the medical discoveries of yesterday, and those discoveries would not have occurred without the willingness of previous generations of patients to volunteer for clinical trials. In return for the benefits of earlier research, we might want to say that patients should be willing to participate in new trials. To put it another way, if people want to share in the benefits of their society, they arguably should share in its burdens, too. Moreover, we might say, no one is *required* to accept the benefits of medical treatment. Indeed, patients enjoy a constitutional right to refuse medical treatment, even life-sustaining treatment. Whether to receive medical treatment remains an option. As an option, its receipt could be made conditional on the willingness of the patient to participate in medical research.

On the other hand, it is questionable whether yesterday's research subjects can by their altruism bind today's patients to similar acts of altruism.³⁵ Participation in medical research is a morally praiseworthy act, but it is ordinarily not a morally required act. The risks of experimental drugs or procedures can be substan-

tial, and substantial risks ought to be assumed only voluntarily. If society were to condition medical treatment on enrollment in clinical trials, we would effectively create a moral duty to participate in research. A voluntary, supererogatory act would be converted into an involuntary, obligatory act.

To be sure, we often impose social obligations on the grounds that they benefit everyone. Speed limits constrain my freedom when I drive, but they also ensure my safety.³⁶ Insisting that patients become research subjects, however, may entail a different kind of sacrifice—that of one's health or life. And our society rejects the idea that people should have to compromise their health for the sake of others.³⁷ Accordingly, we should hesitate to conclude that patients must assume the risks of medical research for the benefit of other persons.

This conclusion is reinforced by the potential consequences of creating duties to participate in medical research. If patients must become involved in medical research as a condition of receiving medical treatment, then some sick people will simply forgo treatment.

Although real duties to participate in medical research are problematic, the importance of medical research suggests that society can do more to encourage in people an inclination to participate in clinical trials. Encouraging more of a sentiment in favor of participation would be particularly appropriate when (1) the risks to the individual are minimal and (2) there is an opportunity for patients to opt out of the clinical study. Patients should not have a duty to risk their health for others, and to the extent that they may feel that even a limited obligation has been created, it should be escapable.³⁸ These qualifications would be satisfied in the kinds of studies that this article suggests. No patient would be subjected to a placebo or an experimental therapy. Rather, all patients would be receiving a well-accepted therapy, which to the best of our knowledge is as effec-

tive as the alternatives. In addition, patients would be free to decline enrollment in the study and seek care from a different physician. As long as the patient could indeed go somewhere else for medical care, no obligation to participate in research would exist.

Answering the Objections

Not only are there strong grounds for conditioning treatment on the willingness of patients to participate in some clinical trials, but the usual justifications for strictly voluntary participation are not present in the kinds of studies suggested by this article.

Risk to patient welfare is not a concern. Most importantly, we do not have to worry about patients being forced to assume a risk to their health. In many clinical trials, a patient may be randomized to either standard therapy or experimental therapy. In such cases, the experimental therapy may not fulfill its promise and may have serious side effects. Patients in the experimental therapy arm of the study would be harmed by their participation. Similarly, if an experimental therapy is compared to placebo when established treatments already exist for the medical condition being studied, patients in the placebo arm and possibly in the experimental arm of the study will suffer by virtue of their participation in the clinical trial.³⁹ In studies comparing well-accepted treatments, on the other hand, the patient would be receiving the same care that would be provided in a visit to a physician's office. In fact, the patient might receive better care by virtue of enrollment in the study; patients participating in research studies receive greater attention to—and more rigorous observation of—their medical conditions than do patients receiving care in their physicians' offices.⁴⁰

One might be concerned about denying patients the opportunity to weigh for themselves the advantages and disadvantages of the alternative

therapies and choose for themselves which treatment to receive. Even if there is no reason to think that one therapy is superior, individual patients might find one therapy's side effects more distressing than those of the alternative therapies. But I do not believe that this concern, although it is legitimate, is decisive. Most patients defer to their physician's recommendation rather than making their own choice. In addition, recall that patients who do not want to enter the trial are free to seek care from another physician and be treated as they prefer. Their freedom to choose would be restricted only if they chose to receive treatment from a physician involved in the clinical trial.

The possibility of coercion is not serious. Voluntary participation in

purpose of the pressure is to encourage them to help society understand and treat disease. There is nothing wrong with reasonable efforts at persuasion when the persuasion is designed to foster socially desirable behavior.

In addition, studies comparing well-established treatments lack the worrisome elements present in situations that are condemned as coercive. For example, people who choose to enroll in the study would not be driven by desperation or by the lack of a good alternative,⁴² nor would they have succumbed to threats of physical harm.⁴³

More precisely, when a physician conditions treatment on a patient's enrollment in a study comparing well-established treatments, the

some interest to which the patient would otherwise be entitled. Whether the patient is worse off depends on whether the first physician has an underlying obligation to care for the patient,⁴⁵ and this takes us back to the earlier point that patients are not entitled to receive care from a particular physician.

In other words, there is a circularity to the argument against the hypothetical version of AFFIRM. Conditioning treatment on participation in the study is said to be unacceptably coercive because the patient would be threatened with the loss of the physician. But the patient ordinarily lacks any entitlement to a particular patient-physician relationship. She would have such an entitlement only if care is denied for a bad reason. In identifying what would constitute a bad reason, we must find something that goes beyond the mere denial of care—racial bias or exposure to a significant health risk, for example. If the bad reason is simply the denial of care, then the argument becomes circular.

By analogy, physicians also do not unduly coerce their patients by raising their fees. The physician effectively tells patients that access to further care will be denied unless the patient agrees to pay more for the care, and patients may be worse off for having to change physicians if they cannot afford the fee increase. Nevertheless, because the patient is not entitled to care indefinitely at a fixed fee, a reasonable fee increase would not be considered unethical coercion.

That the hypothetical study involves a noncoercive offer rather than a coercive threat can be seen from another perspective—what the patient would have to give up by enrolling in the study. Consider in this regard what the physician might say to a patient:

When I first started treating your chronic atrial fibrillation, I mentioned two strategies for treatment, rhythm control and rate control. Many cardiologists and I prefer

Typically, patients are told they need not participate in medical research. But with studies comparing different, well-accepted treatments, it would not be troublesome if patients felt some pressure to enroll.

medical research is important because patients may be reluctant to reject their physicians' invitation to enter a research study. A patient might unduly defer to the physician's judgment because of the physician's greater expertise or because of fear that a refusal to participate might jeopardize the patient's relationship with the physician. Patients might easily feel that they have no real choice when asked to enroll in a study.⁴¹ As a result, ethical guidelines for medical research include provisions to assure patients that they are free to choose not to participate.

But with studies comparing different, well-accepted treatments, it would not be troublesome if patients felt some pressure to enroll. If they agreed to participate, they would not be placed at any greater risk of harm than if they did not. Moreover, the

physician is not presenting the patient with a *threat*. As Alan Wertheimer observes, A threatens B when the consequence of B's declining A's proposal is that B will be worse off than B would otherwise be.⁴⁴ However, the patient who declines to enroll in the study comparing well-established therapies will not be worse off for having refused. The patient will receive treatment with one of the therapies being studied, just as would have happened if the physician had not invited the patient to enroll in the study.

To be sure, the patient who must find another physician after declining enrollment may be worse off when compared with the alternative of declining enrollment and still remaining with the physician. But that is not the relevant moral comparison. The issue is whether the patient is deprived of

rhythm control, but others prefer rate control. As I also mentioned, data are lacking as to which strategy works better. There now is a study comparing the two strategies, and I believe it important that the study be completed so that we can find out if one of the two strategies works better.

Accordingly, I will continue treating your atrial fibrillation if you enroll in the study. If you do, then whether you remain on rhythm control or whether I treat you with rate control instead will be decided randomly. While you are in the study, the costs of your atrial fibrillation treatment will be paid by the study sponsor. If you do not want to enroll in the study, I will refer you to another cardiologist who can continue with the rhythm control strategy, and as now, your insurer and you will be responsible for the costs of your care.

By going into the study, all the patients would have to forgo would be their ability to choose between two treatment strategies when no one really knows which strategy is more desirable. And in return for forgoing this choice, the patients might be relieved of their financial obligations for the costs of care.⁴⁶

Moreover, if physicians were to condition treatment on participation in research, they might be less likely to encourage participation in a biased way. If a physician can only *recommend* that a patient volunteer for research, the physician may be more aggressive with some patients and less aggressive with others in encouraging participation. Physicians might put more pressure on their more vulnerable and less powerful patients, who are less likely to reject their physician's offers. But if the physician links treatment with research participation, then every patient faces the same pressure to enroll in the research trial. In other words, allowing the physician to condition treatment on par-

ticipation in research may simply have the effect of changing the demographics of the research subjects to include a more diverse patient population.⁴⁷ (The fact that conditioning treatment on participation may result in a more diverse population of research subjects provides another important reason for preferring this approach over other ways to promote participation, such as television or radio advertising.⁴⁸)

Note, too, that this article's proposal is less coercive to patients than an alternative proposal, offered by Robert Truog and colleagues, that would entail waiving informed consent for trials that compare established therapies.⁴⁹ Under that proposal, patients would be told about the institution's policy of conducting comparative clinical trials without the usual process of informed consent, but the patients would not be asked for consent before their actual enrollment into a comparative trial. As a condition of receiving care at the institution, patients would lose their ability to choose whether to participate in the institution's comparative trials.

Threat to patient trust. We might be concerned that conditioning treatment on participating in research would undermine patient trust in the medical profession. If patients felt coerced by their physicians' research requirements, they would be inclined to wonder whether their physicians were compromising their interests for the benefit of other interests.

We should be wary of measures that might undermine patient trust. Because patients lack medical expertise and because the patient's health and even life may hang in the balance, patients are highly dependent on their physicians. With so much at stake for the patient and so much power in the hands of the physician, patients will not be willing to rely on their physicians' judgment unless they can trust that physicians use their skills and power on their patients' behalf.

Concerns about patient trust are especially important in medical research. Medical research generally involves patients accepting some risks to their own health for the benefit of future patients. Because medical research is predicated on a sacrifice of patient welfare, it is important to assure patients that the risk will be minimized. Moreover, past abuses of patient welfare in research give patients grounds for skepticism about the trustworthiness of today's researcher. The Tuskegee syphilis study⁵⁰ and the radiation studies of cancer patients⁵¹ are two of the more notable examples of abuse.

While these concerns about trust are important, they should not lead us to reject entirely the possibility of conditioning treatment on participation in research. Past abuses in medical research involved two problematic elements, neither of which is present in the kind of trial suggested by this article. First, many abusive studies involved the deception of the research subjects. They were not given accurate information about the trials in which they were participating. As previously indicated, the ability to condition treatment on research participation would not entail any other changes in the requirements of informed consent. Second, many of the abusive trials placed patients at an unacceptable risk to their health. In contrast, the kinds of studies that satisfy this article's proposal are those in which patients would receive one of two or more well-accepted therapies—therapies that they would receive from any number of doctors whom they might see for care.

Moreover, conducting research that compares established therapies in order to discover whether one is better may well bolster patient trust. Patients ought to be reassured by knowing that their physicians are trying to find out which treatments are optimal. In fact, research on patient reluctance to enroll in research trials indicates that key considerations in the patient's decision are the physician's enthusiasm for the study and whether

the physician is truly uncertain about the value of the different therapies.⁵² Accordingly, conditioning treatment on the patient's willingness to enter the trial can directly respond to patient concerns to the extent that the physician expresses enthusiasm for the study and acknowledges uncertainty about how the treatments compare.

Too Lax or Too Strict

Many people have been unnecessarily harmed by research that did not adhere to sufficiently strict ethical safeguards. Steps should be taken to protect against future harm. At the same time, ethical safeguards can become too strict. Sometimes, important advances in medical understanding are slowed or stymied by unnecessary limits on the ability of physicians to encourage their patients to participate in clinical trials. When a clinical trial compares two or more well-established therapies to determine which is better, physicians ought to be able to condition treatment on a patient's willingness to enroll in the trial.

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14. Connett, "Recruitment of Participants," 46S-47S; W.B. Farrar, "Clinical Trials: Access and Reimbursement," *Cancer* 67 (1991): 1779-82.

15. Kolata, "Companies Facing Ethical Issue."

16. AFFIRM Investigators, "A Comparison of Rate Control and Rhythm Control in Patients with Atrial Fibrillation," 1825-6.

17. A.L. Waldo, "Management of Atrial Fibrillation: The Need for AFFIRMative Action," *American Journal of Cardiology* 84 (1999): 698-700.

18. AFFIRM Investigators, "A Comparison of Rate Control and Rhythm Control in Patients with Atrial Fibrillation," 1826.

19. Ibid. Nonpharmacologic therapies include ablation of the heart cells that generate the abnormal heart rhythm and the maze procedure, which involves surgical incisions to control the transmission of the heartbeat through the atrium. R.H. Falk, "Medical Progress: Atrial Fibrillation," *New England Journal of Medicine* 344 (2001): 1067-78.

20. AFFIRM Investigators, "A Comparison of Rate Control and Rhythm Control in Patients with Atrial Fibrillation"; R.H. Falk, "Management of Atrial Fibrillation—Radical Reform or Modest Modification?" *New England Journal of Medicine* 347 (2002): 1883-84.

21. As to how we know if a therapy is well accepted, a couple of indicia come to mind—if the Food and Drug Administration has approved a drug for use in treating an illness or if leading medical textbooks recommend the therapy.

22. B. Freedman, "Equipoise and the Ethics of Clinical Research," *New England Journal of Medicine* 317 (1987): 141-45.

23. G. Kolata, "Medicare Covering New Treatments, But With a Catch," *New York Times*, November 5, 2004; Centers for Medicare & Medicaid Services, "Factors CMS Considers in Making a Determination of Coverage with Evidence Development: Draft Guidance for the Public, Industry, and CMS Staff," (April 7, 2005), available at <http://www.cms.hhs.gov/coverage/download/guidanceced.pdf>. For CMS's response to concerns raised about its policy, see "Fact Sheet: CMS Responds to Stakeholder Feedback Regarding Coverage with

Evidence Development," available at <http://www.cms.hhs.gov/coverage/download/guidfactsheet.pdf>.

24. 21 C.F.R. Sec. 56.111 (2004).

25. 45 C.F.R. Sec. 46.116(a)(8) (2004).

26. M.A. Hall et al., *Health Care Law and Ethics*, sixth edition (New York: Aspen Law & Business, 2003), 111-12.

27. *Ibid.*

28. "World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects," *Journal of the American Medical Association* 284 (2000): 3043-45 (2000), available at <http://www.wma.net/e/policy/b3.htm>.

29. Council for International Organizations of Medical Sciences, *CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects*, available at http://www.cioms.ch/frame_guidelines_nov_2002.htm. Emphasis added.

30. National Cancer Institute, "Care for Children and Adolescents With Cancer: Questions and Answers," available at http://cis.nci.nih.gov/fact/1_21.htm.

31. K.M. Taylor et al., "Physicians' Reasons for Not Entering Eligible Patients in a Randomized Clinical Trial of Surgery for Breast Cancer," *New England Journal of Medicine* 310 (1984): 1363-67.

32. Brand, "Long-term Multicentre Trial," 21-31.

33. Hall et al., *Health Care Law and Ethics*, 111-2.

34. A.L. Caplan, "Is There a Duty to Serve as a Subject in Biomedical Research?" *IRB: A Review of Human Subjects Research* 6, no. 5 (1984): 1-5.

35. *Ibid.*

36. H. Jonas, "Philosophical Reflections on Experimenting with Human Subjects," *Daedalus* 98 (1969): 219-47, at 224-25.

37. See *McFall v. Shimp*, 10 Pa. D. & C.3d 90 (1978).

38. These are common safeguards elsewhere in the law. For example, even when states may prohibit abortions, they must allow an exception when continuing pregnancy poses a risk to the woman's health

[*Planned Parenthood v. Casey*, 505 U.S. 833, 879 (1992)]. As to allowing people to opt out of duties, parents may avoid their obligations to their children by placing the children in a foster or adoptive home.

39. K.J. Rothman and K.B. Michels, "The Continuing Unethical Use of Placebo Controls," *New England Journal of Medicine* 331 (1994): 394-98.

40. R.J. Levine, "The Role of Assessment of Risk-benefit Criteria in the Determination of the Appropriateness of Research Involving Human Subjects," in The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (Washington, D.C.: The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1978), appendix I:2.1-2.59, 2.36-2.42. There is some disagreement whether patients in clinical trials receive better care by virtue of their participation in the trials. Many studies suggest a benefit, but the data do not come from studies well-designed to sort real effects from spurious effects. D.A. Braunholtz et al., "Are Randomized Clinical Trials Good for Us (in the Short Term)? Evidence for a 'Trial Effect,'" *Journal of Clinical Epidemiology* 54 (2001): 217-24; J.M. Peppercorn et al., "Comparison of Outcomes in Cancer Patients Treated within and outside Clinical Trials: Conceptual Framework and Structured Review," *Lancet* (2004) 363: 263-70.

41. G. Calabresi, "Do We Own Our Bodies?" *Health Matrix* 1 (1991): 5-18, at 8-9.

42. A. Wertheimer, "Remarks on Coercion and Exploitation," *Denver University Law Review* 74 (1997): 889-906, at 899.

43. J.L. Hill, "Moralized Theories of Coercion: A Critical Analysis," *Denver University Law Review* 74 (1997): 907-29, at 912.

44. A. Wertheimer, *Coercion* (Princeton, N.J.: Princeton University Press, 1987), 204-206. Wertheimer goes on to discuss how this basic characterization of coercion

requires further refinement, and these further refinements will be taken up shortly.

45. *Ibid.*, 206-208.

46. Patients and their insurers are not always relieved of the obligation to pay for their care when they enroll in a research study. On the other hand, in some studies, patients not only do not pay the costs of care, but they also receive a cash payment for their participation (N. Dickert et al., "Paying Research Subjects: An Analysis of Current Policies," *Annals of Internal Medicine* 136 [2002]: 368-73).

47. Doing more to encourage patient enrollment in domestic research studies would also respond to the ethical concerns raised when drug companies take their studies overseas because it is easier to enroll patients in other countries (see Kolata, "Companies Facing Ethical Issue").

48. Alternative approaches have some effect, but they do not solve the problem of slow recruitment (Connett, "Recruitment of Participants," 46S-47S; Farrar, "Clinical Trials," 1780).

49. R.D. Truog et al., "Is Informed Consent Always Necessary for Randomized, Controlled Trials?" *New England Journal of Medicine* 340 (1999): 804-807. The proposal by Truog and colleagues would encompass a narrower range of studies, however.

50. J.H. Jones, *Bad Blood: The Tuskegee Syphilis Experiment* (New York: Free Press, 1993).

51. "Research Ethics and the Medical Profession: Report of the Advisory Committee on Human Radiation Experiments," *Journal of the American Medical Association* 276 (1996): 403-409.

52. Mills et al., "Perceptions of Equipoise," 272-82; P.B. Gorelick et al., "The Recruitment Triangle: Reasons Why African Americans Enroll, Refuse to Enroll, or Voluntarily Withdraw from a Clinical Trial: An Interim Report from the African-American Antiplatelet Smoke Prevention Study (AAASPS)," *Journal of the National Medical Association* 90, no. 3 (1998):141-45.