Protection of Human Subjects and Scientific Progress: Can the Two Be Reconciled?

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To the Editor: Over the past several years, both the professional and lay press have made distressing revelations concerning the research enterprise, including financial conflicts of interest involving investigators, NIH managers, and FDA regulatory procedures; insufficient disclosure of research risks; lack of transparency regarding investigators' commercial ties; ghost writing of clinical trial manuscripts by sponsors; failure to publish negative trial results; trials designed to conceal serious drug side effects; failure to systematically assess what is known from existing research before launching new studies; and inadequacies in the ethics review process, including IRB members' level of preparation and the monitoring of ongoing research.

Ironically, these revelations coincide with a rising chorus within the ethics community that advocates relaxing certain well-established norms and values aimed at protecting research subjects. A troubling thread runs through much of the recent literature, both that appearing in the *Hastings Center Report* on "changing standards of research" and elsewhere. The key ethics question has moved from "How can we balance subject protection with the acquisition of knowledge?" to "How can we facilitate research?" I believe this emphasis on tolerating higher levels of risk erodes protections traditionally provided by ethical protocol design and voluntary and informed consent procedures.

Much of this discourse presumes a great deal, including that some subject protections stand in the way of significant scientific advancement. It also assumes that most research is good, or necessary, or important; that all IRBs are competent to assess the risk/benefit balance with surgical precision or that they always know how much risk should be allowed when the benefit is exclusively to future patients; and that "bad deal" or exploitative trials somehow become acceptable, as opposed to doubly unacceptable, with mandatory random assignment to participate. Certain authors assume that distinguishing between research and therapy somehow provides a morally and legally legitimate rationale for weakening physicians' obligations to patients who are subjects, or that failure to demand relevant comparison trials (instead of promoting placebo controlled trials) will not disadvantage future patients looking for effective medication. Should we assume that patients presented with mandatory participation in trials of two approved agents won't see this as a breach of trust by their physicians? That seeing one is as good as seeing another, or that alternative physicians acceptable to patients are always and everywhere available? Some authors assume that once trials of new agents are approved by an IRB, coercion is irrelevant, as they are a "reasonable" choice for all eligible participants; that mentally competent adults who are ill or poor or without adequate social supports are not subject to pressures that inhibit the kind of voluntary choice we ought to insist upon; or that paying research subjects will not result in an "underclass" populated by those in temporary or permanent need of money.

If facilitating research is the real objective, why not place more emphasis on important issues such as improved education for IRB members and research trainees; better administrative support for IRBs; coordination of multicentered clinical trial review; requirements for trial registration and data sharing; improved guidance on research with children and the sick and dying; advice for health and social science researchers for value-laden areas such as racism, sexuality, drugs, or stigma; or the myriad of difficulties surrounding uncertainty and risk in the translation of novel cell research from bench to bedside? Why aren't there more calls from the ethics community for scientific rigor in research, or more debates on social versus scientific benefits of research?

Scientific advancement is a worthy objective, one that can benefit many. But we need a much more rigorous evaluation of whether weakening existing protections is necessary for such advancement—and, if it is, whether this is too high a price to pay. It may be time to remind ourselves of Hans Jonas' admonition that progress is an optional goal, not an unconditional commitment.

Kathleen Cranley Glass
McGill University

To the Editor: David Orentlicher's article "Making Research a Requirement of Treatment" (*HCR*, Sept-Oct 2005) defends an audacious thesis: that a physician could condition medical treatment on the patient's participation in a clinical trial that compares two or more accepted therapies to determine which one is superior. Orentlicher deserves praise for defending such a daring proposal in print and providing bioethicists and clinical researchers with some interesting food for thought. He also makes some tantalizing conceptual moves to try to show that subjects would not be coerced into enrolling in his hypothetical study, including the assertion that patients would not be made worse off or denied access to care by refusing to enroll. He contends that patients would still be able to find adequate medical care and that they have no right to see a particular doctor. His

proposal sounds plausible in theory, but it ignores geographic, financial, and social realities that could make it difficult for patients to obtain access to care.

First, doctors that are not participating in the hypothetical clinical trial might be many miles away. In some parts of the United States, hospitals and medical centers may be more than 150 miles apart. It may not be easy for some patients to find another doctor if they must travel a long distance. Even if a patient can travel the distance to find another doctor, the best doctors may be the ones participating in the clinical trial. Therefore, in areas where large distances lie between hospitals or medical centers, conditioning medical treatment on participation in a clinical trial could deny patients access to care or make them worse off.

Second, the patient's medical insurance company might require that she receive care from a particular doctor. If the company-approved doctors are all participating in the hypothetical study, then the patient might not be covered by insurance if she decides to receive care from doctors not participating in the study. This financial hardship could make the patient worse off and undermine her access to care.

Third, some patients might have difficulty changing doctors due to their strong loyalty to their current doctor. If a patient has been seeing a doctor for many years and has developed a close relationship with that doctor, he might feel that he must accept the doctor's request to participate in the hypothetical study. Patients with personal or practical difficulties making the transition to a different doctor would be made worse off by this hypothetical study.

There is a sound reason why international research guidelines, such as the Helsinki Declaration, stipulate that refusing to participate in a study should not interfere with the patient-physician relationship. The patient-physician relationship is vital to the quality, trustworthiness, and integrity of medicine. Although clinical research is vital to the advancement of medical science and the improvement of therapy, it should not undermine the physician-patient relationship. Orentlicher's proposal could have precisely this effect.

David B. Resnik
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To the Editor: David Orentlicher is correct in suggesting that the poor participation documented in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) should signal the need to promote "a social sentiment in favor of participation in medical research." However, I am concerned about his suggestion that this "social sentiment" could be produced by "pressure." I also find troubling his concession that physicians need not have a good reason to deny care to a particular patient in a pluralistic, fairly diverse society with a history of unequal treatment for several indefensible reasons. I would argue that pressure need not be used, and that it is unethical for physicians to deny care when it is in their power to provide it. As Marcia Angell, former editor-in-chief of the *New England Journal of Medicine* once stated, "Ethical violations are usually not a case of bad people doing bad things for no good reasons, it is usually a case of good people doing bad things for good reasons." I shudder at what would happen if physicians do not have to have any good reasons to deny care.

Orentlicher bases the palatability of his proposal, at least in part, on the dangerous precedent set by the new policy of the Centers for Medicare & Medicaid Services (CMMS) that links Medicare coverage to participation in research trials. He makes the sort of extrapolation that I doubt CMMS would have anticipated. Stripped of its official subterfuge, this policy gives no choice to patients but to participate in medical research. It amounts to an ultimatum or overt coercion that makes the health care of such vulnerable patients dependent on their willingness to risk their lives to benefit others through the capture of as yet unknown fruits of scientific research. Only time will tell if any increase we may see in participation in medical research can be predominantly attributed to such a policy.

Letting doctors pressure patients to participate in research as a requirement of treatment is an iron-fisted approach. I worry that it may take advantage of the vulnerability of sick, less powerful, and economically worse-off persons. If we mean to continue to treat patients as persons, then persuasion rather than pressure may be a softer approach for all persons regardless of how harmless we might believe their participation is.

Stephen O. Sodeke
Tuskegee University
National Center for Bioethics

To the Editor: Without taking a stand as to the validity of the moral worth of David Orentlicher's basic thesis requiring clinical trial participation of patients, there are three points he missed in his discussion.

First, he assumes that while previous independent studies may have shown that two treatments provide essentially the same results in populations with defined diseases, this does not mean that

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physicians are or should be indifferent about which treatment to use. More often physicians use primarily one type of treatment and are therefore more familiar with monitoring effectiveness and side effects, and then adjusting that treatment. In this sense, equipoise is a normative concept, but not a descriptive one: if I know how to do surgery A and am not as familiar or comfortable with surgery B, or if I am familiar with medication X and not as familiar with medication Y, then asking my patients to participate in a study that would provide them with an equal chance of getting A or B, or X or Y, puts them at additional risk.

Second, Orentlicher ignores the cost of finding another physician. It may be true that cardiologist M does not have to take on any willing patient. But that willing patient, once deemed eligible to participate in a clinical trial, has already invested time and funds by undergoing a relevant history and physical, diagnostic tests, and some level of discussion about participating in a study. For that patient to search for cardiologist N to replace M takes substantial time, energy, duplication of effort, and a rebuilding of trust and relationship. Further, it is a significant additional financial burden on the system.

Finally, a potential unstated benefit of Orentlicher's approach is that practitioners are likely to become known as one of two types: those who do clinical research and those who do not. After all, there will need to be cardiologists like N if the patient is to have a choice of another cardiologist. This being the case, the inherent and unresolved problem of the conflict of interest between the clinical researcher and the clinician might be solved in this way: cardiologist M will become known as the one to go to if you want to participate in clinical trials conducted by someone who may not have your best interests in mind, and you would go to cardiologist N if you don't want to participate in clinical trials but want to see a clinician who is not conflicted.

Yet while this conflict of interest is substantially reduced, we may have produced a biased delivery system and a self-selecting clinical trial participant/subject system. This is not the same as what we have—academic centers vs. community centers, for example—because clinical trial activity would spread to all types of settings, although it would not be engaged in by all practitioners. Orentlicher needs to address how this type of clinical practice might change the nature of our clinical trials as a whole.

Halley S. Faust
Joint Centre for Bioethics
University of Toronto

To the Editor: The September-October issue of the *Report* contains an intriguing set of articles that attempt to challenge received wisdom about the ethics of research with human subjects. Instead, they demonstrate how complex and incompletely understood current research ethics standards are. Two in particular, David Orentlicher's proposal to make some standard treatments available only through research participation and Lynn Jansen's analysis of the ethical acceptability of "bad deal trials" ("A Closer Look at the Bad Deal Trial: Beyond Clinical Equipoise," *HCR*, Sept-Oct 2005), especially deserve comment because they address an important, long-standing issue: the similarity—or lack thereof—between clinical research and medical treatment.

Dr. Orentlicher's proposal applies to phase III RCTs comparing standard treatments. His argument depends on clinical equipoise and amounts to asserting that there is no difference between research and treatment in these trials. Making research participation a requirement of the physician-patient relationship is reminiscent of past proposals by others, such as waiving consent to research participation in similar trials.

Head-to-head comparisons of standard treatments are much needed. However, being a subject is different from being a patient in important ways. Disparities almost always exist between receiving protocolized treatment on study and an individually tailored regimen off study. Patients may have meaningful preferences for one treatment over another, even if the relevant medical communities do not. Adverse effects and intervention failures are usually dealt with in research by removing the subject from the trial, whereas a treating physician is free to change the intervention or the dose and continue the relationship. Finally, being a subject entails additional requirements, such as testing, interventions, and follow-up that are not related to treatment. Requiring patients to become research subjects is far from inconsequential, and may promote confusion between research and treatment.

In apparent contrast, Dr. Jansen follows Miller and Brody in rejecting clinical equipoise. Nonetheless, her discussion of "bad deal trials" hinges on defining them as not in the patient's best medical interest. If clinical equipoise is not relevant, why should treatment be the yardstick against which clinical trials are measured? Research isn't supposed to be in any subject's best interests; it is supposed to benefit society through contributions to generalizable knowledge.

Investigators and IRBs should focus on minimizing risks of harm to subjects, rather than maximizing benefits to them. This entails comprehensively evaluating the trial and the data supporting it to yield the best data at the least cost to subjects. IRBs should consider requiring all study subjects be paid, or receive study interventions at no cost, to emphasize that research uses subjects as means of gathering data. Informed consent—with emphasis not on treatment-like benefits, but on what it means to be in research—then helps ensure that, by making their own decisions, subjects are more than mere means.

Equating or blurring research and treatment obscures important differences between them, promotes the therapeutic misconception in subjects, investigators, and clinicians, and devalues the investigator-subject relationship. Conversely, viewing research and treatment in stark opposition makes standard treatment appear clearly beneficial to patients, always effective, and never harmful. No one is served by either misunderstanding. We need a middle way, focused on a clearer conceptualization of the duties and virtues of the investigator-subject relationship—one that does not suffer by comparison with clinicians.

Finally, I want to emphasize that debate about the value of clinical equipoise applies only to phase III randomized controlled trials designed to determine the ultimate treatment-worthiness of studied interventions. Early-phase trials have different goals and evidentiary requirements—safety, feasibility, understanding mechanisms of action, and preliminary efficacy. This difference has been insufficiently addressed. No consideration of the moral warrant for clinical research can be complete without addressing all stages of the research process.

Nancy M.P. King
University of North Carolina

To the Editor: Lynn Jansen's article is the latest in a series of pieces challenging the demand for clinical equipoise in research. Jansen takes seriously Miller and Brody's argument that the clinical equipoise requirement rests on a version of the therapeutic misconception. Medicine and research are distinct activities governed by different ethical standards, they contend. Ethical medicine seeks the best care for individual patients; ethical research seeks better care for future patients, but does so without exploiting research subjects.

Jansen advances the inquiry by suggesting possible replacements for the equipoise requirement. To prevent exploitation, we could require that people enrolled in bad deal trials act out of altruism. Under this regime, investigators would have to show that all participants understood they had chosen a course designed not to meet their medical best interests, but to serve science. When trials presented individuals with an unfavorable ratio of risks to expected benefits, we could require investigators to offer participants payment or medical services. And to ensure a fair distribution of research burdens and benefits, we could adopt a mandatory lottery that would select subjects from the group expected to benefit from knowledge generated in a bad deal trial.

As Jansen observes, a research program that incorporated these measures would differ radically from the one we have now. For example, fewer people would volunteer if there were an altruistic participation requirement. A compulsory lottery could increase the supply of subjects but would conflict with the existing mandate for voluntary research participation.

What is refreshing about Jansen's article and the other recent challenges to clinical equipoise is that they take us back to the moral basics. In insisting on honesty about the objectives of human research, they highlight two major ethical problems with our current trial system. First, many people participate in trials without understanding that the clinicians conducting the trials have different aims than do other clinicians. Even altruistic volunteers may not recognize the extent to which trial participation could compromise their personal interests. Few trials include measures to reduce the therapeutic misconception, partly because improved comprehension could make subject recruitment even harder. Second, the challenges to equipoise raise questions about the justification for at least some clinical trials. If we fear that fully informed individuals won't volunteer for bad deal trials, then perhaps those trials should not be conducted. If we are reluctant to mandate trial enrollment, then perhaps some health advances are not as necessary as they are sometimes portrayed to be.

Jansen and the other scholars invite us to scrutinize the reasons for clinical trials and the morality of exposing people to risks and burdens in the quest for biomedical progress. In a world where trials are portrayed as cutting-edge medical care and investigators struggle to meet subject recruitment goals, it is time to return to these fundamentals of human research ethics.

Rebecca Dresser
Washington University in St. Louis

To the Editor: Lynn Jansen makes a strong case for weaning institutions off clinical equipoise, but she errs on the side of being too critical of her own arguments. For example, she worries that even patients who give informed consent might be exploited if researchers know they hold false beliefs about, say, the therapy-research distinction. But this prospect doesn't have to undermine a nonexploitation rule. We could insist that patients understand information about the research, not simply acknowledge it. It is not enough to obtain a consent form and then tell patients to draw whatever conclusions they want about their chances (if any) of being cured. Why not use the nonexploitation rule as an excuse to improve the application of informed consent?

Dr. Jansen also worries that compensating patients as a way to reduce exploitation might instead tempt researchers to find patients desperate enough to take significant risks in return for trivial payments. But we do not have to fully resolve this issue. The flaw in arguments promoting equipoise is that, by the time we flesh out what it means to actually apply it, we will have accomplished much more than a justification of risks and benefits. We likely will have solved most of the pressing issues in ethics (and a few in metaphysics!). There is no reason to set the bar so high. On the contrary, IRBs could evaluate each

offer of compensation on its own merits. Since what counts as exploitation is subjective, there will no avoiding the tough work of examining each deal that researchers and patients strike. Why not make compromise on just compensation a criterion for nonexploitation? Surely fear of undercompensating subjects should not lead us to conclude that no compensation is preferable.

Lastly, Jansen notes that we might minimize exploitation by randomly drawing conscripts from across society, as opposed to a small group of volunteer patients. This strikes her as a "radical strategy," however, that would have us "abandoning or at least modifying . . . informed consent." But there is more ethical elbow room between abandoning and modifying a practice than she lets on. We could insist that anyone inducted for service be given wide latitude concerning what type of participation was required and which risks would be involved. There is also a larger point. When we set out to reduce exploitation, the broader context of clinical research has to count. It won't do to focus only on the moment when an investigator asks a patient to enroll if society now benefits from the risks that a fairly small, and often disadvantaged, group takes in clinical research. On the assumption that there is already enough exploitation to go around, something like a lottery might more equitably distribute these risks and rewards. There is still something odd about ruling a lottery out on the grounds that it could lead to exploitation, in light of the reasons to think a lottery would help reduce it.

C.D. Herrera
Montclair State University

David Orentlicher replies:

Kathleen Glass and I agree that patients have not been adequately protected in many ways when they participate in research and that much needs to be done to enhance patient protections. Nevertheless, we need not ignore other reforms that can compensate for rules that are designed to enhance patient welfare, but that may in fact compromise it. In particular, we should recognize that different kinds of studies demand different levels of protection—that as the risks to patients rise, safeguards must become more stringent. But to impose the highest level of stringency on all studies makes no more sense than performing MRI scans on all individuals to diagnose disease.

More specifically, Glass worries about patient trust if physicians exert some pressure to encourage patient participation in studies comparing well-established therapies. But as I wrote in my article, patients will likely be reassured when their physicians are trying to find out which of multiple, alternative treatments is best rather than choosing one or another without an adequate basis to do so. Glass and David Resnik also identify important geographic and financial realities that may make it difficult for patients to decline participation in a clinical trial and find another physician to provide care. But in such situations, my proposal would not permit the physician to condition access to care on the patient's participation. My proposal requires that an alternative physician be available.

Stephen Sodeke's letter is shot full of inaccurate characterizations and inflammatory rhetoric that brings more heat than light to the debate. And his main point is misguided—just because pressure can be misused doesn't mean it should never be used. Indeed, society often uses the mandate of the law to foster desirable social behavior. If not for requirements to use seat belts, for example, many fewer people would use them. And if not for civil rights laws, more people would suffer from discrimination. Under the current system of care, many patients receive suboptimal treatment because too few studies compare existing therapies to determine which provides the best care. As I observed in my article, participation would not expose patients to the risks of experimental therapies or placebo pills but only to the same medical risks that they assume when receiving treatment for their condition outside of a study. Thus, Sodeke is simply wrong to characterize my proposal as coercing patients to risk their lives to benefit others. More importantly, in return for participating in a study that does not change their risks, patients would increase their chances of receiving the best available therapy. In short, my proposal is designed not for the benefit of medical researchers or physicians but for the benefit of patients. And as I observed in my article, because physicians would apply their pressure equally to all of their patients, there would be less exploitation of vulnerable patients than currently exists.

I worry less than Halley Faust about physicians having to change their practice patterns to participate in studies that compare alternative, established therapies. If physicians are uncomfortable using one of the alternative treatments, they need not participate in the study. Moreover, if a comparative study demonstrates the superiority of the alternative treatment, it would be important for the physicians to become comfortable using it. As to the costs to patients of switching physicians, a concern that Resnik also raises, they are part of the balance. However, I see the costs as being more than offset by the benefits—assuring patients that they are receiving the optimal therapy for their disease. Finally, it is not clear how permitting doctors to pressure patients to participate in comparative studies will affect whether doctors are researchers, clinicians, or both. If patient A does not want to participate in cardiologist M's study and switches to cardiologist N, it may be that cardiologist N participates in other studies for which patient A is not a candidate.

While Nancy King is correct that receiving a prescription drug for arthritis in a research study comparing the drug to another drug is not exactly like receiving the same drug outside of the study, I

considered many of those differences in my article and concluded that they should not lead to a rejection of my proposal. Thus, for example, research entails more testing and follow-up than does treatment, but the extra attention may benefit patients. And if adverse effects require removing the patient from a comparative clinical trial, the patient's physician would be free to change the intervention or the dose and continue treating the patient outside of the study.

Lynn Jansen replies:

I am in complete agreement with Professor Dresser's claim that research ethics needs to go back to moral basics. I am also in agreement with Professor King's claim that it is important not to blur the distinction between research and therapy. However, I disagree with Professor King's objection to my definition of a bad deal trial as one that sets back the medical best interests of the research subjects. It is crucial to understand that some, not all, research trials are not in the best medical interests of the participants. These trials impose a significant adverse risk/benefit ratio on at least some of the research participants. To be sure, the purpose of conducting these trials is not therapeutic. They are justified, if they are justified at all, because they promise to contribute to generalizable scientific knowledge. Yet the fact that research has a different justifying purpose than therapy should not blind us to the reality that such trials set back the medical best interests of at least some participants. By so doing, these trials run the risk of exploiting these participants for the good of future patients. My definition of "bad deal trials" was intended to underscore this important point.

Dr. Herrera says that I make a "strong case for weaning institutions off clinical equipoise." This was not exactly my intention, however. I am ambivalent about clinical equipoise. On the one hand, I do not believe that it is a requirement that must be satisfied for clinical trials involving human subjects to be ethically justified. To this extent, I am in agreement with those who wish to replace clinical equipoise with an antiexploitation norm. But, on the other hand, I believe that the implications of taking the antiexploitation norm seriously are more radical than many have recognized. If clinical researchers are unable or unwilling to take the antiexploitation norm seriously, then sticking with the requirement of clinical equipoise may be the best bet for protecting research subjects.

I offered a number of proposals for filling in the content of the antiexploitation norm. Dr. Herrera suggests that I err on the side of being too critical of my own proposals. Perhaps he is correct. Still, the proposals I discussed would require significant changes in the way in which clinical research is conducted. I wanted to bring out the difficulties, both pragmatic and ethical, in undertaking these changes. Dr. Herrera also suggests that it is odd that I worry about the possibility that some of my proposals, such as compensating research subjects or implementing a mandatory research lottery, might themselves involve exploitation. This is odd, he thinks, because the proposals are recommended as measures to reduce exploitation. The oddity disappears, however, once it is recognized that exploitation has both a process dimension and an outcome dimension. Efforts to reduce exploitation along one dimension may increase it along the other. This, in turn, raises the difficult question of how to compare or combine the two dimensions of exploitation. This is not something I tried to do in my article. I would resist, however, the suggestion that exploitation is "subjective," and so that reaching some type of compromise between conflicting interests would be an adequate response to the question.

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