

## Clinical Trials and Physicians as Double Agents\*

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Inherent in the dual role of physician-researcher is a conflict of interest arising out of the competing objectives of research and medical practice. Most commentary and policy recommendations on this conflict of interest have focused on the problems that arise in negotiations for informed consent. These are not, however, the only problems presented by this conflict; they are not necessarily even the most important. In order to deal with these problems, several commentators have suggested various procedural safeguards to protect the interests of the patient-subject—for example, separating the roles of physician and researcher, or introducing third parties into the relationship in order to assist in the initial or continuing negotiations for informed consent.

In my view, the necessity for special procedural protections of patient-subject interests should be a discretionary judgment of the Institutional Review Board (IRB). In determining the need for special procedural protections for any research protocol, the IRB should consider three factors. To the extent that any one of these or a combination of two or more seems to present a problem, the IRB should consider it increasingly important to recommend special procedural protections:

1. There are serious impairments of the prospective subjects' capacities to consent.
  2. The risk of physical or psychological injury presented by procedures done in the interests of research exceeds the threshold of "a minor increment above minimal risk."
  3. The protocol is designed to introduce, test, evaluate, or compare therapeutic, diagnostic, or prophylactic maneuvers.
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Conflicts between the roles of physician and researcher are inevitable and, in some circumstances, incorrigible. Such conflicts are especially problematic when one individual attempts to play both roles simultaneously, as is commonly the case in the conduct of clinical trials of new therapies. This paper is an examination of the nature of these conflicts and a consideration of some steps that may be taken to mitigate their consequences.

### PROFESSIONAL ROLES

Let us begin with a deliberately simplistic examination of the roles of physician and researcher: they are, respectively, to practice medicine and to conduct research. The definitions below of these two enterprises are compatible with those adopted by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the National Commission) and are embodied in federal regulations for the protection of human subjects:

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*Abbreviations:* AZT: azidothymidine IRB: Institutional Review Board RCT: randomized clinical trial

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The term “research” refers to a class of activities designed to develop or contribute to generalizable knowledge. By generalizable knowledge is meant theories, principles or relationships (or the accumulation of data on which they may be based), that can be corroborated by accepted scientific observation and inference.

The “practice” of medicine or behavioral therapy refers to a class of activities designed solely to enhance the well-being of an individual patient or client. The purpose of medical therapy or behavioral practice is to provide diagnosis, preventive treatment or therapy [2:p. 3].

According to these definitions, then, when a physician is practicing medicine, he or she is performing activities that are designed solely to enhance the well-being of an individual patient. Superficially, at any rate, it appears that he or she has no competing or conflicting interests. This appearance is not necessarily correct. The physician who is not doing research may have various sorts of conflicting interests. For example, in considering whether to recommend surgery or various diagnostic tests, the judgment of some physicians may be influenced by the fact that positive recommendations yield greater financial rewards for the physician. Thus, particularly when other considerations do not clearly indicate the making of a positive or a negative recommendation, the financial interests of the physician may, in some cases, “tip the balance” toward the positive recommendation.

How do we safeguard the interests of the patient against such competing interests? In my view, the most powerful safeguard is and ought to be a reliance on the professional responsibility of the physician. By this phrase I mean a reliance on the integrity of each individual physician, as well as a reliance on the social pressure that can be brought to bear by his or her colleagues. There is, of course, a second line of defense. This protection is reflected in various laws and institutional policies requiring such things as second opinions for certain sorts of elective surgery and continual peer review of ongoing activities.

Rather than attempt to develop an exhaustive or extensive list of potential conflicts of interest in the practice of medicine, let us just stipulate that there are some. The difference in research is that, by definition, there is invariably something being done that is designed to benefit a persons or persons other than the subject. Thus, when a professional assumes the dual role of physician-researcher in relation to a patient-subject, an inherent conflict exists. Although this conflict may not necessarily differ in kind from those present in the practice of medicine [2:pp. 7–8], it differs in that, in medical practice, the usual presumption should be that there is no important conflict of interest. In research, on the other hand, there is no such presumption; invariably, there is the knowledge that a conflict exists.

## RESEARCH AS A BURDEN OR A BENEFIT

Before proceeding further with considerations of the nature and consequences of the conflicts between the roles of physician and researcher, it is worthwhile to reflect briefly on the assumptions embodied in the ethical codes and regulations designed to safeguard the rights and welfare of human research subjects. These codes and regulations reflect the fact that they were written between 1947 and 1981, when the

prevailing perception of research was that it exposed the subjects to a highly perilous business, one from which they required protection [3,4]. This perception was informed by the events that provided the impetus for the development of the ethical codes—the heinous crimes committed by the Nazi physician-researchers, for which they were tried and most of them convicted at the Nuremberg war crime trials—and U.S. federal regulations—exposés of the sort provided by Henry Beecher [5] and of cases such as the Tuskegee, Willowbrook, Jewish Chronic Disease Hospital, and Obedience to Authority studies [2:pp. 69–72,217–220]. The federal regulations further reflect the fact that they were based on the recommendations of the National Commission, a body that was itself highly influenced by the ethos of the late 1960s and 1970s, exemplified by the civil rights movement, and characterized by challenges to the legitimacy of the authority of governments, corporations, and powerful professions [6]. Medical ethics was preoccupied with “redressing the imbalance of power” between the paternalistic physician and exploitative researcher and their patients and subjects, respectively.

Research was widely perceived as an exceedingly hazardous occupation from which prospective subjects—particularly vulnerable ones—required protection. It is no accident that federal regulations governing research are entitled: “Policy for Protection of Human Research Subjects.”

Subsequently, it has become clear that many persons who are prospective subjects, even highly vulnerable individuals, regard participation as a subject in research as a benefit rather than a burden [3]. Although evidence that this attitude might be the case was published much earlier [7,8], the voices of the patients and prospective subjects were first heard clearly in 1986, during the planning and conduct of the randomized clinical trial (RCT) comparing azidothymidine (AZT) with placebo in the treatment of patients with AIDS. Pointing to the results of very limited pilot studies suggesting the efficacy of AZT in delaying morbidity and mortality, those with AIDS and their doctors identified AZT as “the best available therapy” for AIDS. Now access to an investigational drug was clearly perceived as a benefit and not as a burden, and enrollment in the RCT was regarded as the only way to secure even a 50 percent chance to receive “the best available therapy” [3].

The belief that enrollment in a RCT is the only way to gain an opportunity to receive “the best available therapy” has been associated with a number of alarming behaviors that are detrimental to the validity of some trials. For example, during the placebo-controlled trial of AZT for the treatment of AIDS in 1986, certain patients—with the aid of their physicians—falsified medical histories so that these patients would appear to match the inclusion criteria for the RCT [9]. In the same trial, some patient-subjects shared their pills with others so that all could have an opportunity to receive at least some of “the best available therapy” [9].

Falsification of eligibility criteria with the aid of personal physicians has also been reported in other fields, such as oncology [10]. Furthermore, because RCTs of oncology therapies are, typically, not conducted according to a double-blind design, patients and their physicians know who is to receive which therapy. Some commentators have argued that physicians should refer their patients to such a trial in order to secure access to “the best available therapy” without disclosing to the investigator their plan to withdraw if those patients are assigned to the therapy with which the “best available” is being compared [11]. Such plans may be criticized on several

grounds, including the fact that this type of misrepresentation shows disrespect for the investigator and undermines the validity of the trial.

In passing, it is worth noting that many patients regard participation in RCTs as beneficial for reasons apart from gaining access to otherwise unavailable investigational therapies. Survey researchers have found that the majority of respondents view such participation as a way to gain access to superior medical care [12,13]. For some very poor persons, it may be the only way to get any medical care [4].

### SOME CONSIDERATIONS OF THE CONFLICT

Most published commentary on the conflict between the roles of physician and researcher centers on the issue of informed consent. Who should negotiate informed consent with the patient-subject? Should it be the personal physician, the researcher, or the physician-researcher? Should there be, in some cases, another agent involved, such as a consent auditor or an advocate? Although federal regulations are silent on this matter, the leading ethical codes are not. According to the Nuremberg Code [2:pp. 425–426]:

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

The Nuremberg Code, of course, is not concerned with such complicated roles as physician-researcher or patient-subject. It is designed to provide guidance to researchers who are using nothing but non-therapeutic procedures. Although they might also be physicians, when they are acting according to the guidance provided by Nuremberg, they are performing exclusively in the role of researcher.

Many commentators on the practice of medicine have expressed concern about the imbalance of power between the physician and the patient. Many of these commentators have drawn upon Talcott Parsons's perspective on the social role of "sick person," the privileges and responsibilities of the role, and the dependency of the sick person upon the physician to "legitimate" that role [14]. Thus, when a "sick person" is invited to perform also in the role of subject, there is great concern about the potentialities for exploitation of this imbalance of power.

Considerable debate has also occurred as to whether a physician who is involved in a physician-patient relationship can negotiate fairly with the patient for informed consent to become a subject [2:pp. 121–123]. Spiro, for example, asserts that a physician having a close relationship with a patient can usually persuade that patient to do almost anything [15]. Unlike most commentators, because Spiro emphasizes the importance of the closeness of the relationship, he feels the problem is greater in private practice than it is for ward or clinic patients.

Henry Beecher reviewed the literature on this subject; in his conclusion, he suggests that consent might not be either the only or the most important issue [16]:

An even greater safeguard for the patient than consent is the presence of an informed, able, conscientious, compassionate, responsible investigator, for it is recognized that patients can, when imperfectly informed, be induced to agree, unwisely, to many things. . . .

A considerable safeguard is to be found in the practice of having at least two physicians involved. . . . First there is the physician concerned with the

care of the patient, his first interest is the patient's welfare; and second, the physician-scientist whose interest is the sound conduct of the investigation. Perhaps too often a single individual attempts to encompass both roles.

Beecher was not clear about which of these two physicians he would have negotiate informed consent. The Declaration of Helsinki requires the following [2:pp. 427–429]:

When obtaining informed consent for the research project, the doctor should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a doctor who is not engaged in the investigation and who is completely independent of this official relationship (Principle I.10).

In its report on Institutional Review Boards (IRBs), the National Commission suggests, in its commentary on Recommendation 3D, that the IRB should be aware of the advantages and disadvantages (for the patient-subjects) of having one individual perform the dual role of the physician-researcher [17]. At its discretion, the IRB may require a "neutral person" not otherwise associated with the research or the investigator to be present when consent is sought or to observe the conduct of the research. This "neutral person" may be assigned to play a role in informing subjects of their rights and of the details of protocols, assuring that there is continuing willingness to participate, determining the advisability of continued participation, receiving complaints from subjects, and bringing grievances to the attention of the IRB. Federal regulations developed in response to the recommendations of the National Commission do not, however, reflect these considerations.

With one exception, the National Commission made no recommendations for the development of federal regulations on the dual role of physician-investigator. That exception is Recommendation 1H, in its Report on those institutionalized as mentally infirm, which states that the IRB must determine that [18]:

Adequate provisions are made to assure that no prospective subject will be approached to participate in the research unless a person who is responsible for the health care of the subject has determined that the invitation to participate in the research and such participation itself will not interfere with the health care of the subject. . . .

In its commentary on this recommendation, the National Commission further elaborates that, when the potential subject's physician or other therapist is involved in the proposed research, independent clinical judgment should be obtained regarding the appropriateness of including that patient in the research. This provision is intended to reduce conflicts of interest between the objectives of health care and those of research, while still permitting clinicians, who may be especially knowledgeable regarding promising avenues of research, to apply their expertise in both enterprises. Although this recommendation is addressed to the same problem as Principle I.10 of the Declaration of Helsinki, it does not require that a third party obtain informed consent.

The National Commission recommended that in various situations there should be third parties, in addition to the researcher and the subject, involved in the consent negotiations; in some circumstances, they should also be involved in the continuing

negotiations during the course of the research, in order to see whether the subject wishes to withdraw from the protocol, among other reasons. In the National Commission's several reports, the third parties are variously called "consent auditors," "advocates," "neutral persons," and so on. Except for some types of research on those institutionalized as mentally infirm, the National Commission recommended that the need for such third parties be determined as a discretionary judgment of the IRB.

In my survey of the conditions under which third parties should be intruded into the relationship between researcher and subject, I used the generic terms which follow [2:pp. 130–134]. "Trusted advisor" is a term applied to those who act in an advisory capacity and who are or are not consulted, according to the wishes of prospective subjects or persons authorized to speak for them. "Overseer" is the term I use for agents whose employment is required by the IRB and who are empowered to prohibit the initial or continuing involvement of any particular subject.

When appropriate, there should be a suggestion that the prospective subject might wish to discuss the proposed research with another. When the proposed research entails a consequential amount of risk, discomfort, or inconvenience to the prospective subject, or when there are difficult choices between reasonable alternative therapies, consultation with a trusted advisor should be suggested, particularly if there are factors limiting the prospective subject's autonomy or capacity for comprehension.

Commonly, the trusted advisor is the prospective subject's personal physician, when he or she has no involvement in the research. When the prospective subject has no personal physician or when the personal physician is involved in the conduct of the research, it may be appropriate to offer the services of another physician. In other cases, depending upon the nature of the problem, the prospective subject might wish to consult a trusted minister, lawyer, some other appropriate professional advisor, or even a friend who need not be a professional.

Suggesting consultation with a trusted advisor is quite a different matter from commanding the presence of an overseer. The requirement for an overseer should never be imposed frivolously; it is an invasion of privacy. The magnitude of the invasion can be reduced, in some cases, by allowing the prospective subject to select the overseer. Moreover, the imposition of such a requirement is tantamount to declaring to the prospective subject that his or her judgment, ability to comprehend, ability or freedom to make choices, and the like, is to be questioned. In some cases, however, this action will be necessary.

#### THE PERSONAL PHYSICIAN AS TRUSTED ADVISOR

All too often, statements in consent forms fail to reflect adequately alternatives to participation in the RCT, which some, perhaps most, patients might consider preferable to any of the therapies to be administered in the RCT. Problems are particularly likely to arise in the field of oncology, when the cancer is rapidly progressive and resistant to therapy and the therapies to be compared are highly toxic.

Consider this statement, from a consent form designed by a cooperative oncology group for such an RCT:

Alternatives which could be considered in your case include different drugs or drug combinations, or radiation therapy. Another alternative is no further

therapy, which would probably result in continued growth of the tumor. At this time it is felt that no other therapy is more beneficial than the treatments now proposed.

It is correct that “no further therapy” would probably—indeed, almost certainly—be associated with “continued growth of the tumor.” Not revealed, however, is the fact that either of the two therapies being compared most probably would, similarly, be associated with such continued tumor growth. Moreover, each of the two therapies is likely to cause severe nausea, vomiting, bone marrow depression, life-threatening infections, and other serious and uncomfortable complications. While some patients in the RCT might have satisfactory remissions, most will experience some reduction in the number of days they have to live and in their quality of life during those few remaining days. On balance, the average patient in the RCT will die sooner and will be less comfortable during his or her remaining days than those who choose “no further therapy.”

Without chemotherapy, patients eligible for enrollment in this RCT will experience “continued growth of the tumor,” which, in turn, will be associated with relentless progression of disability and, eventually, death. They are informed that if they elect to participate in the RCT, they will receive one of two new therapies, each of which “have been shown to be active.” But is it fair to say that “no other therapy is more beneficial than the treatments now proposed”?

When patients have diseases that are likely to be lethal within a relatively short period of time, it is vitally important that the doctor and the patient have careful discussions, designed to reach agreements about therapeutic objectives: They may choose to (1) pursue a cure or remission, (2) maintain biologic function, or (3) maximize comfort [19]. Such choices are essential, because pursuit of any one of these objectives entails interventions likely to undermine the accomplishment of either of the others [19,20]. For example, in the RCT from which the statement of alternatives now being discussed was derived, a choice to enroll presupposes, as the therapeutic objective, the pursuit of a cure or remission. This choice, in turn, entails acceptance of detriments to biologic function (e.g., bone marrow depression) and discomfort (e.g., nausea and vomiting).

The problem with the disclosure of alternatives as presented in the consent form is that it is preemptive. It is suitable only for those who have chosen to pursue remission with full awareness of the adverse consequences that they may expect. Only in such cases is it appropriate to say, “[I]t is felt that no other therapy is more beneficial than the treatments now proposed.”

In situations of the sort I am now describing, many patients are likely to choose as their therapeutic objective the maximization of comfort (or palliative) treatment. For this reason, the IRB at Yale–New Haven Medical Center commonly requests the addition to consent forms of language to this effect:

Before you agree to participate in this protocol, you should consult with your personal physician. Please show your physician a copy of this protocol and consent form and ask for his or her advice as to whether you should agree to participate in this protocol.

The addition of such language to the consent discussion and consent form suggest to the prospective subject that he or she use the personal physician as a trusted

advisor. Why not, instead, revise the consent form to include the necessity for identification of therapeutic objectives? Because, in the judgment of the IRB, identification of the therapeutic objective is best accomplished by a patient in collaboration with a personal physician who—one may presume (*supra*)—has no competing interest and with whom the patient has developed a satisfactory doctor-patient relationship.

### RESOLUTION OF THE CONFLICT

I am inclined to agree with the National Commission that the dual role of physician-researcher should generally be permitted. As we have seen, there are some conflicts, but these can usually be resolved. Shortly I shall discuss some approaches to their resolution. First, I want to make it clear that I have not rejected out of hand Beecher's proposal of having at least two physicians involved in the conduct of research—one playing the role of physician-scientist and the other, one whose primary concern is the well-being of the patient. We must take seriously Fried's argument that one of the burdens imposed by participation in most, if not all, RCTs is that the subject is deprived of a relationship with a physician that is characteristic of medical practice—a physician whose only professional obligation is to the well-being of the patient, not complicated by competing obligations to generate high-quality data. In Fried's words, the patient-subject is deprived of the "good of personal care" [21]. Thus, I have argued that programs like RCTs, in which there is a prolonged exposure to both research and therapy—either validated (standard) therapy or non-validated therapy (for example, investigational drugs)—one should take seriously the proposition that there ought to be a separation of the roles of physician and researcher [2:p. 192]. In such cases, though it might be quite appropriate to rely on the physician-researcher to provide day-to-day medical care, it might also be of value to offer the patient-subject the opportunity to maintain a physician-patient relationship with a physician who is not involved in the RCT, but who is sufficiently familiar with the RCT to facilitate the integration of its components and objectives with those of personal care [22].

I also agree with Beecher that informed consent is not merely not the only issue, it is not necessarily even the most important issue. There must be reasonable assurance that the patient-subject has ample opportunity to exercise his or her authority to withdraw without prejudice; moreover, there must be reasonable assurance that some competent professional, having a primary interest in the well-being of the patient-subject, will continue to observe the situation.

Except in cases involving special problems, which are characteristic of the RCT, it seems reasonable to rely on the physician-researcher to provide adequate protection of the rights and welfare of the patient-subject. In the event the researcher is not the personal physician, there should be a general presumption that no patient will be approached with an invitation to become a subject without the approval of the personal physician. Any exception to this general rule requires justification—for instance, in some studies of the doctor-patient relationship, while it is essential to gain the approval of the personal physician for approaching his or her patients in general, it may also be essential for the personal physician not to know which patients are being studied [2:p. 175]. As another example, the intrusion on the doctor-patient relationship may be so minor that specific approval by the personal physician for involvement of each and every subject may serve no interest that justifies the expense



and inconvenience—e.g., most studies of medical records and pathological specimens.

When confronted with a proposal to begin a project in which professionals will play the dual role of physician-researcher, judgments about whether it is necessary to introduce a third party into the relationship between the professional and the patient-subject should be made by the IRB. In my view, there are three factors that should be considered by the IRB in determining the necessity for special procedural protections. To the extent that any one of these three or any combination of two or more seems to present a problem, the IRB should consider it increasingly important to recommend special procedural protections such as trusted advisors or overseers.

1. The extent to which the prospective subjects have impaired capacities to consent must be considered. Are there serious limits to their autonomy, capacity to comprehend information, or are they legally incompetent?

2. The degree of risk presented by procedures performed in the interests of research should be taken into account. By definition, this statement means the degree of risk presented by maneuvers performed in the interests of developing generalizable knowledge. It does not mean the degree of risk presented by therapeutic, diagnostic, or prophylactic maneuvers—their status as “investigational” or “standard and accepted” notwithstanding. When the subjects are to be autonomous adults, the threshold for considering whether the degree of risk is high enough to call for the consideration of special procedural protections should be more than “a minor increment above minimal risk” [2:pp. 247–248].

3. In protocols designed to introduce, test, evaluate, or compare therapeutic, diagnostic, or prophylactic maneuvers, there may be a need for special procedural protections to assure that: there is a clear and accurate statement of alternatives; the prospective subject will be afforded ample opportunity to make a valid choice between alternatives; and the prospective subject will be fully apprised of the consequences of choosing the dual role of patient-subject.

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