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The Institutional Review Board and Beyond: Future Challenges to the Ethics of Human Experimentation

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AS A POLITICAL AND GOVERNANCE INSTITUTION, nothing in the regulatory domain resembles the institutional review board (IRB). To invert the classic story about God delegating authority to a committee to perfect His creations and getting a giraffe in return, the IRB *is* the giraffe, so odd is it when compared to other creatures in the jungle.

Despite its many idiosyncrasies, over the past two decades IRBs have transformed the conduct of research projects involving human subjects. Unquestionably, their very existence has tempered the inevitable propensity of researchers to pursue investigations without dispassionately weighing the risks they are asking others to assume or fully informing their subjects of them. Indeed, IRBs have been so successful as to set an international standard for monitoring clinical research.

Nevertheless, in the American context, the very proliferation of these committees, to the point where they are to be found in every type of institution conducting research, raises critical questions about uniform standards and performance. Is it truly the case that a "one size fits all" approach works well? Are the same general procedures for appointing members and defining their obligations appropriate for reviewing re-

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search conducted not only at the Central Intelligence Agency (CIA), the Bureau of Prisons, and the National Institutes of Health (NIH), but also at for-profit hospitals, local community hospitals, and university-affiliated, tertiary-care centers? Does it make sense to give the leadership of an institution, which by its very nature cannot survive without the funds and fame brought in by clinical research, the responsibility for appointing the membership of a monitoring committee? Or, more broadly framed, is the local and institutional basis of IRB organization still appropriate? Are the assumptions that initially underlay that choice still valid? The goal of this essay is to suggest that the answers to these questions may well be no, and to provide some modest, but potentially important, recommendations for change. IRBs can take credit for remarkable accomplishments, but it may be time to revise the framework governing human experimentation.

The IRB Structure

The IRB system rests on two sets of federal regulations. The first commits various agencies of the U.S. government to securing IRB approval before research is conducted on human subjects, either in house or through the grants they fund for outside projects. Government-supported biomedical research is the paradigm case.[1] Before any federal money can be expended on research involving human subjects, the regulations require that a protocol must be approved by this institutionally based committee, with a membership of no less than five persons, at least one of whom must not be affiliated with the institution. The IRB's central charges are, first, to review whether the benefits of the proposed research outweigh the risks, and second, to make certain that the investigators have explained all the relevant issues so as to secure the subject's informed consent. Although the federal regulations that establish the IRB system apply only to federal activities and federally funded grants, many states require IRB review for all research performed within their jurisdiction, no matter how it is funded. Moreover, the vast majority of academic institutions choose to review all their research protocols through an IRB, rather than reviewing some, but not others, on the basis of who is providing the funding.

[1] 45 Code of Federal Regulations § 46.101 et seq.

Contrary to what many people presume, IRB regulations do not require the review of *all* innovations in medical practice, let alone all instances of physicians following their preferred treatment strategies without ascertaining whether their approach works better than someone else's. The IRB focuses exclusively on activities intended to gain generalizable knowledge, and to the extent that someone, a surgeon for example, forswears an interest in general knowledge and presumes that the best way to treat Parkinson's disease is to burn the brain's pallidum—to take an illustration from the *Wall Street Journal*'s headline story of February 22, 1995—that surgeon need not bring his new technique before an IRB.[2]

Independent of federal funding regulations, the Food and Drug Administration (FDA) requires that protocols involving human subjects and new drugs or medical devices must be approved by IRBs. For example, were a surgeon to use a new commercial medical device in order to accomplish a proposed intervention, FDA procedures would be triggered. Insofar as testing new drugs on human subjects is concerned, FDA regulations are in important respects the same as those imposed by the Department of Health and Human Services (DHHS) on research institutions seeking grants. Yet FDA oversight differs in several important respects. FDA reviewers themselves examine the merits of the protocol and do not leave all decision-making to the IRB. Thus, in ways that overlap or supersede an IRB finding, FDA reviewers may reject research that they consider too risky or may compel investigators to carry out more animal studies before beginning clinical trials. At the same time, the FDA may impose strict regulations on the manufacture of drugs and biologics *before* they are tested, again going well beyond the IRB's usual safety concerns.

The FDA procedures do provide a degree of national oversight for clinical research. In addition, some funding agencies may conduct their own reviews of a protocol's research ethics; NIH study groups, for example, have been known to do this on occasion, rejecting a proposal on ethical grounds that a local IRB has already approved. But many human experiments do not come under either FDA or NIH study group purview, leaving decisions about the ethics of research solely in the hands of the IRB.

[2] On the IRB and FDA regulatory process see, in general: 39 *Federal Register* 18917 (May 30, 1974); National Research Act of 1974, P.L. 93-348, 88 Stat. 342 (Title II), *U.S. Congress and Administrative News*, 93rd Cong., vol. 1, p. 379; and 46 *Federal Register* 8386 (January 26, 1981).

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Thus, the power to approve or disapprove research on ethical grounds is granted to a local institutional committee, composed of members of the same institution (with the one necessary exception) that is seeking the funding. Moreover, by all reports, the members who dominate the IRB discussions are these insiders, not the outsiders (who are everywhere a distinct minority). So, in effect, the key decision-makers on the IRB are colleagues who must live with any disappointed applicants whose protocols they have rejected. Furthermore, most IRB committee members are themselves researchers and the standards they set for others will come back to bite them too.

To be sure, the IRB is uniquely well protected from formal institutional domination. Unlike most committees, which are structured to exercise power delegated by a parent and are ultimately responsible to that parent, an IRB decision to disapprove research may not legally be overturned by the institution. For example, if it believes it has grounds to do so, an IRB can effectively terminate a researcher's career at a particular institution by rejecting his protocols or by insisting on such close supervision that it becomes impossible for him to carry out investigations. At one institution, a researcher, whose casual attitude toward consent was notorious, was required by the IRB to have one of its members present whenever he obtained consent from a subject. The requirement proved so onerous, causing innumerable delays, that the investigator left the institution within months.

Nevertheless, the IRB's autonomy and isolation are largely theoretical, in that no federal controls or regulations exist on how the institution decides who gets appointed to the committee, how long those persons stay, or on what grounds a member may be dismissed or not reappointed. Indeed, powerful people within an institution have a myriad of largely untraceable ways for punishing an obstructionist IRB member: from withholding or delaying promotion to blocking his or her access to other grants—a fact that no IRB member can fail to recognize. Similarly, there are no formal controls on the selection of the outside and unaffiliated members, whose professional qualifications thus may not always be clear. While many of these outsiders may understand and appreciate the scientific or ethical dimensions of research, there is no way to ensure that they are anything other than a friend of a trustee, looking for an opportunity to participate in an institutional activity.

Finally, not only the formal structure but also the actual workings of

(Title II), U.S. Congress and Administrative News, 93rd Cong., vol. 1, p. 379;
and [illegible]

the IRB leave room for dissatisfaction. Despite the amount of time that IRBs devote to examining the language of the consent form, they are not required to investigate whether the consent language they hammer out either is actually used on the floor or serves to educate the patient about the nature of the research he or she has consented to. It is rare for an IRB to leave the confines of its committee room and examine what actually occurs in the consent process.

In effect, then, the regulations governing the IRB are, to say the least, a permeable shield, with no strong framework to ensure that subjects' interests take precedence over institutional ones. The judgments that will be made on this basis need not be so flagrant as to eventually provoke a scandal. Balancing research risks against benefits is complicated, and a committee that consistently makes the calculus in favor of the research will hardly ever be identified. On occasion, a glaring miscalculation will command headlines; the decision of the UCLA IRB to allow investigators to withdraw medication from schizophrenic patients in the course of a trial may be one such instance. But the overriding point is not how typical the UCLA actions are, but how the IRB system provides so few bulwarks against this tilt in decision making (Office for the Protection from Research Risks 1994).

To put the case bluntly, if one were to look at the IRB exclusively in terms of formal structure and organizing principles, it would seem to be a paper tiger. An individual serving on the body and an institution organizing it may fulfill the highest ethical standards; any one participant may claim, with full justice, that his or her IRB is exemplary in its functioning. Nevertheless, there are very few provisions in the regulations that protect against bodies that might be sloppy, venal, or subservient to the institution. Put another way, the quality of an IRB's work depends to an inordinate degree on the conscience and commitment of its volunteer members. The fact that the NIH has created an Office for the Protection from Research Risks (OPRR) in no way mitigates this point. OPRR is empowered to review the membership roster on local IRBs, but because the formal requirements are so minimal, such review is of limited effect. Nor does OPRR have the funds or personnel to conduct regular and ongoing examinations of how individual IRBs normally function. If OPRR does learn about a particular case (either through the institution, the press, or the grapevine), it will investigate the incident. In 1994, however, the office made only 10 site visits (Burd 1995).

The Dark History of Human Experimentation

When and why did the IRBs assume this peculiar structure? Why were such bodies created in the first place, and why was their organization so locally based?

The story opens in the early 1960s, when those charged with administering research funding, particularly at the NIH, took note of the public furor generated by exposés of gross abuses in medical research. These included the uncontrolled promotional distribution of thalidomide throughout the United States, labeled as an experimental drug; the administration of cancer cells to senile and debilitated patients at the Brooklyn Jewish Chronic Disease Hospital; and the uncontrolled distribution of LSD to children of several prominent families at Harvard through Professors Alpert and Leary. Most important, of course, was Henry Beecher's 1966 article in the *New England Journal of Medicine*, detailing 22 protocols of dubious ethicality, and declaring that the roster had been winnowed down from a longer list culled more or less from periodicals crossing his desk (Beecher 1966; Rothman 1987, 1991). NIH officials, as administrators of government funds, were deeply concerned about the impact of these scandals and moved in preemptive ways to ensure that Congress would not curtail research funding.

What accounts for the extraordinary capacity of medical experimentation abuse to be perceived as a major scandal, even when the provable physical harms that resulted from it were small, certainly when compared to the harms done by impaired physicians (an issue that has never sparked public furor)? The answer lies in the unique combination of events that made human experimentation a symbol for the two great nightmares of twentieth-century life. The first is the frightening power of some political ideologies to demand that no private interest impede the accomplishment of the public good. The second is the acute fear that man must adapt to whatever science produces, and that science is ultimately beyond social control.

In imprinting the first nightmare, the significance of the crimes committed by the Nazi doctors cannot be overstated. The U.S. government used the war crimes trials to teach that there must be limits to government power. One could not justify maiming and killing by claiming that the state required answers to pressing medical questions. Even an institution once as prestigious as German medicine was corrupted by succumbing to an ideology that state interests trump other considerations. And

this, of course, was precisely the basis on which America fought the ideological contest in the difficult years of the late 1940s and early 1950s, when the communist movement threatened to win elections in Italy and France and indeed throughout Western Europe (Annas and Grodin 1992; McNeil 1993).

From an American perspective, a maximization of collective welfare was not a legitimate basis for imposing harms of whatever magnitude upon individuals. Theories of individual rights set a limit on government authority, even if the community was then less well off, a position that was taken seriously at a time when the rate of Soviet economic growth allegedly surpassed our own. Although it took some 20 years for Nuremberg to become synonymous with the horrors of human experimentation—what caused the initial period of silence and why it came to an end is still not well understood—by the mid-1960s, and even more prominently in the 1970s and 1980s, the lessons to be drawn from the Nazi experience became widely recognized and shared.

These events represent a fascinating twist in the history of political theory in America. The intellectual leadership of the United States before World War II was profoundly committed to general utilitarian values. For example, one way to characterize the fight over the New Deal was as an argument by opponents that the proposed reforms violated traditional property and contract rights, which was countered by proponents with the claim that such rights should be limited by public needs. In effect, conservatives were defending individual rights and liberals were ready to restrict them in the name of collective well-being. Similarly, such seminal legal thinkers as Oliver Wendell Holmes and Felix Frankfurter were forever extolling the need for general legal standards and for imposing such requirements on people whether or not they could measure up to them. Holmes wrote that he would tell a person about to be executed, who might have had no power to avoid his wrongful deed, that he should regard himself as a soldier in the cause of general deterrence of crime.

This persistent and powerful strain of ideological positivism in the United States was brought into disrepute in the postwar era because it provided no sure stopping point whenever those in power believed a course of action to be absolutely necessary for collective well-being. Indeed, recall Justice Holmes's decision in *Buck v. Bell*, justifying the sterilization of the mentally infirm, and his remark that the sacrifice asked of the woman involved was small compared to that expected of others. Three generations of [illegible] enough that is, enough for the

icists who thought about Sanskrit poems as they watched the mushroom

community. The case of *Buck v. Bell*, not surprisingly, was frequently invoked by German defense lawyers at Nuremberg.[3]

The experience of convicting Nazis has had the ironic result that the victors' earlier confidence in general utilitarian theories was largely superseded by the victors' intelligentsia, in favor of ultimately deontological theories such as John Rawls's *Theory of Justice*. These theories trace their intellectual provenance to Kant, and to the German tradition, which was itself a nineteenth-century rejection of English utilitarian writers like John Stuart Mill and Jeremy Bentham. The result of this change was that medical experiments and social policy toward them became, in our society, the symbol of our acknowledgment of absolute limits on the claims the collective can make on the individual, and the rejection of a principle that anything goes so long as we are persuaded that more will gain than some will lose.

These are not, of course, the only alternatives by which experiments may be judged, but so powerful is the symbol of clinical research without consent that we approach them with extreme reluctance. The controversy over whether to permit experiments in emergency situations, where no consent is feasible, illustrates the attitude. And the recent fervor over the radiation experiments that government agencies conducted during the 1940s and 1950s on unknowing subjects suggests that medical experimentation has lost none of its symbolic power (Burd 1994).

If Nuremberg was one critical underpinning for public attitudes toward human experimentation, the second was the social awareness that new medical breakthroughs affected not simply the individual patient, but also human life more generally, and, given the dimensions of the potential transformations, the innovations had to be reviewed and authorized by someone other than the particular investigator. The rapid growth in transplant procedures was one dramatic instance: do we as a society want to promote a medical technology that makes the body into a collection of spare and reusable parts? Moreover, physicians themselves were often eager to share responsibilities in decision making, not only so as to alert the public to what was going on, but also to share the responsibility for allocating the novel resources. The most noteworthy case was that of the Seattle doctors' move to establish a lay kidney dialysis committee for the purpose of deciding who received the life-saving benefits. The negative reference point, of course, was the fate of physics and physicists who thought about Sanskrit poems as they watched the mushroom cloud, realizing they had altered the course of history without securing a societal consensus about the wisdom of doing so. Indeed, it was the development of nuclear weapons that encouraged biologists to convene the Asilomar Conference and to delay recombinant DNA research until a broader consensus about its safety could be secured (Rothman 1991).

[3] *Buck v. Bell* (274 U.S. 200, 47 S. Ct. 584, 71 L. Ed. 1000).

The Local Character of the IRBs

Although the scandals in human experimentation drove the decision to regulate research, they hardly explain why the results placed such heavy reliance on local, institution-based procedures. One major reason was that the research community was ahead of the curve of public demand, regulating itself before others did so. Local, institutional review was the least intrusive means of allaying public fears. Ask anyone in the pharmaceutical industry whether they fear more their review by an IRB or their fate with an investigational new drug (IND) at the FDA, and you will learn that the IRB is vastly more flexible than the FDA. An IRB is far more apt to communicate quickly what troubles it and how those troubles may be overcome. The public interest, it should be noted, often gains significantly from this flexibility, but it comes, as we shall see, with a price.

The preference for localism drew as well on a whole set of assumptions about the research enterprise and those who conduct it. First, when the IRB mechanisms were put into place over the 1970s, everyone, at least at the NIH, assumed that funds were readily available to do research. The inevitable result of IRB review was to delay things, but the costs of delay could be absorbed in a generous overhead allotment; moreover, the researcher who had to move more slowly on project A could always find support for project B. In other words, by making review local, the penalties of regulation were minimized.

Second, regulators presumed that IRBs would almost always operate within a university teaching hospital where a shared commitment to the ideals of good science would far outweigh any tendency for persons to trade favors or elevate concerns for the financial viability of the institution above their loyalty to the integrity of science or the well-being of subjects. The accepted premise was Robert Merton's persuasive argument that the universal principles of science override narrow academic allegiances. Thus, once science incorporated ethical principles in human ex-

men... into its own system, scientists would effectively enforce them, offsetting any dangers in localism. Moreover, the forces motivating researchers were promotions, prizes, and grants, all of which depended upon the respect of peers. No one would, therefore, risk imperiling the prestige of his or her institution by letting sloppy or unethical research slide by. Thus, it seemed as though the local character of IRB review secured all the advantages that came with being close to or part of the action, without running the risk of having regulators captured by the regulated.

Third, the designers of the IRB system expected that the subjects themselves were likely to be suspicious about human experimentation, adopting a cautious, self-protective stand against involvement. Participation was perceived as both burdensome and risky; experiments were dangerous, and subjects were fully alert to the implications of being a guinea pig. Discussion of research ethics spoke of the need to distribute fairly the *burden* of participation, not relying on and exploiting the poor. All the while, the attention devoted to the specific wording of consent forms was a way to guarantee that subjects would be able to act so as to promote their own self-interest. Well-informed subjects would never put themselves at undue risk. Where subjects were for one or another reason not capable of giving consent (owing to the debilitating effects of illness, mental disability, youth, or confinement to a prison), it seemed right to bar them from being used as subjects. The one exception was in the event that they had a special stake in the research mission; research on retardation, for example, might well require that persons with retardation be the subjects—even then, additional protections had to be employed. Research carried such danger that, although the policy was rarely made explicit, women, particularly women of child-bearing age, also seemed to require special protection. The fair sex should be protected, and even more, the fetus should be protected, lest some experiment adversely affect embryonic development.

The Limits of Localism

Each one of these three premises has now been substantially undercut, with the end result that the localism of the IRB appears to generate more problems than it solves. The confidence that IRB delay or disapproval carried no penalties because a surfeit of research opportunities was available has weakened—really disappeared. Money for research has become very scarce, and researchers have no confidence that there will always be another grant if this one is delayed.

Even more important, many potential subjects no longer regard participation in experiments as a dangerous activity. The line between experiment and therapy has blurred, and human subjects do not necessarily greet departures from accepted procedures, even exceptionally risky ones, with suspicion. Accordingly, the IRB presumption that a well-crafted consent form was a meaningful protection has weakened: subjects may well be simply too eager to obtain what they see as the most advanced and potentially therapeutic intervention. The shock troops leading the assault on the traditional perspective of risk were persons with AIDS. Their perspective is now being shared by advocates for those with Alzheimer's disease, advanced breast cancer, and indeed, for all those with a deadly illness (Edgar and Rothman 1990; Rothman and Edgar 1992).

All the while, new medical technologies continue to move society in totally new directions, with no systemic review of their desirability. Take, for example, the recent announcement from George Washington University that its investigators have begun experiments that may lay the groundwork for human cloning. The research received the approval of the institution's IRB. (It turns out that the IRB approved the protocol without knowing that the investigators had already conducted the research. When it learned of this breach, the IRB penalized the investigators, compelling them to withdraw an abstract of their findings. For our purposes, the critical point is that the local IRB did ratify the protocol and would have allowed the research to go forward [Schwartz 1994]. Those interested in giraffes may note, however, that a committee established pursuant to federal law directed academics not to publish their research, and no widespread discussion of First Amendment implications has ensued.) But precisely who vested George Washington University with the responsibility for deciding whether human material should be so used? Indeed, by what processes were the men and women chosen who made the ultimate determination to approve it? And what did they hear by way of opposition to the researchers' request to go ahead? Surely, some alternative or supplement to such local decision-making seems in order (Fackelman 1994).

So too, the proportion of research that is industry funded, rather than government supported, has increased dramatically, which carries several critical implications for IRB reviews (National Institute of Health 1993). Researchers may have entrepreneurial interests in products being tested

at their home universities. Indeed, the academic institutions face major issues of conflict of interest because medical entrepreneurialism has become a goal of the university itself. For example, whereas Harvard University used to prohibit patenting of medical innovations as contrary to the public interest, it now has established an in-house investment company to provide seed capital for ideas worthy of commercialization, and the proceeds of such commercialization are to be returned to the university and distributed to the inventor, to his or her laboratory, and to research more generally (Gupta 1994). Increasingly, universities take equity positions in faculty-created start-up companies. Although no data are available to ascertain the frequency with which medical institutions hold equity in companies whose products are tested in their facilities, or how often researchers have a substantial financial stake in the products they are investigating, both phenomena now occur, and are all the more likely to occur in the future.[4]

Indeed, some institutions now function economically as packagers of patients with rare diseases. The concentration of patients at the institution makes feasible corporate-sponsored research protocols that could not otherwise be done; the institution profits handsomely by providing experimental options to those sponsors, in effect matching sponsors and volunteers who would not otherwise efficiently find one another. To these ends, a pharmaceutical company recently purchased an advanced cancer treatment center, with the hope, we presume, that along with whatever other benefits the center might bring, it would provide a site for clinical trials. While the results of these trials may well contribute to improving medical treatment, the concern is whether the institution's financial stake in research has grown so great as to jeopardize the independence of locally based IRBs.

In fact, for these reasons, and others as well, the academic center, which served as a paradigm for the IRB, is likely in the future to lose what was once a near monopoly over research. Its role is being usurped from at least two sides. One the one hand, huge multistate and international trials have been, and will be, organized, bringing thousands of patients into a single trial, run by a coordinating group. With research becoming more national, ethics review on the local level makes still less sense. Second, the managed care plan provides a perfect site for many trials. To the extent that health maintenance organizations and other providers develop information bases linking different physicians' treatment patterns to patient outcomes, they are the natural place to conduct research on how much of a difference, if any at all, an intervention brings. Indeed, if we are prepared to insist as part of the managed care revolution that cost-containment measures be researched rather than imposed (which we may not be), then an in-house IRB model is hardly equipped to serve as guardian of patient interests (Freedman 1994).

One final point about the locus of research activity has recently assumed exceptional importance. The original 1960s assumption that the university was the site of most human experimentation minimized the importance of the fact that a number of government agencies, including the Department of Energy (DOE) and the CIA, were already heavily invested in such activities. Although there were discussions and hearings on whether so local and internal a system made sense in this context, and these agencies in time did agree to come under the regulations and establish their own IRBs, not until the 1994 exposé of cold war radiation research did the disadvantages of this arrangement become the center of public attention and policy analysis. Is it truly meaningful for the DOE or the CIA to run its own IRB? In light of what we now know about their activities, the local basis for the regulation of their human experimentation seems less satisfactory.

Taking the "I" out of the IRB

If the old paradigms no longer hold, what revisions should be made in public policy? Where do we go from here?

The IRB system has worked reasonably well, and to dismantle it would be a mistake. Nonetheless, IRBs were a "one size fits all" solution. Obviously, no single reform or institutional structure will be able to provide adequate oversight of all biomedical innovations. Accordingly, public policy innovations should move forward simultaneously on a number of fronts. We mention three.

IRB procedures are completely inadequate to protect the public interest from the ends of research, or to assure sufficient lead time to permit political focus on the limits, if any, that should accompany the development of new technologies. Mechanisms must be found to assure that proposed research that crosses frontiers achieves public visibility and provides opportunity for political choice before it is implemented. In con-

[4] 35 United States Code, §§ 200–12 (annotated).

establishment of a "super" committee or committees, charged at the minimum with a monitoring function, at the maximum with the right to veto research deemed unacceptable.

How can this be done? Throughout the world, various countries have established national ethics committees to serve as ongoing advisors on difficult ethical issues associated with research, and medical practice more generally. Numerous bills have been put forward to establish such a committee in the United States, and the Clinton Administration has expressed interest in such a proposal. But, in the past, initiatives have floundered on the question of who gets to appoint whom to do what, particularly when everyone knows that the issue of abortion may lie in the background (Office of Technology Assessment 1993).

Three principal and interrelated issues must be addressed in the design of an overarching monitoring mechanism:

First, whether to constitute one committee, endowing it with visibility and prestige because of its singularity, or several committees, distributing responsibility among members selected for their particular expertise. The NIH's recombinant DNA advisory group is the prototype of the special committee. And it has worked. Researchers complain about its delays, but it has had a profound impact on securing public consensus that gene research is an appropriate end, and one that can be safely pursued. Such committees should not, however, be appointed ad hoc, as the recent experience with the special committee established to advise the NIH on embryo research demonstrates. The President rejected out of hand a key recommendation—to permit the occasional creation of embryos for limited research purposes—before it was even considered by the NIH. Had procedures been in place that had earned credibility over time, it might not have been possible to dismiss a proposed policy in such politically expedient fashion.

Second, to determine how expansive a committee's jurisdiction should be: whether it will be limited to reviewing funded grant proposals and issuing advisory opinions, leaving the ultimate decisions to local IRBs and researchers, or whether its approval will be required before research is undertaken.

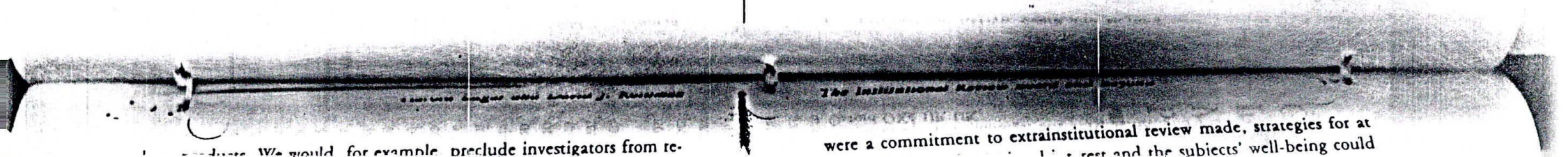
Third, to decide who should appoint such a committee, and what kind of staff it should have, questions that obviously become more or less sensitive depending on what powers the committee is granted.

pointed by DHHS-NIH officials, whose responsibilities would extend to their particular fields of research—neurobiology, genetic therapy, reproduction—without regard to the sources of the research funding, governmental or private.

After considerable hesitation (and an initial difference of opinion between us), we would not grant the committee formal power to halt research. Adding another layer to the review of human investigation would incur too much expense and delay. Instead, we prefer to have such committees stay abreast of research methods and issues, making public the significant questions and providing general guidance to local IRBs about particular protocols. Yes, investigators who can persuade their own IRBs of the propriety of their work will be able to take the first research steps in advance of such review (the George Washington University cloning research is a case in point). But two considerations seem to us to reduce the potential risks. For one, frontier research is usually incremental, in the sense that the relevant professional community knows who is involved with research near the boundary and what the likely pace of advance will be. The presence of professional leaders on a committee with high visibility will encourage people in the field who have doubts about their own or their colleagues' agendas to ask whether and to what extent the issues that concern them have already been analyzed and considered. For another, expert committees will have ready access to the media and to policy makers, for biomedical research is (and will continue to be) in the public spotlight. Accordingly, expert committees will have time to foster debate about the research and ultimately provide the opportunity for an informed political decision on its desirability. In short, controversies about the stopping points in particular lines of research—whether they involve cloning, genetic enhancement, or other novel procedures—will have to be decided ultimately in the political arena, and administrative mechanisms cannot avoid that fact.

The second broad area of reform involves improving the present IRB system to take account of the newly entrepreneurial character of biomedical science that we have described.

Many of the concerns we raised are the appropriate object for formal legal rules. For example, conflict-of-interest guidelines can, and should, specify the limits on researchers and institutions that are simultaneously financially invested in the development of products and the testing of



products. We would, for example, preclude investigators from re-

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those products. We would, for example, preclude investigators from recruiting patients and conducting clinical evaluations where the product being tested is one in which they hold a commercial stake.[5] So too, patients should be told of any financial commitments that would motivate the investigator to select this treatment for the patient rather than the others on hand (Rodwin 1993).

The third direction that reform must take is to strengthen the "outside" elements of the IRBs, while leaving review based in the institution itself. Localism has the advantage of accomplishing review not only more quickly but also with the knowledge, informal as it is, of the character of the investigators. Most important, it greatly facilitates learning that something is going wrong: nurses, residents, physicians do not have to cross institutional lines to inform someone of their concern that a protocol is not being followed.

IRBs processing a substantial number of protocols should, however, include experts drawn from scientific groups outside the institution. Moreover, there must be more focus on the appointment and renewal process. We should also seek to quasi-professionalize the role of outside members, linking them in groups that could come together to study common issues, so that there might be greater uniformity given to concepts like minimum risk. (The programs for IRB members run by such organizations as Public Responsibility in Medicine and by the Office for the Protection from Research Risks itself provide the beginnings of a model for such an effort.) The proposition that outside members can represent a relevant "community" has always seemed suspect to us; and we would prefer to see on each IRB a member who felt loyalty to a newly constituted community of research ethics advisors.

These stipulations about strengthening the outside role in IRB review take on special importance when the research is being conducted by the government itself. To make certain that such bodies as the DOE and the CIA remain well within the bounds of ethical research, it is vital that outsiders play an even more important role in their reviews than elsewhere. To accomplish this change would not be easy, not only because these bodies are very insular, but because outsiders also might well require security clearances and have to assume burdens of confidentiality that would hamper their effectiveness in bringing abuses to light. But were a commitment to extrainstitutional review made, strategies for at once protecting the national interest and the subjects' well-being could be designed.

Finally, and almost certainly, we should have far more effective oversight mechanisms. It would be entirely feasible, for example, for an NIH office to sample (in the technical sense) protocols from research settings (not only universities, but also companies and government agencies), and to include in this effort interviews with the subjects of the research (reviewing the process by which they gave consent, what they understood the experiment to be, and how the research itself was conducted). The very existence of such a procedure might help improve IRB performance.

In sum, it is time to take the superintendence of human research to a different, and more national, level. Whether this change can be accomplished within the current political climate is debatable. The necessity for such a shift is not.

[5] A final Public Health Service rule has just been announced. See 60 *Federal Register*, 35810, issued July 11, 1995.

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A Strategic Framework for Infant Mortality Reduction: Implications for "Healthy Start"

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THE UNITED STATES RANKED 21ST AMONG DEVELoped countries in infant mortality in 1992 (Wegman 1994), despite the fact that it spends 12.2 percent of its gross domestic product on health care (Levit et al. 1991), more than any other nation. Although the provisional U.S. infant mortality rate (IMR) of 8.3 infant deaths per 1,000 live births in 1993 represents a progressive downward trend (Wegman 1994), the health care system has not been successful in closing the gap in IMRs with other developed countries (Liu et al. 1992). Moreover, infant mortality (IM) rates remain persistently high among minority populations and in large urban areas in the United States (Hogue and Hargraves 1993).

The poor international ranking of the United States, coupled with the high IMRs among populations in urban areas, led to the initiation of "Healthy Start" by the federal government in 1991. Healthy Start (HS) is a national program to reduce infant mortality (IM) in 15 selected communities with the nation's highest IMRs (Chu and Reilly 1992). It represents the most recent national effort to reduce IM, following a history

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Guidelines for IRB Review of International Collaborative Medical Research: A Proposal

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The increase in the scope of international collaborative medical research involving human subjects is raising the problem of whether and how to maintain Western ethical standards when research is conducted in countries with very different social and ethical values. Existing international ethical guidelines for research largely reflect Western concepts of human rights, focusing on the bioethical principles of respect for persons, beneficence, and justice. However, in countries and societies where these values are understood differently or are not expressed in local cultures and institutions, it may be impossible or of no practical value to insert them into the research setting.

In the United States, individual informed consent is considered ethically imperative for research involving human subjects. However, this imperative may be difficult to instill in societies that define persons by their relations to others, and important decisions are commonly made by heads of households or group leaders rather than by individuals.[1] The baseline economic and health care conditions in foreign communities may also create ethical conflicts. In a study of acquired immune deficiency syndrome (AIDS) conducted in Tanzania, Western researchers were required by their institutions to include in their protocol that subjects be informed whether they had the human immunodeficiency virus (HIV). But because the country lacked resources even for palliative care, local Tanzanian officials prohibited disclosure of subjects' HIV status out of concern for the distress that the information would cause.[2] More recently, studies of maternal-infant transmission of HIV resulted in a dispute over whether it is acceptable to use placebo controls in drug trials when effective treatments are known but are too expensive to be used as the standard of care in the host country.[3]

In the United States, all federally funded research protocols involving human subjects must by law be approved by an institutional review board (IRB). The IRB, a committee composed of researchers, physicians, and other institutional and lay affiliates, represents the primary investigator's home institution. Its purpose is to screen research protocols to ensure that the rights and welfare of human subjects are protected as required by law. A minimum set of ethical expectations for research involving human subjects is outlined in the *Federal Register*.[4] These include the requirement that subjects' voluntary and informed consent be obtained prior to participation, that risks to subjects be minimized and reasonable relative to the anticipated benefits of research, and that the selection of subjects not unduly benefit or burden particular groups. Individual institutions may develop additional requirements corresponding to the values of the institution and the types of research conducted.

The ethical principles governing Western medical research reflect the historical and anticipated risks for human subjects participating in medical research conducted in the United States. Historical harms include research performed on subjects without their consent, studies that endangered the health of uninformed study subjects, and studies performed on vulnerable populations.[5] Even though contemporary research is designed to minimize the likelihood of these or similar harms, risks of manipulation or exploitation persist. These risks are due to the disparity in social power between physician researchers and subjects, the complexity of medical information that may inhibit subjects' understanding of the research, and subjects' sometimes desperate need for medical care when all previous treatments have been ineffective. These risks are magnified in international collaborative research when subjects' social and cultural norms differ significantly from those of the sponsor-

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ing researchers, or when health care is otherwise minimal or nonexistent. Additional risks may arise due to political or economic systems that foster social inequities or fail to support Western notions of human rights.

Cross-cultural research protocols thus present a problem for IRBs. By what ethical or legal standards should such protocols be reviewed? U.S. regulations acknowledge that ethical conflicts may arise in research conducted in foreign countries, in which case foreign procedures for human subjects protection may be substituted for the U.S requirements—but only if the substituted procedures offer protections "at least equivalent" to those provided by U.S. policies.[6] Beyond this vague provision, the regulations offer no further comment on how to assess risks accurately in foreign countries, or how to conduct IRB review of cross-cultural protocols.

International codes of ethics similarly fail to address cross-cultural research, because they are based primarily on Western ethical standards. Among the most well known are the Nuremberg Code,[7] the Declaration of Helsinki,[8] and the guidelines developed jointly by the Council for International Organizations of Medical Sciences with the World Health Organization (CIOMS guidelines).[9] Each of these codes of ethics delineates principles of conduct that essentially reflect values of respect for persons, beneficence, and justice. The CIOMS guidelines are the most comprehensive, giving significant attention to cross-cultural conflicts in research and making a number of recommendations for IRB review. These guidelines are an important first step, but the recommendations made are not specific enough to be used by IRBs evaluating cross-cultural research. Moreover, to date, they lack any means of enforcement.

In summary, neither the U.S. federal regulations nor any of the established international codes of ethics provide guidelines for IRB review of cross-cultural collaborative research. Absent clear criteria, some approved research may contain unanticipated risks for subjects while other potentially valuable research might be prohibited. In this article, I explore the strengths and weaknesses of two contrasting approaches to IRB review of cross-cultural research, proposing a compromise between the two as a culturally sensitive means of human subjects protection. To set the stage, I begin with a case.

AIDS research in China: a case of unknown risk

A collaborative research protocol between U.S. and Chinese researchers raises issues not only of protecting human subjects, but also of trust, perception, and authority. This protocol involved a multidisciplinary American team that proposed to provide training to a group of Chinese epidemiologists in risk-behavior assessment for sexually transmitted diseases (STDs), including HIV and AIDS. The training was to be done in the United States, following which the Chinese would return to their home university to test a questionnaire developed during their training. In the course of testing, the Chinese planned to conduct over 500 face-to-face interviews with patients attending a clinic for STDs. The interviews contained questions about the participants' sexual practices, history of STDs and HIV, health status, sexual orientation, and current sex risk behaviors.

In the accompanying consent form, the researchers promised to maintain confidentiality by not releasing names without written permission, omitting personal identifiers in published reports, and storing data in a secure location. Subjects were assured of their right to refuse to participate without penalty. The American consent form was translated into Chinese and back into English to ensure accuracy; it was approved by the American institution's IRB as well as the ethics review committee at the Chinese researchers' home institution. The Chinese committee also provided a statement declaring that subjects' confidentiality would not be violated and that subjects would not be punished in any way for participating or refusing to participate.[10]

This protocol raises numerous questions beyond the routine scope of an IRB. First, the research would take place in China, a country widely perceived by Americans as abusive of human rights and about which accurate, comprehensive information is difficult to obtain. Given a Western perspective of human rights in China, the IRB must question how, and by whom, the risks to subjects were determined. Does the consent form reflect the actual risks? Some evidence suggests that discrimination, stigmatization, and involuntary detention following positive diagnosis of HIV or AIDS has occurred.[11] Should the sponsoring researchers or their IRB be expected to find out the extent of these risks? If so, given the difficulty of obtaining sound information, to what lengths should they go? If not, who should be responsible for risk assessment?

Second, in a totalitarian society, how meaningful is the American consent form or the Chinese statement? Can confidentiality really be assured? Who else, besides the researchers, would have access to the data? What are the potential risks to subjects should the data fall into the hands of government officials? Third, given that the American researchers would not be present when the interviews are conducted, how much responsibility do they and their IRB have for the protection of the Chinese subjects? Fourth, if risks to subjects are believed to be significant, should American researchers be participating in this study at all? Finally, by what criteria should the IRB evaluate this proposal?

These questions reveal ignorance and suspicion about conditions in China. We may never know with accuracy what the social consequences are for persons diagnosed with HIV or AIDS in China, or, for that matter, how any particular research project will take shape in a foreign country. Our ignorance of circumstances elsewhere reveals the extent to which IRB review assumes IRB members' familiar-

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ity with the social and political context of medical research as well as investigators' integrity and good faith. Although neither contextual knowledge nor integrity can ever be guaranteed, these assumptions have shaped how the role and responsibilities of IRBs have come to be perceived.

In international research, given the range of sociopolitical circumstances worldwide, these assumptions may not hold. In their absence, an IRB has two options: (1) it may require that research conform to accepted Western ethical standards or (2) it may establish some other set of criteria or procedures for approval. The option chosen depends on whether Western ethical standards are believed to reflect notions of human rights that are universal, absolute, and hence inviolable, or whether, in some cases, it may be considered acceptable and appropriate to modify ethical standards to correspond to the values and circumstances of a subject population. Both positions contain ethical conflicts and practical limitations, for both researchers and subjects. I examine each position in turn.

Narrow view: an ethic of moral fundamentalism

If Western ethical standards reflect a set of ethical principles that is universally applicable, the IRB's mandate can be read narrowly, requiring that approval be granted only to those protocols that satisfy the ethical requirements outlined in federal and institutional policies. This view has been characterized as "moral fundamentalism."[12] Proponents of this view reject the possibility of any relaxation or compromise of Western standards, arguing that doing so suggests ethical relativism and creates new opportunities for exploiting vulnerable populations.[13] By basing IRB approval on Western ethical standards, approved international research could be expected to entail appropriate research design, clear and thorough consent forms, equitable subject selection, and a reasonable balance of medical risks and benefits. Despite these provisions, Western standards may offer insufficient protection for human subjects, chiefly because they neglect sociopolitical, cultural, or economic factors that pose risks that are not normally encountered in Western countries. Overly rigid adherence to moral fundamentalism may also diminish opportunities for potentially valuable research. Finally, this approach suffers from the limitations accompanying IRB review in general.

As is well known, IRBs usually focus on informed consent documents, reviewing them primarily for consistency with research protocols and clarity of expression. Only rarely does an IRB question research design or monitor research it approves. It assumes, on good faith, that researchers will not place subjects at unnecessary risk, will follow the protocol as described, and will provide an adequate informed consent process.[14] Part of the reason research design is rarely contested may be due to increased awareness of the importance of human subjects protection since the institution of IRB review. Depending on the type of protocol, IRB members may also lack sufficient expertise to challenge study design. Most problematic is the fact that the dominant players on IRBs are also members of the medical and research communities. These individuals are likely to value scientific progress as well as have a personal interest in avoiding demands for revision when their own protocols come under review, all of which may bias the IRB toward research approval.[15]

Once a consent form is approved, whether it contributes significantly to the protection of human subjects depends on factors that are not easily regulated. Meaningful informed consent involves a dialogue between researchers and individual subjects to explain the study and answer questions. To be effective, the language used to explain a study and its risks and benefits must be tailored to the study subject. The subject's understanding must be verified, and the greatest possible effort must be made to ensure that subjects' decisions are not influenced by desperation, intimidation, or manipulation.[16] Because monitoring is rare, there is often no way to know whether subjects' decisions are truly informed and voluntary.[17] Unless given evidence to the contrary, IRBs generally assume on good faith that researchers will provide an effective informed consent process, will follow the protocol as described, and will not place subjects at unnecessary risk.

In international research, informed consent is more problematic. If populations are unfamiliar with basic biomedical concepts, the purpose of a particular study or trial may be incomprehensible. Subjects' concerns about the risks and benefits of participation may differ from what Western researchers consider important. Subjects may be so desperate for medical care that obvious risks seem insignificant. Further hindering the process, subjects may be illiterate or may expect some other person to make their decisions for them. Informed consent under these circumstances cannot be considered ethically equivalent to the same process in the United States.

In summary, if Western ethical standards are accepted as universal, IRB approval will be based on specific, legally and institutionally defined criteria. Adherence to Western standards will ensure that certain ethical principles will be upheld (at least on paper). However, because an IRB may be unaware of, or may overlook additional sources of risk that are not specified in the approval criteria, the effectiveness of this standard in protecting human subjects might be limited. Alternatively, if the IRB determines that circumstances are such in the host country that Western criteria cannot be upheld, it may refuse to approve potentially valuable research. Despite the shortcomings of this standard, a stance of moral fundamentalism is currently the most feasible approach for IRB review. Given the practical difficulty of assessing risks in distant countries and cultures, and the absence of clear federal and institutional guidelines for

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review of cross-cultural research, it is at present morally and practically difficult for an American IRB to demand more of research conducted in foreign countries than is legally required for research conducted domestically.

Broad view: an ethic of moral relativism

In a contrasting approach to cross-cultural research, moral fundamentalism has been characterized as "ethical imperialism,"[18] charged with ignoring multiculturalism and postmodern criticism.[19] In this view, notions of human rights and the protections owed to human subjects are believed to be derived culturally, not universally.[20] In terms of IRB review, this approach suggests that Western ethical standards should be modified to correspond to those of the host research environment, research approval being based on whether human subjects are adequately protected given the sociopolitical circumstances, cultural values, and ethical standards of the host country and subject population. The merit of this approach is that it acknowledges the diversity of human communities, and in doing so calls for careful evaluation of the values and circumstances of research subjects. Ideally, this approach should not only lead to better protection for subjects; in some cases, it may also enable research to proceed that would be prohibited by Western ethical criteria.

The chief criticism of this approach is that it suggests ethical relativism—that ethical standards vary with sociocultural context. In concrete situations, it presents the problem of whose or which values take precedence in a given research environment. The values of the dominant social groups in host countries, which usually include medical researchers and institutional and government officials, may not be consistent with those of the subject population. If the aim of the IRB is to ensure that subjects are adequately protected, who decides what protection entails? Also unclear is whether an act constitutes a harm if it is not recognized as such by the persons or groups it affects. For example, would consent given by a group leader rather than by an individual constitute a violation of autonomy if the individual in question does not perceive it as such?

From a sponsoring country's perspective, if ethical standards are taken as culturally relative, then conceivably researchers could be expected to suspend their own values when conducting research in other countries. This is a troubling proposition for three reasons. First, researchers have past histories and personal values that they would probably find difficult to abandon while engaged in work that represents many of their most firmly held beliefs. To expect them to do so would be to ask for a sacrifice of personal integrity that is both morally abhorrent and infeasible in practice. Second, if researchers were permitted or expected to suspend Western ethical principles whenever such principles are deemed incompatible with the research context, soon to follow would be widespread exporting of controversial research to countries where vulnerable populations could be easily exploited. Finally, accepting different ethical standards for each research protocol and subject population may undermine public confidence in the ethical integrity of medical researchers.

If one accepts that ethics are to some extent culturally derived, in order to receive IRB approval, each international research initiative would have to be evaluated on unique ethical criteria corresponding to the values and sociocultural context of the anticipated subject population. Assuming this contextual information can be obtained and corresponding risks assessed, theoretically, an IRB could work with researchers to develop procedures that would provide maximum protection for subjects. The limiting factors in this approach lie in the details of how significant sociocultural factors and risks would be identified, and how, in view of this information, ethical modifications would be made. Neither task is amenable to formulaic procedures or routines. But, if these issues cannot be resolved in a fair and culturally sensitive manner, an ethic of moral relativism may all too easily lead to greater harms for subjects.

IRB review of international collaborative research: a negotiated ethical standard

It appears that whether ethical standards are considered absolute and universal or culturally dependent, the protection of human subjects is far from assured. Despite their limitations, the two ethical approaches for IRB review described above reflect important truths that should be acknowledged in the research review process. In what follows, I propose that by combining these approaches and several of the CIOMS guidelines, viable review criteria for cross-cultural collaborations can be developed. My goal is a culturally sensitive approach to subject protection, structured within a framework of checks and balances that validates the ethical priorities of both the sponsoring and host cultures.[21]

The weaknesses of the two approaches previously described demonstrate that approved research must accommodate the ethical values of both the sponsoring and the host countries. Because the sponsoring researchers are responsible to their funders and institutions for complying with federal and institutional ethical standards, and because publication results may depend on it,[22] it is essential that the research protocol satisfy Western standards of respect for persons, beneficence, and justice. For this reason, the sponsoring IRB should have the last word on whether a protocol is approved. But because local circumstances may affect how Western ethical principles serve to protect subjects, in the details of how research is carried out—how subjects are selected, how informed consent is obtained, or how diagnoses disclosed—host countries should be able to

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...ify Western standards to correspond to the context and ... interests of subject populations. This "negotiated ..."[23] occupies a middle ground between fundamental- ... and relativism in which the ethical standards and socio- ...ural values of both sponsoring and host countries may ...acknowledged.

Inherent in this proposal are two implementation prob- ...s that have already been noted. First, how should sig- ...cant social and cultural factors be identified, correspond- ...risks assessed, and by whom? Second, how should con- ...ts between participating countries be resolved? Mutu- ... satisfactory answers to these two questions must be ...eloped if a negotiated ethical standard is to have any ...ance of success. In what follows, I first explore how an ...RB could go about assessing risks; I then outline a process ...r conflict resolution. Finally, I propose a five-step process ...r IRB review of international collaborative research.

...isk assessment: using subject representatives

...ecause few sponsoring researchers or IRB members are ...ore than superficially acquainted with the cultural con- ...ext of foreign subject populations, a reliable means of as- ...essing subjects' risks and concerns is essential. One way to ...do this is to include representatives from subject popula- ...tions, or their advocates, as members or consultants to the host country's IRB.[24] Subject representatives should be cho- ...sen for their ability to grasp the aims and methods of the proposed research, to identify and articulate any sociocul- ...tural norms or values of their communities that conflict with Western ethical standards or pose additional risks for subjects, and to communicate among potential subjects, researchers, and IRB members about the interests of each. Information sought may pertain to social inequities related to race, ethnicity, socioeconomic class, gender, or the political climate. Other important information would include any variation in obtaining informed consent, such as identifying persons to serve as intermediaries between researchers and subjects; any kinds of gifts or other inducements that may or may not be appropriate given a community's gift-exchange traditions; and any additional concerns felt among the subject population regarding confidentiality and privacy.[25]

The use of subject representatives suggests a direct and feasible way to present subjects' concerns to an IRB, but their use creates additional problems for researchers. First, if subject representatives are included on an IRB, who should select them? Reliance on the primary investigator to make the appointment may result in a bias toward research. Subject populations may not be sufficiently organized or informed to appoint their own representatives. Moreover, individuals with the education necessary for the assignment may not be typical of the subject group as a whole. But if the subject representative is not "representative," a token appearance on an IRB will not serve subjects well. Second, if the subject population is diverse, one or two representatives may not be able to represent different perspectives adequately. How can an IRB be assured that the concerns of all participants have been fairly represented? Third, if no subject representatives are available or feasible, it may be necessary to hire one or more consultants to do the investigation. Again, questions arise about what qualifications and experience would be required for these consultants, and whether it would take more than one consultant to provide an accurate assessment of the concerns of a diverse population. In short, even though including subject representatives on an IRB offers the possibility that subjects' concerns can be identified, their participation does not guarantee that all concerns will be heard or that the IRB will be responsive. Cost issues associated with travel, accommodation, and any interpreters for subject representatives create additional burdens for researchers. But as unsatisfactory as it is, within the current structure of medical research, this approach offers the greatest likelihood that subjects' concerns will be addressed.

Resolving ethical disputes: elements of a process

If the ethical standards of the sponsoring country are to be modified to accommodate the cultural norms and values of the subject population, some criteria or process must be developed that offers maximum protection for subjects while acknowledging the ethical values of the host and the sponsoring countries. One such approach has been proposed by Nicholas Christakis and Morris Panner,[26] who identify a set of principles to serve as basic guidelines for ethical conflict resolution.

First, subject representative(s) in the host country should be presumed to have the greater insight into the social, cultural, and ethical concerns of the subject population. If a conflict arises between the host and sponsoring country, the host country's standards should prevail, if they are the more rigorous. Second, researchers should adhere to the ethical judgment of their home institution, whether or not the collaborating institution approves the research. This rule acknowledges the moral and psychological difficulty of suspending one's own values and the risks inherent in permitting it. What is more important, it would prevent research from going forward without approval from the sponsoring and the host countries. Third, ethical guidelines, once accepted, should be applied equally to all research subjects. In other words, there should be no favoritism or exclusions from protection in the subject population. Fourth, if research is not approved by either country's IRB or fails to meet international standards, rather than abandon the research, the causes of the ethical dispute should be resolved by means of formal and fair negotiations. If consensus is reached, that agreement will supersede other ethical stan-

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dards. If consensus cannot be reached, the research should be abandoned.

The fourth principle limits the function of Western standards to a baseline or a general template, modification of which could be considered appropriate under certain circumstances. The questions remaining are when, and how, ethical disputes should be resolved. Ethical standards should not be altered simply to expedite research; rather, significant ethical conflict must be evident, as well as demonstrated need for the research. In addition, while Christakis and Panner's principles provide a foundation for a dispute resolution process, it is unclear what would be the appropriate forum for negotiations, the criteria by which ethical standards might be modified, the limits or boundaries to these modifications, and who would adjudicate such a process.

IRB review: a five-step process

Assuming potential risks to subjects can be assessed and an effective conflict resolution process developed, IRB review would consist of a five-step process. In this process, the responsibility for subject protection would be divided among the sponsoring and host researchers and their respective IRBs. If no IRB exists for the host country, the external sponsors should provide the financial and educational resources to enable the host country to establish one for independent ethical review.[27] For research to proceed, approval would be required from both IRBs, each having a different role and different approval criteria.

The five steps are as follows: (1) ratification of the CIOMS guidelines by all collaborating countries and/or institutions; (2) initial approval by the sponsoring institution's IRB; (3) review and modification by the host country's IRB; (4) negotiation, if necessary; and (5) final approval by the sponsoring IRB.

First, as a means of demonstrating good faith and providing a basis for accountability, any nations or institutions participating in international collaborations must ratify or otherwise affirm a commitment to the CIOMS guidelines. Second, the IRB from the sponsoring country would review the protocol according to general ethical criteria defined in its national and institutional regulations. These criteria would include establishing that the research design is appropriate; that a legitimate scientific and medical rationale exists for conducting the study in the host country; that risks to subjects are minimized; that the drugs or devices used meet national safety standards; that the proposed research initially satisfies the ethical standards of the sponsoring country or the CIOMS guidelines; and that products developed from research be reasonably available to the population of the host country.

Third, if initial approval is granted by the sponsoring IRB, the host country's IRB would then review the protocol. Approval criteria for the host IRB would include ascertaining that the research goals are appropriate, given the health needs of the country; that an appropriate balance of potential or anticipated benefits to the host population, researchers, and the national government has been established, in view of the nature of the research and the risk involved; that the risk-benefit ratio for subjects is reasonable and subject selection equitable; and that any benefits or products of research will be made available to the population of the host country. With the aid of subject representatives, the host IRB would also identify additional risks or logistical problems arising from the social, political, or cultural environment of the subject population and translate Western ethical standards, such as the requirement of informed consent, into meaningful practices in local communities. Based on this assessment, the host IRB would make recommendations for revision of the protocol.[28]

Fourth, the revised protocol would return to the sponsoring country's IRB for final approval. At this point, any ethical conflicts or logistical problems related to the revisions would be negotiated between the sponsoring researchers and members of the host IRB, according to the principles proposed by Christakis and Panner.[29] If negotiations lead to consensus, in order to receive final approval, any modifications agreed on must be identified and explained to the sponsoring country's IRB with the understanding that, under the circumstances, Western ethical expectations could not be fully upheld. The IRB may accept these modifications, if it is satisfied that: (1) the research is of such importance that it warrants modifying Western ethical standards; (2) the host investigators have a thorough understanding of the risks to the subjects, given the social, cultural, and political context of research; and (3) these risks have been sufficiently minimized in the modified research design. If modifications are accepted, approval by the sponsoring institution may be considered final. If conflicts persist, negotiations may resume until consensus is reached. If no consensus is possible, the research should not proceed.

These guidelines offer a culturally sensitive means of research review in which the ethical standards of sponsoring institutions may be upheld in the main, while, at the local level, specific practices in implementation can be modified to the research context. As cumbersome as the proposal is, it offers an IRB a structured and balanced process by which human subjects protection in cross-cultural research can be uniquely evaluated relative to contextual circumstances. However, many questions remain unanswered. Specifically, these guidelines assume it is possible to provide subjects with qualified representatives, to identify the contextual factors that pose risks to subjects, and to develop a fair and effective process of conflict resolution. It is unclear whether these are realistic assumptions.

Even if they are, absent the integrity and good faith of all participating researchers and IRB members, uncertainty will remain whether the review process is fair and adequately

addresses subjects' protection. For example, had the collaborative research conducted in China been approved through the process described here, it is not clear whether it would have resulted in significant changes in the protocol. Had subjects been represented on the Chinese ethics committee, it might have been possible to know whether they felt the lack of anonymity in the face-to-face interviews put them at additional risk. Other concerns might have included whether subjects trusted researchers to maintain confidentiality, or whether there were hidden incentives for participation. However, the mere inclusion of subject representatives on the Chinese committee is no guarantee that subjects' concerns would be voiced or addressed. One of the most difficult problems with this approach is that, in a political climate of ingrained social and political inequities, without some means of enforcement, normally disenfranchised subjects may be not be heard, especially if the result for the listener is the loss of research support and substantial foreign funding. Thus, the only real leverage for subjects lies in the requirement that the nation or institution ratify the CIOMS guidelines. If monitoring is also possible, subjects have considerably greater chances that their concerns will be addressed.

Conclusion

IRB evaluation of international collaborative research protocols is not currently addressed in existing guidelines or legislation. Strict adherence to Western ethical standards may be inadequate for human subjects protection or may unduly inhibit potentially beneficial research. If ethical standards are to be modified, it is not clear what kinds of information, principles, and institutions should govern these modifications or what new opportunities for harms the modifications may create.

The guidelines for IRB review proposed here attempt to acknowledge the variety of ethical perspectives present in cross-cultural research with the aim of providing maximal protection for study subjects without prohibiting valuable research. They are admittedly imperfect and open to abuse. However, without addressing every possible contingency, they legitimate careful examination of the research environment and actual risks to subjects, and provide an alternative to blind acceptance or categorical rejection of research that fails to fit the Western mold.

Despite an IRB's best efforts, there is a limit to how much administrative control can influence human behavior. Paper documentation is meaningless if it bears little relation to what occurs between researcher and subject. The history of medical research illustrates that it is generally practiced by a social elite who have repeatedly been willing to sacrifice subjects' interests in the name of science. This record of untrustworthiness confirms that researcher integrity cannot be assumed and that IRB effectiveness is limited. Absent widespread monitoring, opportunities for abuse probably cannot be entirely eliminated. Nonetheless, the success of medical research ultimately depends on the integrity of researchers. Because the principles of respect for persons, beneficence, and justice cannot be legislated across cultures, the bottom line is trust. When trust is violated, whether the harms are to human subjects, researchers, institutions, or funding agencies, future collaborations are jeopardized. In this way, the most effective incentive available for human subjects protection may be the necessity of trust.

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6. See Regulations on the Protection of Human Subjects, 45 C.F.R. § 46.101(h).

7. See "The Nuremberg Code," in G.J. Annas and M.A. Grodin, eds., *The Nazi Doctor and the Nuremberg Code: Human Rights in Human Experimentation* (New York: Oxford University Press, 1992): at 2.

8. See World Medical Assembly, "World Medical Association Declaration of Helsinki," in Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (Geneva: CIOMS, 1993): at 47–50 (citing 1989 Declaration of Helsinki).

9. See Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (Geneva: CIOMS, 1993) [hereinafter *CIOMS Guidelines*].

10. This statement suggests the Chinese were aware that subjects might be apprehensive about the consequences of being identified as carrying the human immunodeficiency virus.

11. See Y.G. Wang, "AIDS Policy and Bioethics: Ethical Dilemmas Facing China in HIV Prevention," *Bioethics*, 11 (1997): 323–27; B.R. Liu, "Legal Regulations of AIDS Detection and Administration in P.R. China," *International Journal of Bioethics*, 3 (1992): 25–27; and M.L. McCall, "AIDS Quarantine Law in the International Community: Health and Safety Measures or Human Rights Violations?," *Loyola of Los Angeles International and Comparative Law Annual*, 15 (1993): 1001–28.

12. See R. Baker, "A Theory of International Bioethics: Multiculturalism, Postmodernism, and the Bankruptcy of Fundamentalism," *Kennedy Institute of Ethics Journal*, 8 (1998): 201–31.

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DECLARATION OF HELSINKI

"The potential benefits, hazards & discomfort
of a new method
should be weighed
against the advantages of
the best current diagnostic & therapeutic methods"

DECLARATION OF HELSINKI

"In any medical study, every patient including those of a control group if any, should be assured of the best proven diagnostic and therapeutic method"

HELSINKI DECLARATION

"... the best current or best proven treatment for control groups".
Not "... the best available treatment"
or ..."... the best local treatment".

GUIDELINE 15 CIOMS. 1993

"An external sponsoring agency should submit the research protocol to ethical and scientific review according to the standards of the country of the sponsoring agency, and the ethical standards applied should be no less exacting than ... in the sponsoring country"

RUTH ELLEN BULGER, PhD

Toward a Statement of the Principles Underlying Responsible Conduct in Biomedical Research

Abstract—Biomedical research still does not have clear, written, agreed-upon underlying values (for a number of possible reasons that are discussed), and a variety of new pressures are making it necessary to formulate such principles. Toward that goal, this essay first traces the development of the underlying principles that have been formulated in the sphere of human subjects research, from the ancient Hippocratic injunction of *do no harm* to the three principles identified in 1979 by the National Commission for Protection of Human Subjects of Biomedical and Behavioral Research: *respect for persons*; *beneficence*; and *justice*. Using these principles as a pattern, the following "candidate principles" are proposed for biomedical research to stimulate discussion and the development of consensus among biomedical scientists: *honesty of scientists* (which encompasses the essential values of integrity, objectivity, verifiability, and truthfulness); *respect for others* (including respect for research subjects—both humans and other animals—colleagues, and the environment); *scholarly competence* (which is related to the processes of obtaining and passing on knowledge); and *stewardship of resources* (involving obligations to protect society from the problems intertwined with scientific advances). Guiding principles of this type must be articulated so they can be transmitted to upcoming scientists, who then can productively and responsibly help shape the future of the research enterprise. *Acad. Med.* 69(1994):102–107.

Biomedical scientists *live* the codes of ethics by which they work. As mentors, they pass on these codes to their students as part of the apprenticeship process. Some attributes of these codes have been listed, but there is a lack of both clear, written articulation of their underlying principles and meaningful development of consensus about them among biomedical scientists. In the 1950s, Pigman and Carmichael wrote a prescient article pointing out a "failure of scientists as a group to consider ethics" and stressing that basic science has been a vital force for the advancement or destruction of society. They stressed scientists' obligations to society to explain the nature and purposes of science, to clarify attitudes toward patents and secrecy restrictions, and to affirm obligations to employers, associates, other scientists, assistants, graduates, and those in other professions. Feeling that the pressing ethics problems related to authorship issues, they discussed only those problems in depth and did not further develop the idea of a code.[1]

Robert K. Merton gave the following as the norms of the scientific community: sharing the results of their work; being critical and testing in the laboratory the work of other scientists; conducting their work without regard for material gain or for reputa-

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tion; and assuring that scientific truths and claims should be true everywhere.[2] Recent considerations of scientific norms have dwelt not on what constitutes responsible scientific conduct but on the definition and the causes of misconduct.[3-5]

The present essay traces the development of underlying principles in the sphere of human-subjects research and, using these principles as a pattern, proposes candidates for underlying values in biomedical research, to stimulate discussion and the development of consensus among scientists.

PRINCIPLES UNDERGIRDING HUMAN-SUBJECTS RESEARCH

From at least the time of Hippocrates, who promised that "into whatsoever house I enter, I will enter to help the sick, and I will abstain from all intentional wrongdoing and harm," the duties of health care professionals to their patients have been scrutinized for applicable moral principles.[6] This scrutiny has been particularly important in those cases when the customary therapy is not helping the patient, who then sometimes becomes the subject of a kind of care that borders on experimentation.

This practice of learning from observation and/or experimental treatments during the care of the patient, though typically arising from honorable motives, has led to abuses of the physician–patient relationship. The atrocities committed in the name of science on prisoners of war and civilians during World War II are a constant reminder that human subject abuse can occur. During the Nuremberg military war crimes trials, a set of standards, called the Nuremberg Code, was drafted for judging the physicians/scientists who conducted these wartime human experiments.[7] The Nuremberg Code has served as a stimulus for the development of other codes for protecting human subjects (e.g., the Declaration of Helsinki[8] adopted by the 18th World Medical Assembly, Helsinki, Finland, in 1964, revised in 1975).

In spite of the development of such codes to provide guidance to health care professionals, flagrant abuses concerning the use of humans as research subjects continued to occur in the United States. For example, in a study that began in 1932, rural black men with syphilis, who were the research subjects, were allowed to go untreated long after penicillin treatment had been shown to be efficacious for this condition (and after the Nuremberg Code had been articulated).[9] In another instance, debilitated elderly patients at the Jewish Chronic Disease Hospital in Brooklyn were injected with live cancer cells to determine if the cells would be rejected, in spite of the fact that proper informed consent was not obtained.[10] A series of unethical research experiments was exposed by Henry K. Beecher in a landmark speech and subsequent publication.[11]

Partially in response to these disclosures; the National Research Act of 1974 established a National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research to provide principles and guidelines for the use of humans as subjects in clinical research.[12] Between 1974 and 1978, the National Commission wrote several reports that enunciated basic ethical principles and guidelines that were to underlie ethical research involving human subjects. In a report that became known as the Belmont Report, published in 1979, the commission identified three comprehensive ethical principles that were to serve as an analytical framework to assist physicians/scientists, human subjects, and reviewers of research proposals in understanding the ethical issues inherent in such research.[13] The principles are *respect for persons*; *beneficence*; and *justice*.

The development of some principles governing clinical research ethics, from Hippocrates' time through a complex and tortuous history over the last 50 years, may be regarded as a victory for practical ethics, because clinicians these days understand the values that drive and undergird their efforts far more clearly than they did 50 years ago.

VALUES IMPORTANT IN BIOMEDICAL SCIENCE

The relative clarity of underlying values that now exists in clinical research is not present in basic biomedical research. Underlying principles have not been enunciated in a way that provides a similar analytic framework for areas of the basic biomedical scientific endeavor. This absence of ethical guidelines becomes more obvious as one works with students in formal courses (such as those mandated for trainees supported by the National Institutes of Health[14]) to analyze case studies that probe aspects of the responsible conduct of research scientists.

There are several possible reasons for this absence of enunciated ethical principles to guide actions in the basic science arena: (1) society had previously allowed the self-correcting nature of science and the internal oversight mechanisms of the profession to suffice; (2) members of society previously had more shared political and religious values to guide conduct in all fields; (3) flagrant ethical lapses during the conduct of basic biomedical research had not been evident; (4) the specialized vocabulary of science restricts public access to and understanding of scientific issues; (5) the previous size of the scientific community was smaller, the rate of scientific discovery slower, and the competition for research funding less intense than is presently the case, so fewer ethical issues challenged the scientific community; and (6) the value-laden nature of scientific endeavors previously had not been widely recognized.

More recently, however, the greatly expanded public support of biomedical research, the frequent press accounts of cases of alleged scientific fraud and/or misconduct, the increased pace of developments in biomedical sciences, the more frequent emergence of ethical dilemmas related to science, and the heightened public recognition of the social impacts of technological advances have led to a demand for a new level of accountability from the scientific community. One aspect of this new

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accountability is the necessity of using more formal mechanisms for teaching trainees in the biomedical sciences about how to conduct science responsibly.[14]

However, as scientists and their professional societies have begun to establish guidelines concerning scientific conduct, they have used categories based not on underlying principles but instead on spheres of action such as authorship practices, conflicts of interest and commitment, and proper recording and analysis of data. Although important, such guidelines do not provide the needed answers to students concerning their less administrative and more ethically complex questions in the same way that principles can.

In order to stimulate the formulation of ethical principles for scientific conduct that could provide the needed analytic framework for thinking about obligations to society, the following "candidate principles" are suggested: the *honesty of scientists*; *respect for others*; *scholarly competence*; and *stewardship of resources*.

HONESTY OF SCIENTISTS

Honesty would most likely be the first value invoked by scientists. For example, the National Academy of Sciences report, *Responsible Science. Ensuring the Integrity of the Research Process*, lists honesty, integrity, objectivity, and collegiality as the set of values, traditions, and standards that bind scientists into a community (p. 1). Honesty is the basis of integrity. Indeed, what is called "integrity of the research process" is defined by the report as "adherence by scientists and their institutions to honest and verifiable methods in proposing, performing, evaluating, and reporting research activities" (p. 17). In a second discussion of values, the report lists integrity, honesty, trust, curiosity, and respect for intellectual achievement; of these, truthfulness, both as a moral imperative and as a fundamental operational principle, is singled out as most basic (p. 17). The Massachusetts Institute of Technology's *Report of the Committee on Academic Responsibility* lists as essential values "honesty, performing one's craft with skill and thoroughness, respect and fairness in dealing with others, and responsibility to people and institutions."[15] The majority of the basic values mentioned in these reports (honesty, integrity, objectivity, verifiability, and truthfulness) could be viewed as parts of the overall category of honesty. That is, the honest scientist would act with integrity and would adhere to the facts; the work would therefore be able to be trusted as being truthful and as objective as possible.

Basic to the conduct of scientific research is the attempt to honestly observe, record, and interpret some aspect of the material world—what the modern scientist would express as "seeking the truth." The postmodern scientist might instead point out that such objectivity is impossible, since all information is processed by the observer, including the most truthful scientist. Thomas Kuhn points out that a person who knows what it is to be scientifically legitimate may still reach any one of a number of incompatible conclusions, since "the particular conclusions he does arrive at are probably determined by his prior experience in other fields, by the accidents of his investigation, and by his own individual makeup."[16]

One way to attempt to ensure objectivity is for the scientist to be honest about personal biases. For example, the preferential use of middle-aged white men as the traditional (and sometimes as the only) subjects for clinical studies of disease processes was based not on any overt belief that white men were more worthy or important, but on the unexamined belief that the data would be generalizable to other groups. Only with the recognition and testing of this belief was it possible to appreciate the lack of uniformity of responses by sex, race, and ethnicity.

Another way for the scientist to facilitate honesty is to avoid conflicts of interest with the possible results of the work to be done. Conflicts of interest can be based on either financial or intellectual considerations, or on combinations of the two. It is important, yet relatively easy, to avoid situations in which one's personal financial gain is effected by the scientific result produced in the research undertaken. For example, a scientist doing a clinical trial of the efficacy of a given drug should not own stock in the company that is producing the drug. However, it is more difficult to assure objectivity when favorable experimental results would lead to more publications, additional research funding, and/or job advancements and additional prestige in the community of peers.

A variety of experimental methods are used by scientists to safeguard honesty. The use of concurrent control experiments; blind experiments in which the investigator does not know which observations come from experimental subjects and which from controls; experiments involving multiple, independent observers; and the serial repetition of experiments are all examples of such mechanisms. In addition, the scientist must be prepared to profit by aberrant or unexpected experimental results, since appreciation of the unexpected experimental result provides the opportunity for new insight or discovery.

Only by honesty can *trust relations* be built up among scientists. The trustworthiness of the individual scientist is therefore crucial. Steven Shapin describes trust relations as constitutive of the making, maintenance, and extension of scientific knowledge.[17] The very character of science would change without trust; with an increase in skepticism and distrust, "much of our modern structure of scientific knowledge should be unwound, put in reverse, and ultimately dismantled. Instead of laboratories for the production of new knowledge, we should build great facilities for the close re-inspection of what is currently taken to be knowledge. Grants will be given for checking routine findings; published reports will look more and more like laboratory notebooks."[17]

Honesty also involves being complete in descriptions of methods used and results obtained so that the experiments can be repeated by others. It involves the honest (accurate) use of the ideas or words of others.

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RESPECT FOR THE OTHER

The second basic principle relates to having high regard or esteem for other people and things. These "others" include research subjects (both humans and other animals), the environment, and colleagues (including employees, students, and trainees).

Human Subjects

The ethical principles and the obligations that are part of human-subjects research form a crucial segment of the ethical concerns for biomedical research. They have been well described. For example, the Belmont report, mentioned earlier, discusses *respect for persons*, including the idea that individuals should be treated as autonomous agents and that persons with diminished autonomy are entitled to protection.[13] Participation as a research subject should be undertaken freely and with the awareness of any adverse consequences of that participation. *Beneficence* requires that possible benefits be maximized while possible harms are minimized. *Justice* requires that persons receive benefits to which they are entitled and that undue burdens are not imposed on them. These principles form the basis of the requirements of informed consent (sufficient information, adequate comprehension, and voluntariness), the adequate assessment of risks and benefits, and the fairness of procedures and outcomes in the selection of research subjects.[13] Institutional review boards have the responsibility to assure that these procedures are adequately followed.

Animal Subjects

Similarly in research using animals, respect for animal research subjects entails a commitment to the humane care and treatment of experimental animals. After a careful and sensitive analysis of factors involved with the use of animals in biological research, Caplan[18] concluded that animal experimentation is always morally tragic and that "many animals used in experiments are sentient and purposive, and they have *prima facie* rights to live and be left alone." He therefore finds that it is imperative to reduce waste and duplication in the use of animals, to fund the development of alternatives to animal testing, and to make people aware of the tradeoffs necessary in trying to "achieve human well-being, health, safety, and knowledge at the expense of animal suffering," since it is society that will ultimately decide if such use is warranted. In 1959, Russell and Burch grouped the ideas that scientists conducting research on animals need to consider into the three R's of *refinement*, *reduction*, and *replacement*.[19] Bulger extends the discussion of Russell and Burch and adds to this a fourth R: *review*.[20]

Refinement provides for such actions as a decrease in incidence and severity of the procedures used, including avoidance of unnecessary physical or mental suffering or injury; the introduction of new, less invasive instrumentation to decrease pain; and the use of skilled, qualified investigators in optimal physical facilities. *Reduction* of animal use relates to doing a thorough literature review to ensure that the experiments have not been previously undertaken, that the data obtained be important and therefore valid methods with adequate record keeping be used; and that the results be rapidly published to avoid unneeded repetition by others. *Replacement* focuses on the use of alternative methods such as chemical tests instead of bioassays, audiovisual aids in teaching, and microbiological agents used in screening for carcinogens. It includes the substitution of animals lower on the evolutionary scale. Adequate internal *review* has now been largely replaced by governmental regulation of animal care and use. Investigators must be cognizant of and responsive to their obligations, as specified by regulatory agencies, when they use experimental animals in their research.

The Environment

Respect for the environment is also an issue in laboratory research. Avoiding unnecessary duplication of experimental procedures not only minimizes the number of animals used, but decreases waste of all types. Many laboratories are now involved with recycling of paper, glass, and metal. In addition, the reclaiming of certain expensive chemicals, such as osmium tetroxide, can become a routine laboratory practice. Procedures for the safe disposal of microbiological, chemical, and other wastes (such as syringes and needles) must be established and routinely carried out.

Colleagues

Many factors in modern academic life form barriers to respect or collegiality among faculty or between faculty and students.[21] For example, tensions have developed between clinical and basic science faculty, between MDs and PhDs in clinical departments, and between PhDs in the university and in the medical schools over salary differentials, time available for research, time required for the teaching of students, and independence of research topic selection. Respect for the students is of utmost importance, for it is they who will become the lifeblood of future research. In addition, the frantic pace of life in the highly competitive environment of research-intensive medical centers limits time available for establishing collegial relationships. The increasingly litigious nature of society limits the open self-evaluation of scientists' activities.

However, respect for colleagues can be expressed in many ways that are unique to and necessary for effective laboratory research. Laboratory safety is one such issue. Since the laboratory is frequently a shared environment, common reagents need to be carefully prepared and accurately labeled. Dangerous chemicals, radioactive reagents, and microbiologic agents require safe handling procedures, and spills of harmful chemicals must be cleaned appropriately. Individuals working in the laboratory need to have access to written materials that provide information about the safety requirements of all chemicals that are used.

Colleagueship is also expressed by

The New York Times

NEW YORK, MONDAY, MAY 17, 1999

A Doctor's Drug Studies Turn Into Fraud

By KURT EICHENWALD
and GINA KOLATA

RESEARCH FOR HIRE

Second of two articles.

WHITTIER, Calif. — If ever there was a wonder boy in the lucrative business of drug testing, it was Dr. Robert Fiddes.

In just a few years, Dr. Fiddes transformed his sleepy medical practice here into a research juggernaut, recruiting patients for drug experiments at a breakneck pace. His success made him a magnet for an industry desperately scouring the nation for test subjects. Companies large and small showered him not only with more than 170 studies to conduct, but with millions of dollars in compensation for his work.

Life was good. With bank accounts bulging, Dr. Fiddes and his wife could afford to drive matching BMW's; a Ferrari parked in his garage was ready for special occasions. After a short time in research, the once small-time family practitioner was planning his dream house on a Cayman Islands beach and envisioning the day he would make millions more by selling shares in his business to the public.

But amid the glitter and cash was a fact that no one outside his office knew: It was all a scam.

For Dr. Fiddes was conducting research fraud of audacious proportions, cutting corners and inventing data to keep the money flowing from the drug industry. Fictitious patients were enrolled in studies. Blood pressure readings were fabricated. Bodily fluids that met certain lab values were kept on hand in the office refrigerator, ready to be substituted for the urine or blood of patients who did not qualify for studies.

Monitors for the Government and the industry never noticed any problems with Dr. Fiddes's bogus paperwork, which they reviewed during routine audits. Even when some of Dr. Fiddes's employees alerted those monitors to their suspicions, no investigations were initiated. Instead, their warnings were filed away, while Dr. Fiddes's sterling reputation as a researcher grew.

Finally, in June 1996, the scheme started to unravel when the manager of a neighboring doctor's office, Dennelle Del Valle, told a Government auditor rumors of crimes, lies and fraud she had heard from Dr. Fiddes's own employees. Eventually, to prove the claims, Ms. Del Valle slipped a piece of paper into the auditor's hand. On it was written a

Continued on Page A16

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A Doctor's Drug Trials Were Grounded in Fraud

Continued From Page A1

telephone number and a single name: Susan. It was the tip that would lead the Government to Susan Lester, a former employee of Dr. Fiddes who not only knew what had happened, but had a few records that seemed to back up her story.

So began the multiyear investigation of Dr. Fiddes's Southern California Research Institute, a testing operation that was one of the most corrupt research enterprises ever discovered by law enforcement. The case is set to wind to a close this week, with the scheduled sentencing of the last co-conspirator. But in its wake is wreckage: Dr. Fiddes and several accomplices pleaded guilty to fraud, drug-study results for virtually every company in the business were compromised and the reliability of the private system for testing drugs for safety and efficacy has been thrown into question.

Dr. Fiddes "was putting the health of all these patients at risk," said Alan Knox, the former chief financial officer of Dr. Fiddes's research center, who resigned just months after taking the job when the investigation led him to learn of the fraud. "But he was also skewing samples that could affect the whole American public."

The abuses of this one doctor point to weaknesses in the new system developed in recent years for testing experimental drugs. No longer does the pharmaceutical industry rely on career researchers at academic medical centers, whose professional reputations are forged on the quality of their data. Rather, the industry has turned to thousands of private-practice doctors, for whom testing drugs has become a sideline for making money.

While the researchers and their incentives have changed, the methods of monitoring what they do remain basically the same even though now, since they are paid for each patient they recruit, researchers have an enormous financial incentive to cheat. The case of Dr. Fiddes underscores the ease with which such a system can be deceived — a situation that has not been remedied since the discovery of his crimes.

The story of the corruption at the Southern California Research Institute was pieced together from memos and other internal documents, investigators' notes, drug company and court records, personal diaries and affidavits of participants, as well as interviews with Government officials, lawyers and the former employees and consultants at the company, which is now defunct. The picture that emerges from these documents and interviews is of a research office ruled by a doctor driven by greed. Few employees other than the study coordinators — mostly women of limited financial means — were aware of the magnitude of the swindle. Those bothered by it were repeatedly assured that this was the way the drug industry worked. Faced with that perception, there seemed little they could do without risking their livelihood to stop the influential Dr. Fiddes, a man who believed that the system of monitoring was too poorly designed to ever catch him.

"I don't think he thought he could be touched," said Kathryn Davis, a medical transcriber at the research center. "We just didn't understand why it had to go down the way it did. Maybe he just wanted too much too fast."

Through his lawyer, Dr. Fiddes — who is now serving a 15-month sentence for fraud in the Metropolitan Detention Center in Los Angeles — refused repeated requests for an interview. But in interviews with the Government after he agreed to plead guilty, Dr. Fiddes portrayed himself as a man trapped by the dishonesty of others. He maintained that most researchers are forced to cheat because drug companies issue requirements for test subjects that sound good in marketing material, but are impossible to meet in the real world. He said — with no evidence to back up his claim — that anyone successful in the business was skirting the rules.

Still, at his own research center, Dr. Fiddes laid much of the blame for everything that happened on his study coordinators — again, without providing evidence to support the assertion. While he was the beneficiary of the illegal activity, he maintained that it was the salaried employees working for him who devised the frauds, often without his knowledge. The information provided by Dr. Fiddes has not resulted in any additional investigations.

Despite his refusal to accept the blame, Dr. Fiddes was anguished at being labeled a criminal. In a letter pleading for mercy that he sent last year to Federal District Judge Robert M. Takasugi, he described his torment. "My family has had to endure the humiliation of seeing a husband and father sink from being a widely respected community member to now being visualized as nothing more than a common crook," Dr. Fiddes wrote. "My mother often said, 'The only thing in life that is important is to be able to hold your head up high.' I now know what that means."

The Career

From Family Doctor To Drug Researcher

Robert Fiddes always wanted to be a skater. As a teen-ager in his native Vancouver, British Columbia, he rose most mornings before dawn, walking to a chilly ice arena for his 5 A.M. practice. The hard work paid off; he often told of winning Canada's junior figure skating championship, a victory that set him on the path to going professional.

But when the time came to choose between a career as a figure skater or enrolling in a university, young Robert Fiddes took the academic path. And there he showed that same drive, gaining acceptance to medical school at the University of British Columbia after just three years in college, according to his curriculum vitae.

In 1970, at 25, Dr. Fiddes earned his medical degree and, with his new wife, Rebecca,

came to Long Beach, Calif., for a job as a hospital intern. He went on to join a medical partnership, but in 1981 opened his own practice in Whittier with a medical assistant, LaVerne Charpentier, in a converted house with an awning and flower garden. It was the perfect image for an old-time family doctor, and the practice blossomed.

Dr. Fiddes's wife would later write of those early days in a letter to the judge who sentenced her husband. "His patients adored them and showered the office with everything from home-baked cookies to hand-crocheted dolls," she wrote. "Both Rob and Laverne worked long and hard to provide his patients with the best care."

Eventually, Dr. Fiddes formed a group made up of several family doctors in the area. But by the late 1980's, an obstacle emerged that Dr. Fiddes was unable to sidestep. Managed care was sweeping California, and Dr. Fiddes chafed at the new rules. "He felt his hands were tied in performing whatever tests were necessary to assist in the proper diagnosis of the patient," Mrs. Fiddes wrote in her letter. Patients "felt equally frustrated with the new system."

Growing restless, he decided to pursue a law degree, attending night school. In 1987, he passed the California state bar exam.

But by then, the medical profession had changed so radically that an entirely new specialty presented itself: Doctors were testing the safety and effectiveness of new drugs for pharmaceutical companies, using their patients as subjects. Recognizing the opportunity to get away from managed care, Dr. Fiddes jumped at the chance.

His new clinical-trials business grew rapidly. Dr. Fiddes appointed Ms. Charpentier as his first full-time study coordinator, and raided a private research firm in the area, California Clinical Trials, to build his staff. He began to dream of eclipsing his biggest rivals and taking his new enterprise public, at times doodling his ideas for a corporate logo onto pads of paper.

As the business grew, former employees said, a pattern soon emerged. Dr. Fiddes would meet with patients in his first-floor office, then refer them to the study coordinators on the second floor. Often, the patients who arrived there felt reluctant to take part in the trials.

"They were pushed to go up there," said Susan Lester, the former study coordinator who blew the whistle on Dr. Fiddes. "They often would say, 'I don't want to participate in this, but I don't want to make him mad.' "

In the early days, Ms. Lester and other coordinators would tell wavering patients to take their time, perhaps by sleeping on the idea, before signing an agreement to participate. But Dr. Fiddes and Ms. Charpentier, who also declined interview requests, quickly put an end to such solicitousness.

"I was told that it was a big mistake to let them think about joining," Ms. Lester said. "They said, 'You don't tell them they have any choice about it. You put them in.' "

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The Fraud

Falsifying Records, Endangering Patients

Kimberly Carlon's interviews for a job at the Southern California Research Institute had been going well. She had only one more hurdle to clear: speaking to Dr. Fiddes himself. If he approved of her, Ms. Carlon, a certified respiratory therapist, would become the research site's latest study coordinator. Sitting in front of Dr. Fiddes's desk in early 1996, she listened as he described a hypothetical situation. Suppose, he said, that a patient was available for a study, but was taking medication prohibited by the study protocol. The answer seemed obvious, Ms. Carlon replied: she would send the patient on his way.

Well, Dr. Fiddes told her, that was not the way he did things. At the Southern California Research Institute, he said, the patient would be entered into the trial; that would require the center to falsify records so that the violation of study rules could be hidden.

Ms. Carlon got the job. But she would later describe her discussion with Dr. Fiddes as the first moment she should have realized something was wrong.

Like every other study coordinator who passed through Dr. Fiddes's research center, Ms. Carlon found herself being pushed to break the rules. When she ran a 1996 study for a new asthma inhaler sponsored by Fisons, a British drug maker, she found a patient who had been enrolled even though she had an incurable lung disease that should have disqualified her. When a monitor hired by Fisons asked to see the patient's medical chart, Ms. Carlon approached Delfina Hernandez, a more senior employee, and asked what to do. .

Ms. Hernandez quickly fetched the patient's medical chart, and pulled out every page that made reference to the lung disease. Then, according to investigative documents, she turned the remaining records over to the monitor. The violation went undetected.

Ms. Hernandez, who later pleaded guilty to fraud, declined to comment.

Again and again, study coordinators were instructed by Dr. Fiddes and his top aide, Ms. Charpentier, to ignore the requirements of the drug studies. The rules called for excluding smokers from an asthma study? The coordinators were told to put the smokers in anyway, and not mention their habit in the medical records. A certain blood pressure was required for patients to participate in a hypertension study? Then the coordinators were expected to write that level into the chart, regardless of the truth. Patients' medical records contained health histories that precluded them from participating in a test? Then the offending pages were ripped out and destroyed, and the patients placed on the experimental medication despite the dangers.

Over time, the frauds orchestrated by Dr. Fiddes grew ever more audacious. Eventually, according to Government documents, it was not just the records that were being falsified. Instead, medical tests were rigged — and at times, patients simply invented. Outside monitors reviewed the documentation, but since there were real lab records for the rigged tests, they had no clue that they were being deceived.

The office refrigerator became the source of human bodily fluids that met the requirements of various studies. A jug of urine was often found there on Monday mornings, provided by Carol Rose, an employee. Ms. Rose's urine contained high levels of protein — just the trait patients needed to qualify for certain studies. Dr. Fiddes paid Ms. Rose $25 each time she collected her urine and brought it to the office, where over time it was divvied up among specimen cups labeled with other people's names and presented for testing.

The refrigerator also proved useful when the research center was conducting studies on hormone replacement therapy for menopausal women. The studies required women with blood serums that showed low levels of

estrogen and high levels of follicle-stimulating hormone — signs that a woman is going through menopause. To make sure that the patients' tests qualified, Dr. Fiddes sent out a memo specifying the hormone levels required for the study. "We need some serum that scores these numbers in the frig at all times," he wrote.

Another study on an antibiotic required that patients have a certain type of bacteria growing in their ear. No problem for Dr. Fiddes. He bought the bacteria from a commercial supplier and shipped them to testing labs, saying they had come from his patients' ears.

Dr. Fiddes's coordinators, paid bonuses for recruiting patients into studies, soon began improperly enrolling themselves and members of their families. Often, names were changed to avoid detection by drug company monitors. At times, family members took part in several studies at once — a violation of the rules because studies require that participants not be taking other medications, so that the data obtained relate only to the drug under study.

Employees "were running around doing E.K.G.'s on each other, if the patient couldn't pass," said Sloan A. Bergman, a former study coordinator who quit working for Dr. Fiddes after less than a year because of ethical concerns. "I wasn't happy, but I needed a job."

Yet all the while, there were constant reminders that the true cost of the frenzied drug testing was being borne by sick and vulnerable patients.

In the summer of 1995, the research institute began work on a study of Cozaar, a hypertension medication sponsored by Merck & Company. Among the patients enrolled by Dr. Fiddes was Arlene Roberts, a 70-year-old woman with high blood pressure. Instead of dropping, her blood pressure rose dangerously when she took the drug. Dawn Simons, the study coordinator, became alarmed and sent Ms. Roberts to see Dr. Fiddes. Rather than taking her out of the study, Dr. Fiddes prescribed two other hypertension drugs. The triple dosage not only violated the study rules, it made it impossible to gauge the effect of Cozaar.

A few days later, Ms. Roberts returned. Her face was bruised, her speech was slurred and she had trouble walking. She told Ms. Simons that she had passed out over the weekend while bathing. Ms. Simons took her pulse and found that her heart was barely beating — a result, the coordinator thought, of bombarding her body with hypertensive drugs. Worried that Ms. Roberts was headed toward cardiac arrest, Ms. Simons asked Ms. Lester, her fellow study coordinator, for assistance. The two helped Ms. Roberts, who by then could barely walk, to Dr. Fiddes's office.

"He said, 'It's no big deal. She's probably making more of it than it really is,' " Ms. Lester recalled in a recent interview.

Ms. Simons, dismayed at what was happening, thought Ms. Roberts should be dropped from the study. But Dr. Fiddes refused, keeping her on the medications for several more weeks. Ms. Roberts was soon seeing another doctor in a hospital for the problems that emerged during the study. Ms. Simons, the study coordinator, resigned from her job, but not before surreptitiously copying all the medical records and turning them over to Ms. Roberts in case she wanted to bring a lawsuit. Ms. Roberts, who recovered at the hospital, never sued.

Dr. Fiddes received payment in full from Merck — his reward for keeping Ms. Roberts in the study through its completion.

Avoiding Detection

The F.D.A. Ignores An Early Warning

Ilse Beverly finally decided that Dr. Fiddes had to be stopped. While working for him for five years handling laboratory tests like blood work, Ms. Beverly had seen signs of his willingness to cheat on drug studies. And so in January 1995, almost immediately after leaving her job, Ms. Beverly telephoned investigators with the Food and Drug Administration.

She reported her own experiences, such as the time in 1990 that Dr. Fiddes had asked her — without explaining why — to find a way to alter lab values in urine tests. She also provided the names of study coordinators who knew that testing data were being manipulated to enroll larger numbers of patients. With her revelations, the Government had its first solid lead on what was happening in Dr. Fiddes's office fully 17 months before Ms. Del Valle exposed his crimes to an F.D.A. auditor. Investigators wrote memos about Ms. Beverly's allegations, and forwarded them from Los Angeles to the clinical investigations branch of the F.D.A.

There, the memos were filed away. No investigation was begun.

Brad Stone, a spokesman for the F.D.A., said that, because aspects of the case have not been finished, the agency could not comment at this time.

Dr. Fiddes had always found it easy to elude detection by the crews of company monitors and Government auditors that visited his offices, even when his employees spelled out their suspicions about what was happening. It was not that he was particularly adept at dodging their questions; rather, they seemed reluctant to challenge such a prominent figure in the drug-testing business. "This business can be run on words, and I have learned the words," Dr. Fiddes wrote in a 1995 memo. " 'We have no problems' is our motto, and tell this to every monitor."

When Dr. Fiddes's efforts to enroll patients were thwarted by system safeguards intended to insure accurate test data, he often found ways around the problem.

In a 1995 study of an experimental pain reliever for arthritis called PHZ 136 that was sponsored by the Zambon Corporation, Dr. Fiddes faced a particularly difficult impediment. The patients were supposed to have arthritis of the knee, as verified by X-rays.

Dr. Fiddes tried to recruit patients. Again and again, he sent their X-rays to an independent radiologist for review. And almost every time the answer came back the same: The patient did not have arthritis, and so did not qualify for the study. Frustrated, Dr. Fiddes told the coordinator of the study, Ms. Lester, to look through his medical files for patients with arthritis of the knee. Then, he said, she should offer each of those patients $25 to come in and get multiple X-rays, which he could substitute for the X-rays of patients who did not qualify. But Ms. Lester drew the line, and refused.

The ever-resourceful Dr. Fiddes found a way around that obstacle, however. Through his staff, he got in touch with the project manager at Pharmaceutical Product Development Inc., which was managing the study for Zambon, and asked a question: Because he was a doctor, couldn't he just interpret the patients' X-rays himself, rather than send them to a certified radiologist?

The company was happy to oblige. Researchers "may interpret knee X-ray films obtained on candidates," Julia Dixon, the project manager, wrote in a letter to Dr. Fiddes. "There is no need for a radiological consult."

From that moment on, Dr. Fiddes had no trouble finding patients who qualified for the study. "That kind of opened it up for him right there and then," Ms. Lester said. "Everyone understood that if he was going to read the X-ray, he was going to lie."

Not long afterward, Dr. Fiddes received a letter from one of the testing company's study monitors. "CONGRATULATIONS on meeting your enrollment deadline!" the monitor, Cheryl Grant, wrote in a letter dated Feb. 19, 1996. "I performed a 100 percent source document verification, and found no outstanding issues."

Through Pharmaceutical Product Devel-

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opment, a testing company, Dr. Fiddes was paid $45,268 for his effort in the Zambon study. The company never detected his fraud. Zambon declined to comment, citing confidentiality of the study, as did Pharmaceutical Product Development. But Nancy Zeleniak, a spokeswoman for the testing company, said its monitoring was of the highest quality. "We have standard operating procedures for detecting fraudulent or fabricated data," she said. "We are helping to set standards in the industry."

Another company came closer to putting him on the spot. Several former coordinators for Dr. Fiddes said they had reported his unethical conduct to Pat Pryor, an independent study monitor working with Pfizer Inc. Tipped off to the discrepancies, Ms. Pryor sharply challenged Dr. Fiddes and his staff in her reviews of their paperwork.

Dr. Fiddes chafed at the challenges, feigning outrage. "Our integrity and reputation for performing high-quality clinical trial work has been injured, and we are justifiably upset," Dr. Fiddes wrote in a July 1995 letter to Pfizer, complaining about Ms. Pryor's demands. He insisted Pfizer "have a new monitor assigned to our site immediately."

Not long afterward, Dr. Fiddes announced the news at a staff meeting: Pat Pryor would not be returning to monitor the Southern California Research Institute.

Pfizer said that the company replaced monitors if there seemed to be a conflict. "In order to insure the most objective and best monitoring, we generally recommend that if there is personal conflict, and no certainty of irregularities, that a new neutral person is assigned to review all of the data," said Betsy Raymond, a spokeswoman for Pfizer.

But in the Fiddes case, that policy did not improve the monitoring. "We have an extensive system of checks and balances," Ms. Raymond said. "Even with all of that, we didn't uncover the fraud."

Why was Dr. Fiddes able to fool the monitors so easily? Because the oversight system is mostly designed to catch errors, not fraud. To protect patient confidentiality, monitors are forbidden even to know the names of test subjects, meaning that no spot-checks are ever performed by the companies to make sure that researchers are not making up lab values or inventing patients.

But Dr. Fiddes's luck in avoiding detection would not hold. By May 1996, more than half a dozen study coordinators — including Ms. Simons and Ms. Bergman — resigned, fearful that the fraud would cost them their nursing licenses or certifications. Ms. Lester likewise decided she could take no more, and wrote a letter to Dr. Fiddes declaring that she would no longer participate in fraudulent, unethical work.

A response came quickly. Ms. Lester was ordered to clean out her desk immediately, and was escorted from the building. On her way out the door, she bumped into Kathryn Davis, another Fiddes employee. With tears in her eyes, Ms. Lester made Ms. Davis a promise.

"She told me before she left that she was going to bring Dr. Fiddes to his knees," said Ms. Davis, a former employee. "I had no idea that she meant it seriously."

The Cover-Up

'You MUST Be Able To Dump Your Files'

Alan Knox, the chief financial officer of the research center, was working in his office in the summer of 1996 when its chief operating officer burst in. The officer, Elaine Lai, demanded that Mr. Knox pull a series of invoices documenting payments to an employee, Carol Rose.

Mr. Knox fished the invoices from a filing cabinet. As he read them, he grew concerned. Written clearly across the $25 invoices were the words "urine sample." For the first time, he was seeing the evidence that Ms. Rose was being paid to substitute her own urine for that of patients.

Wary of what was happening, Mr. Knox copied the invoices, and kept the originals. As he handed the copies to Ms. Lai, he asked her and Ms. Hernandez, the longtime senior employee of Dr. Fiddes, what was going on. Well, came back the response, apparently Susan Lester had gone to the F.D.A., and worse, was contacting other former coordinators and trying to persuade them to talk to the Government about the way Dr. Fiddes conducted his research.

"I remember inquiring with Delfina and Elaine and saying, 'What's the big deal?' " Mr. Knox said in a recent interview. "They looked at me, they looked at each other and said, 'We have to tell him the truth.' " As he listened to them recount the trickery that had taken place at the institute, he said, "I was just taken aback by the level of fraud."

His first thought, he said, was that Dr. Fiddes and his top aides should confess everything to the F.D.A. But unknown to him, they were at that very moment planning a cover-up that would involve destroying incriminating documents and manufacturing new ones that might place the blame for any problems on Ms. Lester.

Dr. Fiddes was most concerned about the urine substitution, out of fear that Ms. Rose would talk, according to notes of investigator interviews. So, in August 1996, he called a meeting at the Hilton Hotel in Whittier with Ms. Lai, Ms. Hernandez and his longtime assistant, Ms. Charpentier.

To solve the Carol Rose problem, Dr. Fiddes told the group, he would create a bogus medical chart and false patient history for her. If asked, he would say that urine had been collected as part of her medical treatment.

The following Saturday, Ms. Lai called a meeting for what she called "chart review." The actual mission was to go through the medical charts and destroy any evidence of wrongdoing.

Days later, on Aug. 21, Ms. Lai called for another meeting for strategic planning. In a memo to Dr. Fiddes, Ms. Charpentier and Ms. Hernandez, she made clear the need to move quickly.

"F.D.A. is busting down our door on Monday," Ms. Lai wrote. "You MUST be able to dump your files to your car when F.D.A. knocks."

Ms. Lai added in the letter that they had to agree to scripted responses to all questions the Government might ask.

As Dr. Fiddes and his allies were secretly working on their cover-up, Mr. Knox was reaching out to regulatory experts who he thought could help the company in its talks with the F.D.A. He got in touch with Gretchen McKelvey, a quality assurance consultant for clinical trials, who was quickly hired to help out. Ms. McKelvey was stunned by the magnitude of the fraud she discovered at Dr. Fiddes's office. But even more incomprehensible was the blasé attitude Dr. Fiddes demonstrated as he calmly informed her of his cover-up plans.

"I explained to him that what had happened here was considered criminal, and that he could be prosecuted for conspiracy and fraud," Ms. McKelvey said in an interview. "Dr. Fiddes replied that they were going to blame Susan Lester for all of the problems, and he was going to say he had no knowledge of what was going on."

About that time, Ms. McKelvey learned that Dr. Fiddes had moved all of the patient records off site. When she asked where they were, she said, he replied that they were in storage. Days later, when she pressed for them again, Dr. Fiddes told her the records had been lost.

"I was starting to get really scared," she said. "I don't like to be messed with."

As the situation deteriorated, Ms. McKelvey decided the situation was too big to handle alone, and required someone with mor pertise in dealing with the Government sought advice from Michael Hamrell, a sultant who specialized in the F.D.A. Hamrell arrived at the research site f briefing from the company's top execut including Dr. Fiddes and Mr. Knox. made no bones about all the protocol v tions they had committed. Why would Fiddes be so open? Because, as Mr. Ham learned quickly, he still believed that he c outsmart the system.

"He told me that he knew the law be than the F.D.A., and that the F.D.A. cou touch him," Mr. Hamrell said. "He told m was a lawyer, and he wasn't responsible

Many of those who worked for him, like Knox and Ms. McKelvey, saw the writin the wall and resigned soon after being hi But others who for years had accepted Fiddes's repeated assurances that every in the industry did the same things w shaken and agonized about whether to fess.

"I want to spill my guts, but what is goin happen to me and my future?" Delfina H nandez, one of Dr. Fiddes's top aides, wrot her diary as investigators closed in. "(forgive me if you think I did wrong, punish me if I did anything to hurt the patients."

She soon found out what would happen her future. On Feb. 16, 1997, teams of Fede agents swarmed into the Southern Califor Research Institute's office. The entire st was ordered to move to the front of t building, as the agents seized box after box documents. One agent with a video came filmed every employee's face for use in futu identifications.

With employees facing such intimidati law enforcement tactics, cracks began emerge in the conspiracy to lie to investig tors. Ms. Hernandez was the first to decide provide evidence to the Government, and t other dominoes quickly fell. By Septemb 1997, Dr. Fiddes, Ms. Hernandez and M Charpentier agreed to plead guilty. Ms. L pleaded guilty soon afterward.

Now, with Dr. Fiddes compelled to coope ate as part of his plea agreement, the Gover ment hoped to learn more from him th would help in the battle against researc fraud. On Oct. 10, at 10:30 A.M., Dr. Fidde met for an interview with William Leitner an Hetal Sutaria of the F.D.A.

For five hours, the agents grilled D Fiddes. He told them that fraud was rampar in the research industry. He named names c doctors he suspected of engaging in practice similar to his own. And he described som telltale signs that should raise suspicions c possible fraud.

But, the investigators asked, what evidenc of fraud is there in the records reviewed b monitors and the Government? What coul the watchdogs have seen that would have allowed them to detect his fraud?

Nothing, Dr. Fiddes replied. Had it not beer for a disgruntled former employee, he would have still been in business.

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Finding the Loopholes

The oversight system for trials of new drugs was developed during the era of university research. But, as research has become a lucrative business for private doctors, oversight has not changed to account for the chance that some might cheat to make more money. Dr. Robert Fiddes relied on holes in the blanket of oversight to perpetuate a huge fraud.

	RESEARCH STEP	OVERSIGHT	LOOPHOLE
1	Doctor signs contract to test drugs.	Must be registered with the F.D.A.; those who have been found breaking the rules are barred from participating.	For drug studies, usually no qualifications other than a medical license are required.
2	Drug company provides rules for conducting a particular study to doctor.	All studies involving humans, as well as ads for recruiting patients, must be approved by an independent ethics board.	Such boards have been criticized by the Government as being overwhelmed by too much work.
3	Doctor speaks to patients about joining studies.	None.	Industry monitors do not know patient identities. Cannot check what doctor said to sign subjects up.
4	Doctor presents informed consent form to patients.	Forms must be reviewed and approved by ethics boards.	No one checks if patient understands or has read the form; adequate consent not obtained about half the time.
5	Doctor conducts tests to see if patients qualify for study.	Monitors review paperwork from tests to be sure it meets study requirements.	No method exists for detecting if a doctor falsifies the underlying lab records or writes down inaccurate results for tests such as blood pressure.
6	Doctor provides trial medicine to patients and conducts tests such as screening urine and blood.	Monitors check these records both during and after a study, and may conduct audits comparing results to more detailed patient records. Government monitors may audit these records as well.	Not even spot checks with patients by industry monitors are permitted. So if test is faked, it is undetectable. The Government rarely checks with patients, and usually only when they have evidence of fraud.

From Parties to Prison

In the mid-1990's, Dr. Robert Fiddes and his staff celebrated another successful year of drug studies at a Christmas party. The festive mood soon ended, as some of those present revealed his research fraud, leading to several guilty pleas.

LAVERNE CHARPENTIER

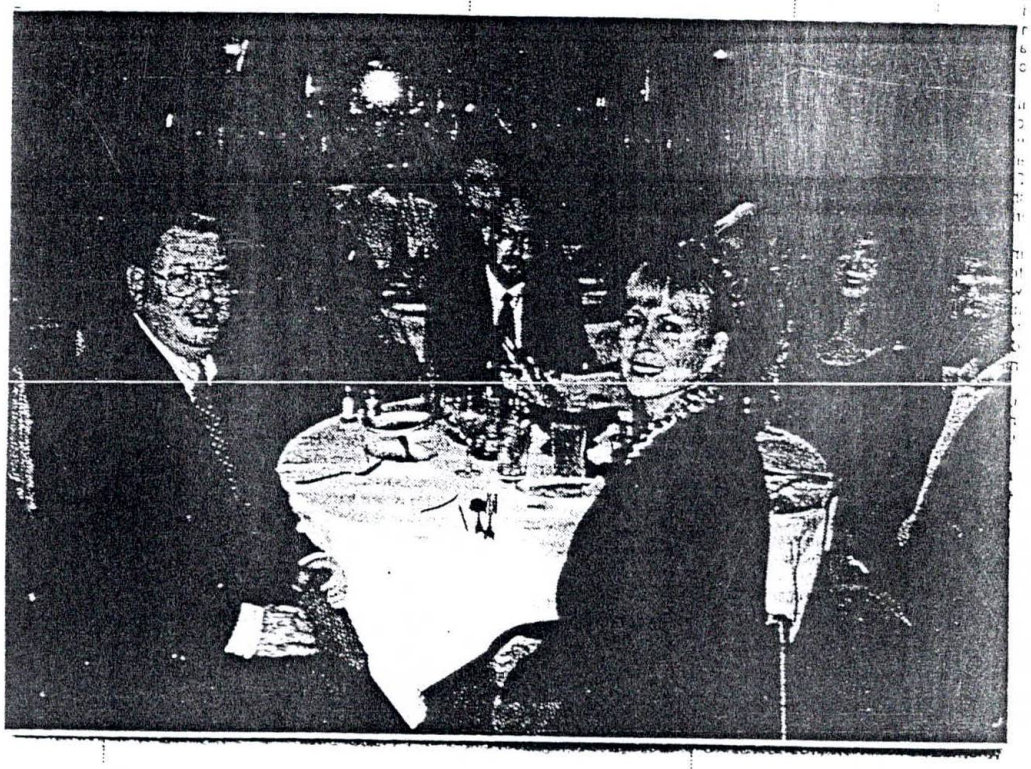
A longtime medical assistant for Dr. Fiddes, she began working as a study coordinator when he turned to drug research.

ROLE IN THE CASE Pleaded guilty to conspiracy; is scheduled for sentencing this week.

SUSAN LESTER

Worked as a study coordinator, f
Dr. Fiddes beginning in 1994

ROLE IN THE CASE Blew the whistle;
the wrongdoing in 1996. Continue
to work in drug research



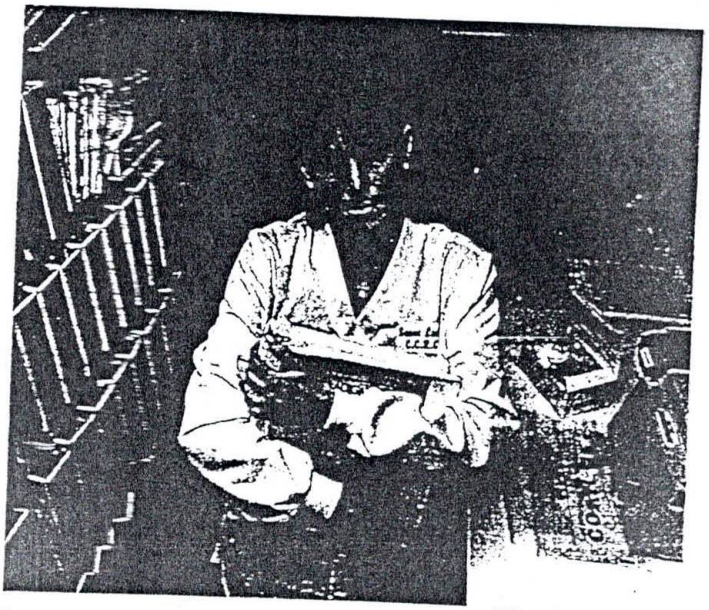
ROBERT FIDDES

After years of working as a private-practice doctor, opened up his own drug research business, called Southern California Research Institute.

ROLE IN THE CASE Pleaded guilty to conspiracy. Is currently serving a 15-month sentence in a Federal prison in California.

REBECCA FIDDES

Wife of Dr. Fiddes, and an administrator at his office



Ed Carreon for The New York Times

Susan Lester, a former employee of Dr. Robert Fiddes, said patients were "pushed" to participate in drug studies. Supervisors, she said, ordered her to enroll more patients.

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The New York Times

SUNDAY, MAY 16, 1999

A flood of advertisements has led to a big increase in the number of private doctors who enroll their patients as subjects in drug testing. Aggressive recruiters can earn as much as $1 million a year.

Drug Trials Hide Conflicts for Doctors

By KURT EICHENWALD and GINA KOLATA

When Thomas W. Parham visited his doctor in the summer of 1995, he expected just another routine checkup. But his doctor had something else in mind.

The doctor, Peter Arcan, suggested Mr. Parham might want to join a study of a new drug to shrink enlarged prostates, according to records of the encounter. Mr. Parham was puzzled — his prostate was fine. But Dr. Arcan brushed aside the retired metal worker's questions, saying the experimental drug might prevent future problems. Satisfied, Mr. Parham, a 64-year-old resident of La Habra, Calif., agreed to participate.

But there was one question Mr. Parham did not ask: What was in it for Dr. Arcan?

The answer was money. The drug's maker, SmithKline Beecham P.L.C., was paying $1,610 for each patient that doctors signed up — money that covered study expenses while allowing a portion to end up as profit for Dr. Arcan and his associates.

Mr. Parham had no idea. "Nothing was mentioned about money," he said in an interview. "It's a situation where you have faith in your doctor." Through his secretary, Dr. Arcan declined comment.

RESEARCH FOR HIRE

First of two articles.

With his decision, Mr. Parham had unwittingly joined hundreds of thousands of other patients recruited by their personal physicians into a booming venture: the business of testing experimental drugs on people.

Once clinical research was a staid enterprise primarily administered by academic researchers driven by a desire for knowledge, fame, or career advancement. Now, it is a multibillion-dollar industry, with hundreds of testing and drug companies working with thousands of private doctors.

In this new industry, patients have become commodities, bought and traded by testing companies and doctors. Almost daily, the industry urges doctors to join the gold rush, bombarding them with faxes and letters blaring such come-ons as "Improve Your Cash Flow" and "Discover the Secret For Obtaining More Funded Studies." In an era of managed care, the pleas are seductive: the number of private doctors in research since 1990 has almost tripled, and top recruiters can earn as much as $500,000 to $1 million a year.

This new system is a boon for drug companies because it reaches out to a vast pool of test subjects who have never before been available for experimentation. But it also injects the interests of a giant industry into the delicate doctor-patient relationship, usually without the patient realizing it.

These changes have prompted little public debate, mostly because the full scope of what is happening is hidden. The industry treats research agreements as corporate secrets and contractually forbids doctors to disclose them. As a result, few people outside the industry, including Government officials, have seen the contracts or know the magnitude of the money involved.

But in a 10-month investigation, The New York Times obtained such contracts and thousands of other confidential documents that present a view of the research industry that has never before been available.

These records, and interviews with participants, reveal a system fueling a pharmaceutical renaissance, but fraught with conflicts of interest; that places a premium on speed and meeting quotas; that relies on Government and private monitoring that can be easily

Continued on Page 28

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Fast-Growing System of Drug Testing

Hides Conflicts for Doctors

Continued From Page 1

fooled and that some researchers said is inadequate, and that secretly offers a share of the cash to other health professionals who might influence patients to join a study. At bottom, the only thing separating a trusting patient from a study that could be inappropriate or potentially harmful is the judgment of a doctor torn by these unseen conflicts and pressures.

The documents, including contracts, protocols or related financial records from more than 300 recent drug studies, were provided by a number of people in the industry concerned about its direction. The Times also conducted a computer analysis of more than 200,000 filings with the Government and related data submitted by doctors who want to conduct research, and interviewed doctors, patients, ethicists, industry executives and Government officials.

These are among the specific findings of The Times's investigation:

¶Drug companies and their contractors offer large payments to doctors, nurses and other medical staff to encourage them to recruit patients quickly. And doctors do not even have to conduct trials to get paid: There are finder's fees for those who refer their patients to other doctors conducting research.

¶Doctors who recruit the most patients receive additional perquisites, such as the right to claim a coveted authorship of published papers about the studies — even though the true author is a ghost writer using an analysis from the drug company. Those who fail to meet the recruitment goals are usually dropped from future studies.

¶Testing companies often use doctors as clinical investigators regardless of their specialty, at times leaving patients in the care of doctors who know little about their condition. For example, psychiatrists have conducted Pap smears and asthma specialists have dispensed experimental psychiatric drugs.

¶A growing number of doctors conducting drug research have limited experience as clinical investigators, raising questions among some experts about the quality of their data.

In interviews, industry officials and researchers said the emerging drug-approval system was dedicated to quality and offers significant benefits. Since patients are seeing their own doctors, researchers said, it adds a level of continuity and personal contact to the process — something unavailable from full-time researchers.

Moreover, industry officials said, the new pool of test subjects is a resource of incalculable value that is allowing the development of an avalanche of new compounds. Drug tests "can get delayed if the patients aren't out there and available," said Chris Knebler, the chairman and chief executive at Covance Inc., a giant testing company.

But some experts said patients were being pushed to participate in the studies because of the financial interests of their doctors.

Doctors working as researchers "are enticing and cajoling patients who are in no position to resist their blandishments to enter clinical studies," said Dr. David S. Shimm, a member of the ethics committee at Porter Adventist Hospital in Denver who has written about research conflicts.

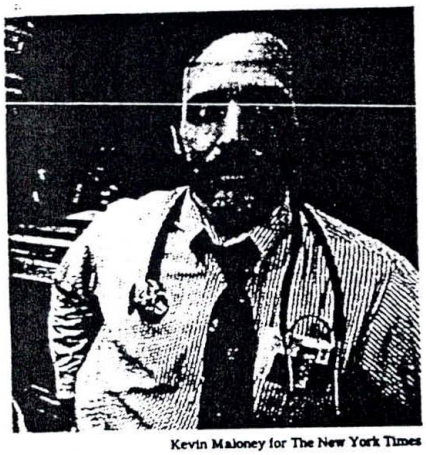
"What the patients are not seeing is that the clinical investigator is really a dual agent with divided loyalties between the patient and the pharmaceutical company," he said.

While patients must sign detailed consent forms to enroll in drug studies, they are often in no position to question their doctor's suggestion that they join.

"The physician has enormous power over you," said Uwe E. Reinhardt, a health care economist at Princeton University, who himself recently agreed to participate in a clinical trial run by his doctor — in part because he feared annoying him — and who had no idea that money might be involved. "You want to keep his favor. If you say no, you'll worry that he may not like you."

That is what happened with Mr. Parham and Dr. Arcan. In joining the study, Mr. Parham said: "I just followed his advice, just like if he said to take two aspirin instead of one. He's a doctor and I'm not."

In truth, Mr. Parham should never have been signed up for the prostate study. According to his medical records, he had been hospitalized the previous year with a chronic slow heart rate, a condition that specifically disqualified him for the study. But, saying that Mr. Parham's heart rate was only mildly slow, an administrator handling the paperwork for Dr. Arcan sought an exemption from SmithKline. Based on those representations, the drug company granted the exemption; it was not told about Mr.



Kevin Maloney for The New York Times

Researchers "are enticing and cajoling patients who are in no position to resist their blandishments to enter clinical studies."

Dr. David S. Shimm, a member of the ethics committee at Porter Adventist Hospital in Denver who has written about research conflicts

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Parham's earlier hospitalization.

Soon after joining, Mr. Parham complained of fatigue, a symptom of his slow heart rate. Dr. Arcan dismissed the complaints as emotional. Within weeks, Mr. Parham asked to be dropped from the study. Days later he was hospitalized and given a pacemaker; Mr. Parham never brought legal action and it is impossible to know whether his participation in the study affected his heart condition.

His experience underscores a potential danger of the emerging drug-testing system: Doctors with money at stake may persuade patients to take drugs that are inappropriate or even unsafe. Under the current system of monitoring, such actions are almost impossible to catch and no statistics are collected on such events. Within the industry, most of the planning focuses on conducting studies quickly. Patient issues, some researchers said, are often lost in the rush.

"You go to the trade meetings on clinical research; you go for two entire days, and patients are not mentioned," said Dr. Robert M. Califf, the director of the Duke Clinical Research Institute, an academic drug-testing center in Durham, N.C., affiliated with Duke University. "The patient is an object to make money. Having patients is just the dirty price for doing business."

The Incentives

Putting a Price On Every Patient

The letter last July from Merck & Company was nothing if not sympathetic. The company recognized that doctors involved in its study of a hypertension medication were having trouble finding qualified patients. And so, with the letter, Merck offered a little encouragement for them to work harder.

Instead of paying $2,955 for each test subject enrolled, Merck offered $500 more in the study comparing the drug Losartan with a placebo. For those doctors who enrolled their quota of 14 patients by Sept. 30, the company would kick in an additional $2,000 — making that 14th patient worth $5,455 if recruited in time, and the entire group potentially worth more than $50,000.

"We will forward the first check as soon as the first four additional patients are enrolled," the letter said.

After discovering how effective paying doctors to recruit patients can be, the drug industry has opened the financial floodgates. Special cash bonuses for signing up specified numbers of people by a given date, a practice once unheard of in clinical research, are becoming part of the landscape. Moreover, those payments — to private doctors, research firms and even to university medical centers — are only one of a number of incentives that are being dangled by drug and testing companies to entice the medical community.

There are payments to everyone in the system who can come up with a patient, from other doctors who refer them for research to the study coordinators in the researcher's office who screen patients to see if they qualify.

None of these benefits are scrutinized by Government regulators, who said in interviews that they saw little difference between providing grants for university research and paying doctors directly. For academics "the money is just as important as with the internal medicine guy trying to beat the H.M.O.," said Dr. Murray M. Lumpkin, the deputy director of the Center for Drug Evaluation and Research at the Food and Drug Administration.

But unlike block grants, today's incentives can grow almost day by day, if the doctor works the way the drug companies want. And the variety of the incentives is almost endless.

The most basic form of compensation is a flat fee paid for each patient enrolled. The amount of money paid to the researchers varies widely, depending on the complexity of the study, the number of tests involved and the difficulty in finding patients.

For example, in 1996, a study of a migraine drug sponsored by Janssen Pharmaceutica, a unit of Johnson & Johnson, paid doctors $3,600 for each enrollment. Another study that year sponsored by Organon Inc. on a new birth control pill paid $1,100 for each patient. And a Wyeth-Ayerst study of drugs for hormone replacement in women paid $4,581.

While all of these payments were made to specific clinics, the exact amounts on a single test could vary slightly by region, or even by clinic.

Many executives from drug or testing companies refused to discuss their research programs, citing confidentiality. Those who did grant interviews gave consistent explanations of their payments: They are necessary compensation for the doctors' work.

"We set up contracts that hopefully reimburse investigators adequately for the time they put in to screen patients, bring them in, and provide data to us that is as clean as possible," Dr. Elizabeth Stoner, the vice president for clinical research and contract management at Merck Research Laboratories in Rahway, N.J., said.

Additional payments can be made, she said, when there is "additional effort above and beyond what they anticipated."

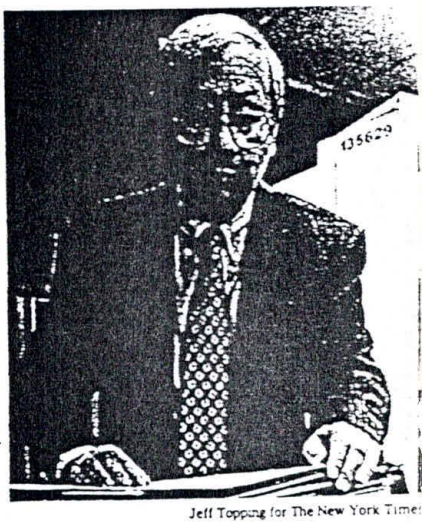
But doctors who are particularly successful in recruiting study patients and keeping down their costs can make huge profits.

"There are physicians who can net about $500,000 to $1 million a year doing clinical research," said Ismail A. Shalaby, the chief executive of Nema Research Inc., a network of doctors and hospitals in the Baltimore area performing clinical research. "And that is not bad."

The benefits to the doctors who conduct research are not simply financial. Once, researchers said, the names that appeared on papers describing drug studies were those of the actual authors. That is no longer always the case. Today, the coveted right to claim authorship is often just another reward for doctors who recruit the most patients — even if they wrote nothing and analyzed no data.

"They used to ask you to write," said Dr. Thierry Le Jemtel, a cardiologist at Montefiore Medical Center in the Bronx who is a longtime academic researcher. "Now, they send you a paper all written by a medical writer" hired by the drug company.

Dr. Jay Grossman, a private-practice doctor who is an allergy and respiratory specialist with Vivra Asthma and Allergy Inc. in Tucson, Ariz., said he was often a lead author



Jeff Topping for The New York Times

"I really feel I can offer my patients more. I know more what the cutting edge is. I know what will be the recommended therapy two years from now."

Dr. Jay Grossman of Vivra Asthma and Allergy in Tucson.

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on publications because he had been a top patient recruiter in the clinical trials, even though he rarely did much — if any — of the actual writing. "That's common," he said. "It's orchestrated by the drug company's medical writer."

For example, Dr. Grossman cited a study for a SmithKline Beecham asthma medication that was published in The Journal of Asthma and another on an allergy medication sponsored by Boehringer Ingelheim Pharmaceutical published in The Journal of Allergy and Clinical Immunology. While the articles are written by a drug company writer, Dr. Grossman said, he often suggests modifications.

As drug companies compete for top study doctors who will quickly accrue patients, a financial arms race has developed, with each company seeking new ways to use cash and benefits to spur the research.

One practice is to offer finder's fees to doctors who are not conducting studies for referring patients to doctors who are. For example, a letter from a testing company handling the research on a vaginal suppository for the Bayer Corporation in 1996 promised "a $75 referral fee for physicians and area/federally funded clinics, i.e., Planned Parenthood, etc."

Even study coordinators — the nurses and medical assistants who oversee the administrative details of a study and screen patients to see if they qualify — are offered fees for finding test subjects. In 1995, for example, Pharmaceutical Product Development Inc. of Wilmington, N.C., which coordinates drug tests, needed a way to speed up enrollment in a study of a drug developed by the Zambon Corporation in East Rutherford, N.J.

So the company sent a fax to medical staff members who were screening patients around the country, offering them bonuses for fast enrollment.

"EVERY study coordinator has the chance to receive $750 just by reaching the enrollment goal of 30 evaluable patients," the fax said. "So GET BUSY!"

The stepped-up competition among drug companies for the services of doctors led to the development of cash bonuses for them, one of the most controversial incentives now offered. But even companies that were uncomfortable with the idea found it hard to resist.

"It's a tough issue," said Dr. Cynthia M. Dunn, the director of the Clinical Research Institute at the University of Rochester and a former drug industry executive. "On one hand, many companies recognize it's part of what we have to do to be competitive. On the other hand, they recognize they are setting up potential conflicts of interest" for doctors.

Some large drug companies have refused to offer bonuses out of ethical concerns. "You don't want to provide an advantage that can be misinterpreted," said Dr. Joseph Camardo, the senior vice president of clinical research and development for Wyeth-Ayerst Research in Radnor, Pa.

The bonuses all reward the same behavior: enrolling patients fast. For example, a contract last year by Ibah Inc., a testing company owned by Omnicare Inc., provided a $750 bonus for each patient enrolled by June 15 or $500 for those enrolled between June 15 and July 16 — upping the ante for doctors whose enrollments were lagging.

Such incentives outrage some experts. Bonuses in clinical research are "inappropriate, potentially illegal and certainly unethical," Dr. Robert Tenery, a Dallas doctor who is the chairman of the council on ethical and judicial affairs for the American Medical Association, said of such payments in general. "Why would you get an extra $500? How can you explain the rationale? Maybe you took a patient who really didn't need to be enrolled."

If something goes wrong, doctors might never be able to escape the nagging doubt that the bonus program was to blame. "How would you like to confront the family when a family member got hurt, and you got a bonus for enrolling?" asked Michael Leahey, the director of the office of clinical trials at Columbia-Presbyterian Medical Center in New York.

A system that offers so much cash and so many benefits for quick recruitment assumes that doctors would never allow money to distort their judgment — in this case by causing them to put undue pressure on reluctant patients or to include patients who do not qualify. But the assumption that doctors can resist financial temptations has been proved wrong repeatedly in other situations.

For example, throughout much of the 1980's, doctors could refer patients to treatment centers — such as physical or radiation therapy sites — in which they had a stake. The practice was outlawed after studies found that doctors were overusing treatments and tests when they had financial interests in the centers that provided them. A 1992 study published in The New England Journal of Medicine found that doctors with investments in radiation sites prescribed such treatment as much as 60 percent more often than those without the financial conflict.

With such studies demonstrating the effects of financial incentives on doctors, experts who have studied these conflicts said they were troubled by the emergence of research for hire.

"You have a recipe for trouble or abuse," said Marc A. Rodwin, an associate professor of law and public policy at the School of Public and Environmental Affairs at Indiana University and the author of a book on financial conflicts in medicine. "The risk is that the doctor will subconsciously downplay the risks or overplay the benefits" of a particular study in order to persuade a patient to participate.

Complicating matters, companies sometimes fail to consider how difficult it will be to find patients to meet the requirements they set for admission into a study. Then, when recruitment falls short of expectations, they offer to pay more to meet an unrealistic goal — looking, for example, for patients with a disease that their drug can treat but who have no other health problems that could affect the study.

"The simplest solution that inexperienced people think of first is to increase the number of sites or to increase the amount of money you're offering," said Dr. Bert Spilker, the senior vice president of scientific and regulatory affairs at the Pharmaceutical Research and Manufacturers of America, the trade group for large drug companies. "You can offer to triple the amount of money and it will make zero difference if the doctors are doing everything they can do. It may be that the patients don't exist."

But, with so much money dangling in front of them, doctors could be tempted to bend the rules to get patients into studies, and could get away with it, according to Dr. Martha L. Elks, an associate dean at Morehouse School of Medicine in Atlanta. "Let's say you're dealing with an angina study where the requirement for entry is a certain level of pain on a certain number of days of the week," Dr. Elks said. And "suppose the patient's history is not quite that but is borderline."

Dr. Elks said she overheard two doctors talking recently about bonuses. One was

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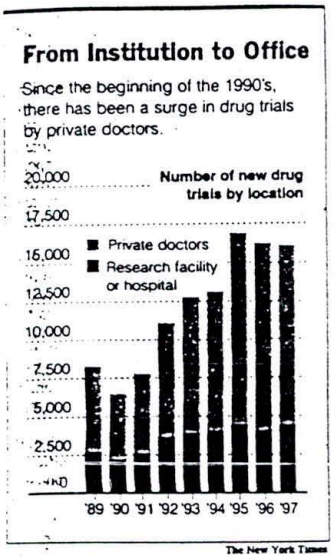

telling the other that he would get $500 if he could sign up some patients in the next 24 hours.

"I knew this guy," Dr. Elks said. "He is a practitioner of the highest ethics." But, she said, "he was talking about how to massage entry criteria."

Dr. Elks said she then noisily cleared her throat. "I sort of a-hummed," she said, at which point the doctors "stepped back for a minute," suddenly realizing what one of them had been saying.

What happened next, she said, she was not privy to know.

The Doctors

Drug Trials Provide New Source of Income

The year was 1989, and Dr. Stuart R. Weiss was bored with private practice.

To liven up his work, the San Diego endocrinologist tried his hand at drug studies. It was an audacious idea — at the time most trials were conducted by university scientists. But Dr. Weiss worked hard to convince a skeptical drug industry to take a chance on someone with his background.

"I beat the bushes," he said. "I lobbied long and hard with several organizations to give me a shot."

Eventually, he focused on a Merck study of a new drug to treat osteoporosis, a degenerative bone disease. To show his eagerness, he offered to fly to New Jersey to meet with Merck executives at their world headquarters. Then Dr. Weiss went further, spending his own money to buy an expensive piece of equipment that measures bone density. Merck finally gave in, asking him to find 20 patients.

He came up with 40.

And there, in the entrepreneurial spirit displayed by Dr. Weiss, lay the solution to a problem that was suddenly dogging the pharmaceutical industry — the slow pace of research in university laboratories.

For decades, drug companies had been able to increase their prices almost at will, and thus had little incentive to develop new products. For the comparatively small number of drugs the companies did test, they turned to a trusted group of medical school researchers who dictated how trials were conducted. And the drug companies had to wait in line: Research financed by Government grants was far more prestigious; in the eyes of many academics, drug-company trials were to research what McDonald's hamburgers were to food.

In those days, researchers were reimbursed much differently than they are today. Payments went to the university, not to the investigator. The university doctors were often paid a flat fee for their work, no matter how many patients they actually enrolled.

Then, in the early 1990's, the economics of drug development changed. Managed care put the squeeze on drug prices, leaving companies one option: increase the number of drugs they were selling. As a result, the companies began a rush to drug development, something that was aided by reforms at the Food and Drug Administration that speeded up the approval process for new drugs.

Companies at first turned to their coterie of medical school researchers, but found the academic world was incapable of adapting rapidly to the increasingly intense competition.

"We had concretized bureaucracies," Dr. David R. Bickers, chairman of the dermatology department at Columbia University's College of Physicians and Surgeons, said of the academic response. "And for companies, time is money. Companies figure that out."

Quickly, the drug companies began recruiting a new breed of private-practice doctors like Dr. Weiss, willing to mine their patient base for research subjects.

The transformation is evident in a Times computer analysis of thousands of forms submitted each year to the Food and Drug Administration from doctors wanting to conduct research. According to the analysis, 11,662 private doctors conducted drug studies in 1997, almost three times the number in 1990, when 4,307 doctors conducted such studies. And while the number of researchers and medical schools also grew in that period — to 4,431 from 2,225 — their share of the business dropped from a third, to a quarter of the total, according to the analysis.

Private-practice doctors in research said the change was for the better, because the doctor was not simply tending to the patient's needs for the few weeks of a study, but often for a lifetime. "Even though the physician may want to make money, the moment he sits across from the patient, he is not only responsible to himself, he is responsible to that patient," said Dr. Norman Zinner, a Los Angeles doctor who in 1994 formed Affiliated Research Centers, an organization of private-practice urologists who conduct drug studies. "I have got to look you in the eye. I have got to see you again."

Not only that, these doctors said, but participation in research allows them to know the latest ideas for treatment. "I really feel I can offer my patients more," said Dr. Grossman of Vivra Asthma and Allergy. "I know more what the cutting edge is. I know what will be the recommended therapy two years from now."

Because anyone licensed to practice medicine is eligible to be a researcher, medical communities have been transformed in towns where the onslaught of managed care spawned legions of doctors scrambling to replace lost income. In 1980, when clinical research was the fief of medical schools, there were only eight projects in Tucson, Ariz., and all but two were at hospitals affiliated with the University of Arizona. Today, researchers are scattered in offices dotting the city — in places like the sun-baked barrios and the homely strip malls — conducting 157 studies in 1997 alone. Drug studies, and with them the competition for patients, have become as common in Tucson as the towering saguaro cactus.

Now, with federally financed research on the wane, it is the academic researchers who are banging on the doors of the drug companies, asking for a second chance. But they are finding it hard to keep up with the private doctors, who have shown themselves more willing to sign contracts overnight, advertise widely, offer financial incentives for patients and open their offices at unusual times to accommodate patient schedules.

"It's very difficult to conduct drug studies at the medical school because of the competition" from private doctors, said Dr. Mark A. Brown, a pediatric asthma specialist at the University of Arizona. "It's difficult to find patients."

To keep up with the competition from private doctors, some academic medical centers have recently begun setting up research divisions to draw on their own private patients for drug studies. But it is a fledgling effort, limited to a handful of universities.

Still, some junior faculty members are now abandoning academia to get into the drug-study business. Dr. Andrew Cutler, a psychiatrist, left the faculty at the University of Chicago to join the Psychiatric Institute of Florida in Orlando, a private practice with a research business. Then last year, he formed his own company, Coordinated Research of Florida, to perform drug studies full time.

Without a patient base to draw from for studies, Dr. Cutler found other ways to recruit subjects, including serving as a nursing home consultant.

"I will strategically pick a nursing home that has a large population that meets the criteria for a study," he said. "If there is a large community practice in town, I may work out a referral arrangement, or make them a co-investigator, and the arrangement is that they would be providing the patients."

But the industry is not passively waiting for doctors to knock on its door. Instead, over the last few years it has been aggressively recruiting doctors with the lure of cash. Every day, in hundreds of medical offices around the country, blandishments arrive by fax, mail and E-mail, encouraging doctors to grab their piece of the research pie.

"Discover the secret for obtaining more funded studies," says a 1992 letter to doctors from Research Investigator's Source, which charges $275 to place doctors' profiles on lists of researchers consulted by drug companies.

A 1998 letter from Clinmark Dotcom, an on-line listing service for researchers based in Irvine, Calif., offered to list doctors for $350 the first year and $195 in the second. But the letter made no secret about the reasons to join.

"Investigator grants average $43,000 per study," it said.

Then there are the ubiquitous seminars, sponsored by the industry, with enticing titles to attract doctors, both fledgling and experienced in studies. Some teach the basics, with such titles as "How to Find Clinical Trials: A Physician's Perspective" and "How to Develop or Evaluate a Patient Recruitment Media Plan."

But nothing captured the transformation of research more than a seminar on clinical trials in Nashville, sponsored in 1996 by Associates of Clinical Pharmacology, a professional association.

The title? "Successful Patient Recruitment: The Heart and Soul of Your Business."

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Quality Questions

Testing Puts Value On Speed Above All

Doctors and drug company executives milled around a racing car parked on the floor of the John B. Hynes Veterans Memorial Convention Center in Boston last year, waiting their turn to be photographed at the wheel. Nearby, other images of speed dotted the exhibit hall at the annual meeting of the Drug Information Association, an industry trade group. Checkered flags appeared on corporate booths and T-shirts. One exhibit featured a giant photograph of a cheetah; another showed a mural of a horse race.

To some at the meeting on drug development in the global marketplace, the images were a perfect metaphor for the industry today: The push to finish trials quickly and move the drugs onto the market has overshadowed every other goal.

"A few years ago it was 'better, faster, cheaper,' " said M. Jane Ganter, the editor in chief of Applied Clinical Trials, an industry publication. "Nobody is saying 'better' or 'cheaper' anymore. The big emphasis is on speed."

The driving forces behind the desire for faster studies are the industry's financial stakes. With the clock ticking on a new drug's patent even as it is being tested, every day's delay is revenue that will never be earned. "Time is money," said James Patricelli, an analyst of the drug-testing industry with Dain Rauscher Wessels. "Speed is the key."

But some in the industry worry that such singlemindedness has led testing companies to tap an increasing number of doctors with little or no experience in drug testing and only a fuzzy understanding of the rules.

The Times analysis showed that during the 1990's, 70 percent of the doctors conducting human experiments had been involved in three or fewer previous drug studies, a number unlikely to give them mastery over the process. A quarter of all doctors who did human experiments in 1997, the last year for which complete data are available, conducted only one experiment.

"Some of the companies would be embarrassed if they saw the quality of the people doing the research," said Dr. Angela Bowen, the president of the Western Institutional Review Board, a private ethics board based in Olympia, Wash., that reviews proposed research on human subjects. "I call them clueless."

One reason may be the predominance of generalists taking part in the studies. The studies test drugs for particular diseases, like asthma, in which a doctor's experience and specialized training are crucial in making assessments such as distinguishing between drug reactions and disease symptoms. But doctors conducting clinical trials often have no particular expertise in the disease they are treating. The Times computer analysis showed that the largest single group of doctors conducting investigations was general internists; one in five was either a general internist or a family practitioner. These, of course, are the doctors most Americans see for checkups and are thus the industry's most efficient recruiters.

But some doctors who do clinical research say that they often are offered studies that would require them to stretch far beyond their areas of medical expertise.

"I wouldn't do studies for hematology or neurology or lung disease or epilepsy," said Dr. Roy Fleischmann, the chief executive of Rheumatology Research International, a national network of clinical research sites that specialize in arthritis and skeletal diseases. But, he said, "We get calls about them all the time."

Not every doctor has the power to refuse.

"There was a lot of pressure for me to do things I did not feel comfortable doing," said Dr. Claudia Baldassano, a psychiatrist and neurologist who worked for a commercial research center on the East Coast. "They thought because I have an M.D., I should be comfortable doing all studies."

She said, for example, that she was asked to do Pap smears as part of a study of hormone replacement and was asked to treat patients with diabetes.

"I said I hadn't done a Pap smear since medical school, and I didn't feel comfortable," she said.

For the diabetes study, "I said how could you expect a physician who is not trained" as a diabetes specialist to run the trials, she said. "I was told by a vice president of operations that I could do diabetic studies with my eyes closed."

In the end, Dr. Baldassano stood her ground on the diabetes study, but participated in the one on hormone replacement. She resigned from the business after just a few months, and now works in academic research.

Why would drug companies accept research even from doctors who doubt their own expertise? Because, experts said, the industry has grown so quickly that no one has yet developed a good measurement of quality. Drug companies are left to review two factors: speed and cost. Systems of measurement for quality "haven't been established to differentiate these companies," said Mr. Patricelli of Dain Rauscher.

In an attempt to protect the quality of data and patients, the Government and industry have put into effect some means of oversight. The first line of defense for the integrity of the data is the dispatch of study monitors employed by the testing companies to the doctors' offices to pore over the test results.

But the explosive growth of the industry has left experienced monitors in short supply.

As a result, "They utilize some people who have very little experience in the disease entity, or the drug, or in pharmacology," said Dr. Fleischmann of Rheumatology Research International. The monitors "don't understand what they are doing."

"They are looking for boxes to fill in," he said.

For example, he said, the most common form of arthritis, osteoarthritis, is also called "degenerative joint disease." A testing company monitor who came to examine his data announced that his patients were not qualified for the study because she did not know the two terms meant the same thing, he said.

"If they don't have that knowledge," Dr. Fleischmann asked, "how can they read a chart and know what is real and what is not real?"

Some experts said there was a decided difference between the quality of monitors who work for the drug industry and those who work for the testing companies. Monitors sent by testing companies can be so unknowledgeable, said Margaret Chokreff, the president of Margaret Chokreff & Associates, which works with a network of private doctors conducting research in Ohio, that she and her nursing staff must sometimes train them about their own studies.

The monitors' sole task is protecting not patients. That job falls largely to a patchwork system of ethics boards, ... that are required by Federal law to approve research proposals involving humans. The main responsibility of these panels is to insure that test candidates are fully informed of the benefits and risks of a particular study and that they are not coerced to participate.

But the review boards last year fell under criticism from Government officials for reviewing too many studies too quickly and for lacking expertise. And while these boards will get involved in deciding the appropriate language to be used for an advertisement for patients, they do not consider whether patients should be told of their doctors' financial stake.

Dr. Shimm of Porter Adventist Hospital in Denver recalled that when he served on an ethics board at a university medical school, a good deal of time was spent discussing whether payments to patient volunteers were coercive. The concern was that patients might enter studies for the money rather than out of altruism, the ideal that is sought. But, immediately after such a discussion at one meeting, another proposal came up in which a doctor stood to receive thousands of dollars from the drug company for each patient recruited.

"I said, 'Wait a minute,' " Dr. Shimm said. "If it is coercive to pay a patient $500, why is it not coercive to pay the clinical investigator $5,000?"

But other members of the research board were not interested in the topic.

"I was told," Dr. Shimm said, "to sit down and shut up."

Next: Inside a research fraud.

Jennifer Warburg for the New York Times

"You go to the trade meetings on clinical research, you go for two entire days, and patients are not mentioned."

Dr. Robert M. Califf, the director of the Duke Clinical Research Institute, an academic drug-testing center in Durham, N.C., affiliated with Duke University.

From Prospect to Prescription, How a Drug Comes to Market

From the initial spark of an idea to the approval for use by the public, the process of getting a new drug to the consumer takes an average of 12 to 20 years. Here is a look at how that process works:

Research and Development

Focuses on laboratory and animal testing.

DISCOVERY

Researchers work through thousands of compounds in an effort to find those with some impact on a disease.

PRE-CLINICAL TESTING

Hundreds of potential drugs are put through laboratory and animal tests to check the biological effect on the disease. Those found to have beneficial effects with reasonable safety are proposed for clinical study.

Clinical Trials

Human test subjects become involved at this stage. = 100 patients

PHASE I

PATIENTS: 20-80

Volunteers are used to study the safe dosage range and how the drug is absorbed and metabolized by the body.

PHASE II

PATIENTS: 100-300

Volunteer patients, who have the disease, are used to test the drug's effectiveness and side effects.

PHASE III

PATIENTS: 1,000-5,000

The drug is studied in a larger, more diverse group of patients.

Results are analyzed, and if positive, a New Drug Application is submitted for approval.

F.D.A. Approval

The Food and Drug Administration reviews the application, assessing the quality of the research and whether the drugs are safe and effective.

Post-Market Trials

PHASE IV

PATIENTS: Number varies

Used to learn more about patients' reactions to the drug. Can be mandated by the F.D.A.

The proposal is submitted to the Food and Drug Administration.

Source: PhRMA, Tufts Center for the Study of Drug Development

The New York Times

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Cost-Cutting Gives Rise to New Research Industry

Drug companies used to supervise all their research, from the discovery of the drugs to the animal tests to the preliminary human tests to the large studies involving hundreds or thousands of patients.

No more. A multibillion-dollar industry has sprung up to take care of all that and more, including designing the studies, finding doctors and patients, analyzing the data, meeting with the Food and Drug Administration, writing the scientific papers and preparing the truckload of documents that must be submitted before a drug is approved.

These new companies have sliced the drug-testing business in every possible way. Some are little more than a Rolodex of the names of doctors willing to help test drugs. Others are major corporations, essentially drug companies without the drugs.

It is an industry that arose to fill a need: the enormous pressure that began around 1992 from managed care companies and health insurers on drug companies to hold down prices, according to industry analysts. Until then, the drug companies had been profitable, making money mostly by increasing prices, not by developing new drugs.

The companies now had to find a new way of generating profits. "Their vulnerability became transparent to the world," said James Patricelli, an industry analyst with Dain Rauscher Wessels in Minneapolis. "What you had was a drug industry that suddenly had to make investments in its future."

The companies' response was to search for blockbusters — the Prozacs and Viagras hidden within the laboratory chemicals. The Food and Drug Administration gave the companies another incentive by speeding up its approval process, with the median review time for new drug applications dropping from more than 22 months in 1990 to just over 14 months in 1997, according to the F.D.A.

"The industry has flip-flopped," said Kim Lamon, corporate senior vice president with Covance Inc., a giant drug-testing and development company. "There is a push for novel, innovative, blockbuster drugs, and to be the first or second to market."

Drug companies found they had to put more effort and money into finding drugs while at the same time slashing their development costs. For many, their solution was to largely dismantle their divisions that ran clinical trials and to turn the work over to smaller companies that emerged to fill the need.

> Many companies are ready to help take care of the details.

"Everyone had auditors, kids right out of college, telling us how to do it cheaply," said Dr. Cynthia M. Dunn, a former vice president for medical affairs at Fisons, a British drug maker later acquired by Rhône-Poulenc Rorer Inc., and now the director of the Clinical Research Institute at the University of Rochester. "They really pushed the outsourcing."

With the new companies came a variety of new names. Contract research organizations were composed of companies that ran parts or all of the clinical trials. Site management organizations — groups of doctors willing to offer their services to conduct trials — soon followed.

The growth in this sector has been enormous. Roughly $3.2 billion was paid to the contract research organizations in 1997, up 52 percent from just two years earlier, when payments were $2.1 billion.

Covance, one of the largest contract research organizations, doubled its staff and revenues from 1994 to 1998. Today, the Princeton, N.J., company is an industry giant, with 7,000 employees and more than $700 million in revenues in 1998.

"It's an industry that has been growing and growing and growing," said Ismail A. Shalaby, the chief executive of Nema Research Inc., a clinical research network based in Baltimore. "A drug company doesn't have to invest a lot of its own time and money to develop a drug anymore."

In fact, some industry experts said, a drug company barely even needs to be a drug company any more. For example, Neurobiological Technologies Inc. in Richmond, Calif., has no factories, 11 employees, 3 scientists and less than $1 million in cash. Yet it is using the new testing industry to conduct huge clinical trials, involving dozens of research sites and doctors around the country.

"You could have a company of one person, working out of their home, with no office, develop a drug," said Dr. Bert Spilker, a senior vice president of scientific and regulatory affairs with the Pharmaceutical Research and Manufacturers of America, a trade association. "You could have totally virtual companies."

Longtime members of the industry marvel at the change, which has occurred in just a few years.

"One called me; they had two employees," said Dr. Leigh Thompson, a drug-industry consultant in Charleston, S.C., who is a former chief scientific officer at Eli Lilly. "They have a molecule and hope but nothing else."

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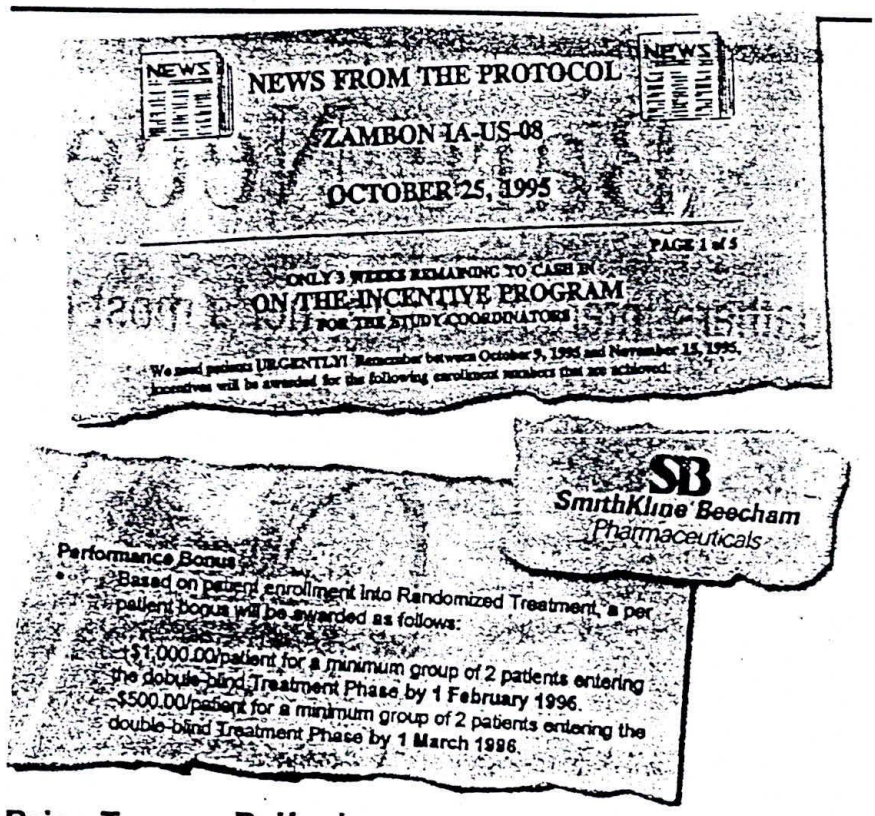

NEWS FROM THE PROTOCOL

ZAMBON LA-US-08

OCTOBER 25, 1995

PAGE 1 of 5

ONLY 3 WEEKS REMAINING TO CASH IN

ON THE INCENTIVE PROGRAM

FOR THE STUDY COORDINATORS

We need patients URGENTLY! Remember between October 9, 1995 and November 15, 1995, incentives will be awarded for the following enrollment numbers that are achieved:

SB SmithKline Beecham Pharmaceuticals

Performance Bonus

Based on patient enrollment into Randomized Treatment, a per patient bonus will be awarded as follows:

$1,000.00/patient for a minimum group of 2 patients entering the double-blind Treatment Phase by 1 February 1996.

$500.00/patient for a minimum group of 2 patients entering the double-blind Treatment Phase by 1 March 1996.

Price Tags on Patients

Incentive forms like the ones shown above encourage the enrollment of more patients in a particular study. Below are the amounts paid to private doctors, which can vary from site to site, who participated in specific studies.

SPONSOR	*DRUG*	*DISEASE*	*PAYMENT PER PATIENT**
SmithKline Beecham	Eprosartan	Diabetes	**$4,410**
Janssen Pharmaceutica	Alniditan	Migraine	**$3,600**
Merck	Losartan	Hypertension	**$2,955**
Rhône-Poulenc Rorer	Sparfloxacin	Sinusitis	**$2,670**
Glaxo Wellcome	Ceftin	Sinusitis	**$1,730**
SmithKline Beecham	SB 216469-S	Enlarged prostate	**$1,610**
Zambon Pharmaceutical	PHZ-136	Osteoarthritis	**$1,600**
Bayer	Clotrimazole	Vaginitis	**$1,200**
Organon	CTR 99 & CTR 77	Birth control	**$1,100**
Bristol-Myers Squibb	Butorphanol Tartrate	Migraine	**$1,000**

*Amounts do not include bonuses paid for performance.

The New York Times

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U.S. Food and Drug Administration

PAGE 2

Food and Drug Administration

INFORMATION SHEETS

Guidance for Institutional Review Boards and Clinical Investigators

1998 Update

FREQUENTLY ASKED QUESTIONS

The following is a compilation of answers to questions asked of FDA regarding the protection of human subjects of research. For ease of reference, the numbers assigned to the questions are consecutive throughout this section. These questions and answers are organized as follows.

I. IRB Organization

1. What is an Institutional Review Board (IRB)?

Under FDA regulations, an IRB is an appropriately constituted group that has been formally designated to review and monitor biomedical research involving human subjects. In accordance with FDA regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. This group review serves an important role in the protection of the rights and welfare of human research subjects.

The purpose of IRB review is to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in the research. To accomplish this purpose, IRBs use a group process to review research protocols and related materials (e.g., informed consent documents and investigator brochures) to ensure protection of the rights and welfare of human subjects of research.

2. Do IRBs have to be formally called by that name?

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No, "IRB" is a generic term used by FDA (and HHS) to refer to a group whose function is to review research to assure the protection of the rights and welfare of the human subjects. Each institution may use whatever name it chooses. Regardless of the name chosen, the IRB is subject to the Agency's IRB regulations when studies of FDA regulated products are reviewed and approved.

3. Does an IRB need to register with FDA before approving studies?

Currently, FDA does not require IRB registration. The form FDA-1572 "Statement of Investigator" for a study conducted under an IND requires the name and address of the IRB that will be responsible for review of the study. IRBs that approve studies of FDA regulated products must be established and operated in compliance with 21 CFR part 56.

4. What is an "assurance" or a "multiple project assurance?"

An "assurance," is a document negotiated between an institution and the Department of Health and Human Services (HHS) in accordance with HHS regulations. For research involving human subjects conducted by HHS or supported in whole or in part by HHS, the HHS regulations require a written assurance from the performance-site institution that the institution will comply with the HHS protection of human subjects regulations [45 CFR part 46]. The assurance mechanism is described in 45 CFR 46.103. Once an institution's assurance has been approved by HHS, a number is assigned to the assurance. The assurance may be for a single grant or contract (a "single project assurance"); for multiple grants ("multiple project assurances" - formerly called "general assurances"); or for certain types of studies such as oncology group studies and AIDS research group studies ("cooperative project assurances"). The Office for Protection from Research Risks (OPRR), is responsible for implementing the HHS regulations. The address and telephone number for OPRR are: 6100 Executive Boulevard, Suite 3B01 (MSC-7507), Rockville, MD 20892-7507; (301) 496-7041.

5. Is an "assurance" required by FDA?

Currently, FDA regulations do not require an assurance. FDA regulations [21 CFR parts 50 and 56] apply to research involving products regulated by FDA - federal funds and/or support do not need to be involved for the FDA regulations to apply. When research studies involving products regulated by FDA are funded/supported by HHS, the research institution must comply with both the HHS and FDA regulations. Also, see the information sheet entitled "Significant Differences in HHS and FDA Regulations for the protection of Human Subjects."

6. Must an institution establish its own IRB?

No. Although institutions engaged in research involving human subjects will usually have their own IRBs to oversee research conducted within the institution or by the staff of the institution, FDA regulations permit an institution without an IRB to arrange for an "outside" IRB to be responsible for initial and continuing review of studies conducted at the non-IRB institution. Such arrangements should be documented in writing. Individuals conducting research in a non-institutional setting often use established IRBs (independent or institutional) rather than form their own IRBs. Also see the information sheets entitled "Non-local IRB Review" and "Cooperative Research."

7. May a hospital IRB review a study that will be conducted outside of the hospital?

Yes. IRBs may agree to review research from affiliated or unaffiliated investigators, however, FDA does not require IRBs to assume this responsibility. If the IRB routinely conducts these reviews, the IRB policies should authorize such reviews and the process should be described in the IRB's written procedures. A hospital IRB may review outside studies on an individual basis when the minutes clearly show the members are aware of where the study is to be conducted and when the IRB possesses appropriate knowledge about the study site(s).

8. May IRB members be paid for their services?

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The FDA regulations do not preclude a member from being compensated for services rendered. Payment to IRB members should not be related to or dependent upon a favorable decision. Expenses, such as travel costs, may also be reimbursed.

9. What is the FDA role in IRB liability in malpractice suits?

FDA regulations do not address the question of IRB or institutional liability in the case of malpractice suits. FDA does not have authority to limit liability of IRBs or their members. Compliance with FDA regulations may help minimize an IRB's exposure to liability.

10. Is the purpose of the IRB review of informed consent to protect the institution or the subject?

The fundamental purpose of IRB review of informed consent is to assure that the rights and welfare of subjects are protected. A signed informed consent document is evidence that the document has been provided to a prospective subject (and presumably, explained) and that the subject has agreed to participate in the research. IRB review of informed consent documents also ensures that the institution has complied with applicable regulations.

11. Does an IRB or institution have to compensate subjects if injury occurs as a result of participation in a research study?

Institutional policy, not FDA regulation, determines whether compensation and medical treatment(s) will be offered and the conditions that might be placed on subject eligibility for compensation or treatment(s). The FDA informed consent regulation on compensation [21 CFR 50.25(a)(6)] requires that, for research involving more than minimal risk, the subject must be told whether any compensation and any medical treatment(s) are available if injury occurs and, if so, what they are, or where further information may be obtained. Any statement that compensation is not offered must avoid waiving or appearing to waive any of the subject's rights or releasing or appearing to release the investigator, sponsor, or institution from liability for negligence [21 CFR 50.20].

II. IRB Membership

12. May a clinical investigator be an IRB member?

Yes, however, the IRB regulations [21 CFR 56.107(e)] prohibit any member from participating in the IRB's initial or continuing review of any study in which the member has a conflicting interest, except to provide information requested by the IRB. When selecting IRB members, the potential for conflicts of interest should be considered. When members frequently have conflicts and must absent themselves from deliberation and abstain from voting, their contributions to the group review process may be diminished and could hinder the review procedure. Eve n greater disruptions may result if this person is chairperson of the IRB.

13. The IRB regulations require an IRB to have a diverse membership. May one member satisfy more than one membership category?

Yes. For example, one member could be otherwise unaffiliated with the institution and have a primary concern in a non-scientific area. This individual would satisfy two of the membership requirements of the regulations. IRBs should strive, however, for a membership that has a diversity of representative capacities and disciplines. In fact, the FDA regulations [21 CFR 56.107(a)] require that, as part of being qualified as an IRB, the IRB must have "... diversity of members, including consideration of race, gender, cultural backgrounds and sensitivity to such issues as community attitudes ...."

14. When IRB members cannot attend a convened meeting, may they send someone from their department to vote for them?

No. Alternates who are formally appointed and listed in the membership roster may substitute, but ad

hoc substitutes are not permissible as members of an IRB. However, a member who is unable to be present at the convened meeting may participate by video-conference or conference telephone call, when the member has received a copy of the documents that are to be reviewed at the meeting. Such members may vote and be counted as part of the quorum. If allowed by IRB procedures, ad hoc substitutes may attend as consultants and gather information for the absent member, but they may not be counted toward the quorum or participate in either deliberation or voting with the board. The IRB may, of course, ask questions of this representative just as they could of any non-member consultant. Opinions of the absent members that are transmitted by mail, telephone, telefax or e-mail may be considered by the attending IRB members but may not be counted as votes or the quorum for convened meetings.

15. May the IRB use alternate members?

The use of formally appointed alternate IRB members is acceptable to the FDA, provided that the IRB's written procedures describe the appointment and function of alternate members. The IRB roster should identify the primary member(s) for whom each alternate member may substitute. To ensure maintaining an appropriate quorum, the alternate's qualifications should be comparable to the primary member to be replaced. The IRB minutes should document when an alternate member replaces a primary member. When alternates substitute for a primary member, the alternate member should have received and reviewed the same material that the primary member received or would have received.

16. Does a non-affiliated member need to attend every IRB meeting?

No. Although 21 CFR 56.108(c) does not specifically require the presence of a member not otherwise affiliated with the institution to constitute a quorum, FDA considers the presence of such members an important element of the IRB's diversity. Therefore, frequent absence of all non-affiliated members is not acceptable to FDA. Acknowledging their important role, many IRBs have appointed more than one member who is not otherwise affiliated with the institution. FDA encourages IRBs to appoint members in accordance with 21 CFR 56.107(a) who will be able to participate fully in the IRB process.

17. Which IRB members should be considered to be scientists and non-scientists?

21 CFR 56.107(c) requires at least one member of the IRB to have primary concerns in the scientific area and at least one to have primary concerns in the non-scientific area. Most IRBs include physicians and Ph.D. level physical or biological scientists. Such members satisfy the requirement for at least one scientist. When an IRB encounters studies involving science beyond the expertise of the members, the IRB may use a consultant to assist in the review, as provided by 21 CFR 56.107(f).

FDA believes the intent of the requirement for diversity of disciplines was to include members who had little or no scientific or medical training or experience. Therefore, nurses, pharmacists and other biomedical health professionals should not be regarded to have "primary concerns in the non-scientific area." In the past, lawyers, clergy and ethicists have been cited as examples of persons whose primary concerns would be in non-scientific areas.

Some members have training in both scientific and non-scientific disciplines, such as a J.D., R.N. While such members are of great value to an IRB, other members who are unambiguously non-scientific should be appointed to satisfy the non-scientist requirement.

III. IRB Procedures

18. The FDA regulations [21 CFR 56.104(c)] exempt an emergency use of a test article from prospective IRB review, however, "... any subsequent use of the test article at the institution is subject to IRB review." What does the phrase "subsequent use" mean?

FDA regulations allow for one emergency use of a test articl e in an institution without prospective IRB review, provided that such emergency use is reported to the IRB within five working days after such use. An emergency use is defined as a single use (or single course of treatment, e.g., multiple doses of antibiotic) with one subject. "Subsequent use" would be a second use with that subject or the use with

another subject.

In its review of the emergency use, if it is anticipated that the test article may be used again, the IRB should request a protocol and consent document(s) be developed so that an approved protocol would be in place when the next need arises. In spite of the best efforts of the clinical investigator and the IRB, a situation may occur where a second emergency use needs to be considered. FDA believes it is inappropriate to deny emergency treatment to an individual when the only obstacle is lack of time for the IRB to convene, review the use and give approval.

19. Are there any regulations that require clinical investigators to report to the IRB when a study has been completed?

IRBs are required to function under written procedures. One of these procedural requirements [21 CFR 56.108(a)(3)] requires ensuring "prompt reporting to the IRB of changes in a research activity." The completion of the study is a change in activity and should be reported to the IRB. Although subjects will no longer be "at risk" under the study, a final report/notice to the IRB allows it to close its files as well as providing information that may be used by the IRB in the evaluation and approval of related studies.

20. What is expedited review?

Expedited review is a procedure through which certain kinds of research may be reviewed and approved without convening a meeting of the IRB. The Agency's IRB regulations [21 CFR 56.110] permit, but do not require, an IRB to review certain categories of research through an expedited procedure if the research involves no more than minimal risk. A list of categories was last published in the Federal Register on January 27, 1981 [46 FR 8980]. The list is reproduced as Appendix D of this document.

The IRB may also use the expedited review procedure to review minor changes in previously approved research during the period covered by the original approval. Under an expedited review procedure, review of research may be carried out by the IRB chairperson or by one or more experienced members of the IRB designated by the chairperson. The reviewer(s) may exercise all the authorities of the IRB, except disapproval. Research may only be disapproved following review by the full committee. The IRB is required to adopt a method of keeping all members advised of research studies that have been approved by expedited review.

On November 9, FDA published in the *Federal Register* concurrently with OPRR a new Expedited Review List. The entire *Federal Register* publication, including the FDA preamble, was published on pages 60353 - 60356 of the November 9, 1998 *Federal Register* and is available on the World Wide Web at the Dockets Management Page of the FDA home Page at http://www.fda.gov/ohrms/dockets/98fr/110998b.txt (or use suffix ".pdf"for Adobe Acrobat version) or alternatively at the Government Printing Office site at http://www.access.gpo.gov/su_docs/fedreg/a981109c.html and scroll down to Food and Drug Administration.

21. The number of studies we review has increased, and the size of the package of review materials we send to IRB members is becoming formidable. Must we send the full package to all IRB members?

The IRB system was designed to foster open discussion and debate at convened meetings of the full IRB membership. While it is preferable for every IRB member to have personal copies of all study materials, each member must be provided with sufficient information to be able to actively and constructively participate. Some institutions have developed a "primary reviewer" system to promote a thorough review. Under this system, studies are assigned to one or more IRB members for a full review of all materials. Then, at the convened IRB meeting the study is presented by the primary reviewer(s) and, after discussion by IRB members, a vote for an action is taken.

The "primary reviewer" procedure is acceptable to the FDA if each member receives, at a minimum; a copy of consent documents and a summary of the protocol in sufficient detail to determine the appropriateness of the study-specific statements in the consent documents. In addition, the complete

documentation should be available to all members for their review, both before and at the meeting. The materials for review should be received by the membership sufficiently in advance of the meeting to allow for adequate review of the materials.

Some IRBs are also exploring the use of electronic submissions and computer access for IRB members. Whatever system the IRB develops and uses, it must ensure that each study receives an adequate review and that the rights and welfare of the subjects are protected.

22. Are sponsors allowed access to IRB written procedures, minutes and membership rosters?

The FDA regulations do not require public or sponsor access to IRB records. However, FDA does not prohibit the sponsor from requesting IRB records. The IRB and the institution may establish a policy on whether minutes or a pertinent portion of the minutes are provided to sponsors.

Because of variability, each IRB also needs to be aware of State and local laws regarding access to IRB records.

23. Must an investigator's brochure be included in the documentation when an IRB reviews an investigational drug study?

For studies conducted under an investigational new drug application, an investigator's brochure is usually required by FDA [21 CFR 312.23(a)(5) and 312.55]. Even though 21 CFR part 56 does not mention the investigator's brochure by name, much of the information contained in such brochures is clearly required to be reviewed by the IRB. The regulations do outline the criteria for IRB approval of research. 21 CFR 56.111(a)(1) requires the IRB to assure that risks to the subjects are minimized. 21 CFR 56.111(a)(2) requires the IRB to assure that the risks to subjects are reasonable in relatio n to the anticipated benefits. The risks cannot be adequately evaluated without review of the results of previous animal and human studies, which are summarized in the investigator's brochure.

There is no specific regulatory requirement that the Investigator's Brochure be submitted to the IRB. There are regulatory requirements for submission of information which normally is included in the Investigator's Brochure. It is common that the Investigator's Brochure is submitted to the IRB, and the IRB may establish written procedures which require its submission. Investigator's Brochures may be part of the investigational plan that the IRB reviews when reviewing medical device studies.

24. To what extent is the IRB expected to actively audit and monitor the performance of the investigator with respect to human subject protection issues?

FDA does not expect IRBs to routinely observe consent interviews, observe the conduct of the study or review study records. However, 21 CFR 56.109(f) gives the IRB the authority to observe, or have a third party observe, the consent process and the research. When and if the IRB is concerned about the conduct of the study or the process for obtaining consent, the IRB may consider whether, as part of providing adequate oversight of the study, an active audit is warranted.

25. How can a sponsor know whether an IRB has been inspected by FDA, and the results of the inspection?

The Division of Scientific Investigations, Center for Drug Evaluation and Research, maintains an inventory of the IRBs that have been inspected, including dates of inspection and classification. The Division recently began including the results of inspections assigned by the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health. This information is available through Freedom of Information Act (FOIA) procedures. Once an investigational file has been closed, the correspondence between FDA and the IRB and the narrative inspectional report are also available under FOI.

26. If an IRB disapproves a study submitted to it, and it is subsequently sent to another IRB for review, should the second IRB be told of the disapproval?

Yes. When an IRB disapproves a study, it must provide a written statement of the reasons for its decision to the investigator and the institution [21 CFR 56.109(e)]. If the study is submitted to a second IRB, a copy of this written statement should be included with the study documentation so that it can make an informed decision about the study. 21 CFR 56.109(a) requires an IRB to "... review ... all research activities [emphasis added] ...." The FDA regulations do not prohibit submission of a study to another IRB following disapproval. However, all pertinent information about the study should be provided to the second IRB.

27. May an independent IRB review a study to be conducted in an institution with an IRB?

Generally, no. Most institutional IRB have jurisdiction over all studies conducted within that institution. An independent IRB may become the IRB of record for such studies only upon written agreement with the administration of the institution or the in-house IRB.

28. Could an IRB lose its quorum when members with a conflict of interest leave the room for deliberation and voting on a study?

Yes. "The quorum is the count of the number of members present. If the number present falls below a majority, the quorum fails. The regulations only require that a member who is conflicted not participate in the deliberations and voting on a study on which he or she is conflicted. The IRB may decide whether an individual should remain in the room."

29. Does FDA expect the IRB chair to sign the approval letters?

FDA does not specify the procedure that IRBs must use regarding signature of the IRB approval letter. The written operating procedures for the IRB should outline the procedure that is followed.

30. Does FDA prohibit direct communication between sponsors and IRBs?

It is important that a formal line of communication be established between the clinical investigator and the IRB. Clinical investigators should report adverse events directly to the responsible IRB, and should send progress reports directly to that IRB. However, FDA does not prohibit direct communication between the sponsor and the IRB, and recognizes that doing so could result in more efficient resolution of some problems.

FDA does require direct communication between the sponsors and the IRBs for certain studies of medical devices and when the 21 CFR 50.24 informed consent waiver has been invoked. Sponsors and IRBs are required to communicate directly for medical device studies under 21 CFR 812.2, 812.66 and 812.150(b). For informed consent waiver studies, direct communication between sponsors and IRBs is required under 21 CFR 50.24(e), 56.109(e), 56.109(g), 312.54(b), 312.130(d), 812.38(b)(4) and 812.47(b).

IV. IRB Records

31. Are annual IRB reviews required when all studies are reviewed by the IRB each quarter?

The IRB records for each study's initial and continuing review should note the frequency (not to exceed one year) for the next continuing review in either months or other conditions, such as after a particular number of subjects are enrolled.

An IRB may decide, to review all studies on a quarterly basis. If every quarterly report contains sufficient information for an adequate continuing review and is reviewed by the IRB under procedures that meet FDA requirements for continuing review, FDA would not require an additional "annual" review.

32. 21 CFR 56.115(a)(1) requires that the IRB maintain copies of "research proposals reviewed." Is the

"research proposal" the same as the formal study protocol that the investigator receives from the sponsor of the research?

Yes. The IRB should receive and review all research activities [21 CFR 56.109(a)]. The documents reviewed should include the complete documents received from the clinical investigator, such as the protocol, the investigator's brochure, a sample consent document and any advertising intended to be seen or heard by prospective study subjects. Some IRBs also require the investigator to submit an institutionally-developed protocol summary form. A copy of all documentation reviewed is to be maintained for at least three years after completion of the research at that institution [21 CFR 56.115(b)]. However, when the IRB makes changes, such as in the wording of the informed consent document, only the finally approved copy needs to be retained in the IRB records.

33. What IRB records are required for studies that are approved but never started?

When an IRB approves a study, continuing review should be performed at least annually. All of the records listed in 21 CFR 56.115(a)(1) - (4) are required to be maintained. The clock starts on the date of approval, whether or not subjects have been enrolled. Written progress reports should be received from the clinical investigator for all studies that are in approved status prior to the date of expiration of IRB approval. If subjects were never enrolled, the clinical investigator's progress report would be brief. Such studies may receive continuing IRB review using expedited procedures. If the study is finally canceled without subject enrollment, records should be maintained for at least three years after cancellation [21 CFR 56.115(b)].

V. Informed Consent Process

34. Is getting the subject to sign a consent document all that is required by the regulations?

No. The consent document is a written summary of the information that should be provided to the subject. Many clinical investigators use the consent document as a guide for the verbal explanation of the study. The subject's signature provides documentation of agreement to participate in a study, but is only one part of the consent process. The entire informed consent process involves giving a subject adequate information concerning the study, providing adequate opportunity for the subject to consider information, obtaining the subject's voluntary agreement to participate and, continuing to provide information as the subject or situation requires. To be effective, the process should provide ample opportunity for the investigator and the subject to exchange information and ask questions.

35. May informed consent be obtained by telephone from a legally authorized representative?

A verbal approval does not satisfy the 21 CFR 56.109(c) requirement for a signed consent document, as outlined in 21 CFR 50.27(a). However, it is acceptable to send the informed consent document to the legally authorized representative (LAR) by facsimile and conduct the consent interview by telephone when the LAR can read the consent as it is discussed. If the LAR agrees, he/she can sign the consent and return the signed document to the clinical investigator by facsimile.

36. 21 CFR 50.27(a) requires that a copy of the consent document be given to the person signing the form. Does this copy have to be a photocopy of the form with the subject's signature affixed?

No. The regulation does not require the copy of the form given to the subject to be a copy of the document with the subject's signature, although this is encouraged. It must, however, be a copy of the IRB approved document that was given to the subject to obtain consent [21 CFR 50.27(a) or 21 CFR 50.27(b)(2)]. One purpose of providing the person signing the form with a copy of the consent document is to allow the subject to review the information with others, both before and after making a decision to participate in the study, as well as providing a continuing reference for items such as scheduling of procedures and emergency contacts.

37. If an IRB uses a standard "fill-in-the-blank" consent format, does the IRB need to review the filled

out form for each study?

Yes. A fill-in-the-blank format provides only some standard wording and a framework for organizing the relevant study information. The IRB should review a completed sample form, individualized for each study, to ensure that the consent document, in its entirety, contains all the information required by 21 CFR 50.25 in language the subject can understand. The completed sample form should be typed to enhance its readability by the subjects. The form finally approved by the IRB should be an exact copy of the form that will be presented to the research subjects. The IRB should also review the "process" for conducting the consent interviews, i.e., the circumstances under which consent will be obtained, who will obtain consent, and so forth.

38. The informed consent regulations [21 CFR 50.25 (a)(5)] require the consent document to include a statement that notes the possibility that FDA may inspect the records. Is this statement a waiver of the subject's legal right to privacy?

No. FDA does not require any subject to "waive" a legal right. Rather, FDA requires that subjects be informed that complete privacy does not apply in the context of research involving FDA regulated products. Under the authority of the Federal Food, Drug, and Cosmetic Act, FDA may inspect and copy clinical records to verify information submitted by a sponsor. FDA generally will not copy a subject's name during the inspection unless a more detailed study of the case is required or there is reason to believe that the records do not represent the actual cases studied or results obtained.

The consent document should not state or imply that FDA needs clearance or permission from the clinical investigator, the subject or the IRB for such access. When clinical investigators conduct studies for submission to FDA, they agree to allow FDA access to the study records, as outlined in 21 CFR 312.68 and 812.145. Informed consent documents should make it clear that, by participating in research, the subject's records automatically become part of the research database. Subjects do not have the option to keep their records from being audited/reviewed by FDA.

When an individually identifiable medical record (usually kept by the clinical investigator, not by the IRB) is copied and reviewed by the Agency, proper confidentiality procedures are followed within FDA. Consistent with laws relating to public disclosure of information and the law enforcement responsibilities of the Agency, however, absolute confidentiality cannot be guaranteed.

39. Who should be present when the informed consent interview is conducted?

FDA does not require a third person to witness the consent interview unless the subject or representative is not given the opportunity to read the consent document before it is signed, see 21 CFR 50.27(b). The person who conducts the consent interview should be knowledgeable about the study and able to answer questions. FDA does not specify who this individual should be. Some sponsors and some IRBs require the clinical investigator to personally conduct the consent interview. However, if someone other than the clinical investigator conducts the interview and obtains consent, this responsibility should be formally delegated by the clinical investigator and the person so delegated should have received appropriate training to perform this activity.

40. How do you obtain informed consent from someone who speaks and understands English but cannot read?

Illiterate persons who understand English may have the consent read to them and "make their mark," if appropriate under applicable state law. The 21 CFR 50.27(b)(2) requirements for signature of a witness to the consent process and signature of the person conducting consent interview must be followed, if a "short form" is used. Clinical investigators should be cautious when enrolling subjects who may not truly understand what they have agreed to do. The IRB should consider illiterate persons as likely to be vulnerable to coercion and undue influence and should determine that appropriate additional safeguards are in place when enrollment of such persons is anticipated, see 21 CFR 56.111(b).

41. Must a witness observe the entire consent interview or only the signature of the subject?

FDA does not require the signature of a witness when the subject reads and is capable of understanding the consent document, as outlined in 21 CFR 50.27(b)(1). The intended purpose is to have the witness present during the entire consent interview and to attest to the accuracy of the presentation and the apparent understanding of the subject. If the intent of the regulation were only to attest to the validity of the subject's signature, witnessing would also be required when the subject reads the consent.

42. Should the sponsor prepare a model informed consent document?

Although not required by the IND regulations, the sponsor provides a service to the clinical investigator and the IRB when it prepares suggested study-specific wording for the scientific and technical content of the consent document. However, the IRB has the responsibility and authority to determine the adequacy and appropriateness of all of the wording in the consent, see 21 CFR 56.109(a), 111(a)(4) and 111(a)(5). If an IRB insists on wording the sponsor cannot accept, the sponsor may decide not to conduct the study at that site. For medical device studies that are conducted under an IDE, copies of all forms and informational materials to be provided to subjects to obtain informed consent must be submitted to FDA as part of the IDE, see 21 CFR 812.25(g).

43 . Is the sponsor required to review the consent form approved by the IRB to make sure all FDA requirements are met?

For investigational devices, the informed consent is a required part of the IDE submission. It is, therefore, approved by FDA as part of the IDE application. When an IRB makes substantive changes in the document, FDA reapproval is required and the sponsor is necessarily involved in this process.

FDA regulations for other products do not specifically require the sponsor to review IRB approved consent documents. However, most sponsors do conduct such reviews to assure the wording is acceptable to the sponsor.

44. Ar e there alternatives to obtaining informed consent from a subject?

The regulations generally require that the investigator obtain informed consent from subjects. Investigators also may obtain informed consent from a legally authorized representative of the subject. FDA recognizes that a durable power of attorney might suffice as identifying a legally authorized representative under some state and local laws. For example, a subject might have designated an individual to provide consent with regard to health care decisions through a durable power of attorney and have specified that the individual also has the power to make decisions on entry into research. FDA defers to state and local laws regarding who is a legally authorized representative. Therefore, the IRB should assure that the consent procedures comply with state and local laws, including assurance that the law applies to obtaining informed consent for subjects participating in research as well as for patients who require health care decisions."

Alternatives 1 and 2 are provided for in the regulations and are appropriate. Alternative 3 allows a designated individual to provide consent for a patient with regard to health care decisions and is appropriate when it specifically includes entry into research. FDA defers to state and local laws regarding substituted consent. Therefore, the IRB must assure itself that the substituted consent procedures comply with state and local law, including assurance the law applies to obtaining informed consent for subjects participating in research as well as for patients who require health care decisions.

45. When should study subjects be informed of changes in the study?

Protocol amendments must receive IRB review and approval before they are implemented, unless an *p300X

Those subjects who are presently enrolled and actively participating in the study should be informed of the change if it might relate to the subjects' willingness to continue their participation in the study (21 CFR 50.25(b)(5)). FDA does not require reconsenting of subjects that have completed their active participation in the study, or of subjects who are still actively participating when the change will not

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affect their participation, for example when the change will be implemented only for subsequently enrolled subjects.

VI. Informed Consent Document Content

46. May an IRB require that the sponsor of the study and/or the clinical investigator be identified on the study's consent document?

Yes. The FDA requirements for informed consent are the minimum basic elements of informed consent that must be presented to a research subject [21 CFR 50.25]. An IRB may require inclusion of any additional information which it considers important to a subject's decision to participate in a research study [21 CFR 56.109(b)].

47. Does FDA require the informed consent document to contain a space for assent by children?

No, however, many investigators and IRBs consider it standard practice to obtain the agreement of older children who can understand the circum stances before enrolling them in research. While the FDA regulations do not specifically address enrollment of children (other than to include them as a class of vulnerable subjects), the basic requirement of 21 CFR 50.20 applies, i.e., the legally effective informed consent of the subject or the subject's legally authorized representative must be obtained before enrollment. Parents, legal guardians and/or others may have the ability to give permission to enroll children in research, depending on applicable state and local law of the jurisdiction in which the research is conducted. (Note: permission to enroll in research is not the same as permission to provide medical treatment.) IRBs generally require investigators to obtain the permission of one or both of the parents or guardian (as appropriate) and the assent of children who possess the intellectual and emotional ability to comprehend the concepts involved. Some IRBs require two documents, a fully detailed explanation for parents and older children to read and sign, and a shorter, simpler one for younger children. [For research supported by DHHS, the additional protections at 45 CFR 46 Subpart D are also required. The Subpart D regulations provide appropriate guidance for all other pediatric studies.]

48. Does FDA require the signature of children on informed consent documents?

As indicated above, researchers may seek assent of children of various ages. Older children may be well acquainted with signing documents through prior experience with testing, licensing and/or other procedures normally encountered in their lives. Signing a form to give their assent for research would not be perceived as unusual and would be reasonable. Younger children, however, may never have had the experience of signing a document. For these children requiring a signature may not be appropriate, and some other technique to verify assent could be used. For example, a third party may verify, by signature, that the assent of the child was obtained.

49. Who should be listed on the consent as the contact to answer questions?

21 CFR 50.25(a)(7) requires contacts for questions about the research, the research subject's rights and in case of a research-related injury. It does not specify whom to contact. The same person may be listed for all three. However, FDA and most IRBs believe it is better to name a knowledgeable person other than the clinical investigator as the contact for study subject rights. Having the clinical investigator as the only contact may inhibit subjects from reporting concerns and/or possible abuses.

50. May the "compensation" for participation in a trial offered by a sponsor include a coupon good for a discount on the purchase price of the product once it has been approved for marketing?

No. This presumes, and inappropriately conveys to the subjects, a certainty of favorable outcome of the study and prompt approval for marketing. Also, if the product is approved, the coupon may financially coerce the subject to insist on that product, even though it may not be the most appropriate medically.

51. Must informed consent documents be translated into the written language native to study subjects who do not understand English?

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The signed informed consent document is the written record of the consent interview. Study subjects are given a copy of the consent to be used as a reference document to reinforce their understanding of the study and, if desired, to consult with their physician or family members about the study.

In order to meet the requirements of 21 CFR 50.20, the consent document must be in language understandable to the subject. When the prospective subject is fluent in English, and the consent interview is conducted in English, the consent document should be in English. However, when the study subject population includes non-English speaking people so that the clinical investigator or the IRB anticipates that the consent interviews are likely to be conducted in a language other than English, the IRB should assure that a translated consent form is prepared and that the translation is accurate.

A consultant may be utilized to assure that the translation is correct. A copy of the translated consent document must be given to each appropriate subject. While a translator may be used to facilitate conversation with the subject, routine ad hoc translation of the consent document may not be substituted for a written translation.

Also see FDA Information Sheets: "A Guide to Informed Consent Documents" and "Informed Consent and the Clinical Investigator"

52. Is it acceptable for the consent document to say specimens are "donated"?

What about a separate donation statement? It would be acceptable for the consent to say that specimens are to be used for research purposes. However, the word "donation" implies abandonment of rights to the "property". 21 CFR 50.20 prohibits requiring subjects to waive or appear to waive any rights as a condition for participation in the study. Whether or not the wording is contained in "the actual consent form" is immaterial. All study-related documents must be submitted to the IRB for review. Any separate "donation" agreement is regarded to be part of the informed consent documentation, and must be in compliance with 21 CFR 50.

53. Do informed consent forms have to justify fees charged to study subjects?

FDA does not require the consent to contain justification of charges.

VII. Clinical Investigations

54. Does a physician, in private practice, conducting research with an FDA regulated product, need to obtain IRB approval?

Yes. The FDA regulations require IRB review and approval of regulated clinical investigations, whether or not the study involves institutionalized subjects. FDA has included non-institutionalized subjects because it is inappropriate to apply a double standard for the protection of research subjects based on whether or not they are institutionalized.

An investigator may be able to obtain IRB review by submitting the research proposal to a community hospital, a university/medical school, an independent IRB, a local or state government health agency or other organizations. If IRB review cannot be accomplished by one of these means, investigators may contact the FDA for assistance (Health Assessment Policy Staff 301-827-1685).

55. Does a clinical investigation involving a marketed product require IRB review and approval?

Yes, if the investigation is governed by FDA regulations [see 21 CFR 56.101, 56.102(c), 312.2(b)(1), 361.1, 601.2, and 812.2]. Also, see the information sheet entitled " 'Off-label' and Investigational Use of Marketed Drugs and Biologics" for more information.

VIII. General Questions

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56. Which FDA office may an IRB contact to determine whether an investigational new drug application (IND) or investigational device exemption (IDE) is required for a study of a test article?

For drugs, the IRB may contact the Drug Information Branch, Center for Drug Evaluation and Research (CDER), at (301) 827-4573.

For a biological blood product, contact the Office of Blood Research and Review, Center for Biologics Evaluation and Research (CBER), at 301-827-3518. For a biological vaccine product, contact the Office of Vaccines Research and Review at 301-827-0648. For a biological Therapeutic product, contact the Office of Therapeutics Research and Review, CBER, at 301-594-2860.

For a medical device, contact the Program Operation Staff, Office of Device Evaluation, Center for Devices and Radiological Health (CDRH), at (301) 594-1190.

If the IRB is unsure about whether a test article is a "drug," a "biologic" or a "device," the IRB may contact the Health Assessment Policy Staff, Office of Health Affairs, at (301) 827-1685.

57. What happens during an FDA inspection of an IRB?

FDA field investigators interview institutional officials and examine the IRB records to determine compliance with FDA regulations. Also, see the information sheet entitled "FDA Institutional Review Board Inspections" for a co mplete description of the inspection process.

58. Does a treatment IND/IDE [21 CFR 312.34/812.36] require prior IRB approval?

Test articles given to human subjects under a treatment IND/IDE require prior IRB approval, with two exceptions. If a life-threatening emergency exists, as defined by 21 CFR 56.102(d), the procedures described in 56.104(c) ("Exemptions from IRB Requirement") may be followed. In addition, FDA may grant the sponsor or sponsor/investigator a waiver of the IRB requirement in accord with 21 CFR 56.105. An IRB may still choose to review a study even if FDA has granted a waiver. For further information see the information sheets entitled "Emergency Use of an Investigational Drug or Biologic," "Emergency Use of Unapproved Medical Devices," "Waiver of IRB Requirements" and "Treatment use of Investigational Drugs and Biologics."

59. How have the FDA policies on enrollment of special populations changed?

On July 22, 1993, the FDA published the Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs, in the Federal Register [58 FR 39406]. The guideline was developed to ensure that the drug development process provides adequate information about the effects of drugs and biological products in women. For further information, see the information sheet entitled "Evaluation of Gender Differences in Clinical Investigations."

On December 13, 1994, FDA published a final rule on the labeling of prescription drugs for pediatric populations [59 FR 64240]. The rule [21 CFR 201.57] encourages sponsors to include pediatric subjects in clinical trials so that more complete information about the use of drugs and biological products in the pediatric population can be developed.

60. What is a medical device?

A medical device is any instrument, apparatus, or other similar or related article, including component, part, or accessory, which is: (a) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them; (b) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in humans or other animals; or (c) intended to affect the structure or any function of the human body or in animals; and does not achieve any of its principal intended purposes through chemical action within or on the human body or in animals and is not dependent upon being metabolized for the achievement of its principal intended purposes.

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Approximately 1,700 types of medical devices are regulated by FDA. The range of devices is broad and diverse, including bandages, thermometers, ECG electrodes, IUDs, cardiac pacemakers, and hemodialysis machines. For further information, see the information sheets entitled "Medical Devices," "Frequently Asked Questions about IRB Review of Medical Devices" and "Significant Risk and Nonsignificant Risk Medical Device Studies."

61. Are *in vitro* diagnostic products medical devices?

Yes. The definition of a "device" includes *in vitro* diagnostic products - devices that aid in the diagnosis of disease or medical/physiological conditions (e.g., pregnancy) by using human or animal components to cause chemical reactions, fermentation, and the like. A few diagnostic products are intended for use in controlling other regulated products (such as those used to screen the blood supply for transfusion-transmitted diseases) and are regulated as biological products.

62. What are the IRB's general obligations towards intraocular lens (IOL) clinical investigations?

An IRB is responsible for the initial and continuing review of all IOL clinical investigations. Each individual IOL style is subject to a separate review by the IRB. This does not, however, preclude the IRB from using prior experience with other IOL investigations in considering the comparative merits of a new lens style. All IOL studies are also subject to FDA approval.

63. Considering the large number of IOL studies, how does an IRB approach the review of a new IOL style?

Full IRB review is required for all new IOLs that exhibit major departures from available lenses. Minor changes to existing lenses may be approved through expedited review. FDA designates new IOL styles as either major or minor changes based upon a predetermined classification scheme and advises the sponsor of its determination. The sponsor, through the investigator, should provide the IRB with the investigational plan which indicates the FDA study requirements, as well as the informed consent document and other comparative information on the proposed lens that describes its characteristics. It is the IRB's prerogative to request any relevant information on a new IOL to arrive at a decision or to be more rigorous in its evaluation than FDA considers minimally required.

64. Must a manufacturer comply with 21 CFR 50 and 56 when conducting trials within its own facility using employees as subjects?

Yes. This situation represents a prime example of a vulnerable subject population.

65. Do Radioactive Drug Research Committees (RDRCs) have authority to approve initial clinical studies in lieu of an IND?

No. An IND is required when the purpose of the study is to determine safety and efficacy of the drug or for immediate therapeutic, diagnostic or similar purposes. RDRCs are provided for in 21 CFR 361.1 *Radioactive Drugs for Certain Research Uses*. Radioactive drugs (as defined in 21 CFR 310.3(n)) may be administered to human research subjects without obtaining an IND when the purpose of the research project is to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a radioactively labelled drug or regarding human physiology, pathophysiology, or biochemistry. Certain basic research studies, e.g., studies to determine whether a drug localizes in a particular organ or fluid space and to describe the kinetics of that localization, may have eventual therapeutic or diagnostic implications, but the initial studies are considered to be basic research within the meaning of 21 CFR 361.1. Such basic research studies must be conducted under the conditions set forth in 21 CFR 361.1(b).

All RDRC approved studies must also be approved by an IRB prior to initiation of the studies.

66. Does FDA approve RDRCs?

Yes. An RDRC must obtain and maintain approval by the Food and Drug Administration, as outlined in 21 CFR 361.1(c). RDRCs must register with the Division of Medical Imaging and Radiopharmaceutical Drug Products, (HFD-160), Center for Drug Evaluation and Research, FDA, 5600 Fishers Lane, Rockville, Maryland 20857. The FDA contact for compliance issues is the Human Subject Protection Team (HFD-343), CDER, FDA, 7520 Standish Place, Rockville, MD 20855.

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Thyroid Storm

To study, to finish, to publish.

—Benjamin Franklin

I stopped a flawed study that would have put millions of patients at risk.

—Carter Eckert

In this issue of THE JOURNAL, we are publishing a report[1] of work that started 9 years ago, was concluded in December 1990, and the data from which were published in another journal in July 1995. Given that we at *JAMA* like to keep up-to-date and that we try never to republish what others have already put in print, the reader might well ask what is going on. The story necessary to answer this question provides a cautionary tale that illustrates the sharply differing views of research taken by the university researcher and the company sponsoring that research, if the company's product is at stake. At a time when an increasing proportion of research funding is provided by private companies,[2] the story holds lessons for both, as well as for university faculties, administrators, regulatory agencies, and for physicians who prescribe on the basis of evidence.

See also pp 1199, 1205 and 1224.

In this Editorial, I shall be discussing events that took place at the University of California, San Francisco (UCSF), which is where the West Coast office of *JAMA* is situated. I should make it plain that until *JAMA* became involved, I did not know, and had never had contact with, any of the research workers involved.

Background

The issue of the potency, reliability, and bioequivalence of levothyroxine preparations has continued to raise controversy.[3] Natural thyroid extracts were marketed before the regulations of 1938 and so were exempted from amendments to the Food, Drug, and Cosmetic Act requiring that drugs be proved safe and effective. Synthroid, the first synthetic version, had come to dominate a $600 million a year market[4] that was essentially unregulated because the Food and Drug Administration (FDA) had no approved standards for bioavailability and bioequivalence and no mechanism to evaluate them, and there were no adequate well-controlled trials. Such dominance was unusual, given that other competing formulations of levothyroxine had been available for years, and it was greatly assisted by the manufacturer's claims that other preparations were not bioequivalent.

In 1987, to establish that Synthroid was truly more effective than competing preparations, Flint Laboratories, then the manufacturers of Synthroid, approached Betty J. Dong, PharmD, at UCSF. This seemed a good choice because in 1986, Dong et al[5] had published a letter showing that the levothyroxine content of different thyroid products, 2 brand-name products and 7 generic, differed widely. They noted that the 2 brand-name preparations, 1 of them Synthroid, were the preparations of choice. Flint and Dong signed a lengthy protocol/contract to finance comparative studies of the bioequivalence of Synthroid and 3 other preparations, and both sides expected the study to show that Synthroid was superior (letter from B. J. Dong to N. M. Kurtz, March 31, 1994). The contract detailed the experimental design and analysis of the data. Representatives of Flint, and after their takeover, Boots Pharmaceuticals Inc, made regular site visits, about 3 a year, to satisfy themselves that the work was being done properly. During these visits small problems were ironed out, but there was no hint of any bigger cloud.

In January 1989, at a time when there was a move to add a competitor's preparation to the Massachusetts formulary,[4] Boots, in the first of their site visits, began asking for the preliminary results of a parallel in vitro study in which tablets were compared, and because this would have meant breaking the masking code and therefore invalidating that particular study, Dong et al refused to comply. By the end of 1990, the major in vivo study was finished, and Dong sent all the results to Boots: it was clear that all 4 preparations were bioequivalent.

Over the next 4 years, Boots waged an energetic campaign to discredit the study and prevent publication of the drafts Dong and her colleagues sent to them for comment, claiming that the study was seriously flawed. Boots cited scores of purported deficiencies, including failure to carry out procedures not called for in the protocol. They alleged deficiencies with patient selection criteria and compliance, with assay reliability, with study administration, with measuring bioequivalence, and with the statistical analysis. Boots also cited unspecified ethical problems and demanded disclosure of any financial conflicts of interest, past, present, or future. Dong answered the catalog of complaints in a detailed letter (to N. M. Kurtz, March 31, 1994), noting her "serious objections to the allegations made" by Boots and agreeing to meet.

Boots also sent their complaint to the chancellor, all the vice chancellors, and several department heads at UCSF. Two investigations by the university found nothing but the most minor and easily correctible problems (letter from J. E. Goyan to N. M. Kurtz, June 5, 1992; memo from S. Fields to B. J. Dong, June 2, 1992). The company's interactions with Dr Dong were considered "harassment" to prevent publication of results the company did not like (memo from L. Z. Benet to J. E. Goyan, September 9, 1992). Dr Leslie Benet, then chairman of the Department of Biopharmaceutical Sci-

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ences, characterized the company's representatives as "deceptive and self-serving."[6] UCSF found the study to be rigorously conducted in a way that complied fully with the contract. Minor deviations, made with the full knowledge of Boots, met clinical and ethical standards, and there were no violations of human subjects' procedures. Furthermore, the statistical procedures Boots criticized had been agreed on by Boots and had been performed well.

Boots had alleged numerous breaches of research ethics, but when asked by UCSF to make specific allegations that UCSF could formally investigate, Boots did not respond. Noting that all records and data had been open to Boots, who had monitored the study closely, UCSF told Boots, in August 1994, that there was no reason to suppress the manuscript and to do so would be an unprecedented intrusion upon academic freedom (letter from P. Lurie and S. M. Wolfe to D. A. Kessler, May 29, 1996). Later, they agreed to meet again with Boots, but suggested that this time it should be in the presence of officials from the FDA. That meeting never took place. Dong et al made numerous changes in their manuscript to accommodate Boots, but finally decided they would publish.

JAMA Becomes Involved

We at *JAMA* knew none of this when, in April 1994, *JAMA* received a manuscript, "Bioequivalence of Generic and Brand Levothyroxine Products," by Dong and 6 other coworkers at UCSF. The paper reported a 4-way crossover trial comparing 2 generic (Geneva Generics and Rugby) and 2 brand-name levothyroxine preparations, Synthroid (Boots) and Levoxine (renamed Levoxyl, Daniels Pharmaceuticals Inc, now Jones Medical Industries) in hypothyroid patients. The patients received the 4 preparations in a random sequence to ensure that potential carryover effects from the previous formulation would introduce no systematic bias. Each preparation was given for at least 6 weeks, and the primary investigators, including the statisticians, were blinded to the preparation. They looked at 3 aspects of bioequivalence (area under the curve, peak serum concentration, and time to peak concentration), measured for 3 indexes of thyroid function (thyroxine [T_4], triiodothyronine [T_3], and free T_4 index), and concluded that for these patients with primary hyothyroidism the 4 formulations were bioequivalent according to the FDA's general criteria for oral preparations and were therefore interchangeable. The authors calculated that if the generics or the other brand-name preparation were substituted for Synthroid, $356 million might be saved annually.

With the manuscript came a letter explaining that the work had been funded by Boots. It went on: "Boots Pharmaceutical Company has been very critical of this study despite our numerous meetings with them. . . . we have sent them all the data, including a copy of this manuscript." The letter also mentioned individuals who were paid consultants to Boots, and asked that they not be reviewers, and some who the authors thought, not always correctly, were free of such ties. The manuscript was sent out to 5 expert reviewers, some revealing themselves as consultants to Boots. It was revised and was accepted for publication under a revised title in November 1994. Proofs were circulated and a publication date set for January 25, 1995, when, on January 13, 1995, we received a letter from Dr Dong abruptly withdrawing the manuscript from publication. She gave as their reason "impending legal action by Boots Pharmaceuticals, Inc against the University of California, San Francisco and the investigators." When I inquired, Dr Dong explained to me that in the protocol/contract she had signed back in May 1988, there was a restrictive covenant which read: "All information contained in this protocol is confidential and is to be used by the investigator only for the conduct of this study. Data obtained by the investigator while carrying out this study is also considered confidential and is not to be published or otherwise released without written consent from Flint Laboratories, Inc." They did not have this permission, and she had just been told by a UCSF attorney that because of this clause, the university advised her to withdraw the paper, saying it would not defend the authors if a suit was brought by Boots.

Knowing that the University of California forbids such restrictions on the right to publish, I asked how she had managed to sign such an agreement. She said that she had assumed the clause to be routine. It was in fact common, partly because until 1993, there was no general requirement for centralized review of such contracts, and the university attorney was told only after the fact. Dr Dong had not previously informed *JAMA* because she had been reassured by the university lawyers that such contracts had never before prevented publication, and she had repeatedly informed the company that she intended to publish. UCSF was now convinced that the company would forbid publication. The senior author claimed to have been twice threatened with the possibility of lawsuit should sales of Synthroid suffer as a consequence of publication. The company has vigorously denied making such threats.[4]

The Position at the University

At the University of California, "Freedom to publish is fundamental to the university and is a major criterion of the appropriateness of a research project."[7] At the most, the sponsor could be allowed 30 days for comment and, where a patent application was to be filed, an extra 60 days. Dong had in fact signed a clause giving a sponsor veto rights over publication, which somehow failed to receive the requisite administrative review. Despite this, the university counsel whom she consulted advised her that, though it was improper of Dong to have signed a contract with this restrictive clause, not least because she would be in breach of their contract with the university which states that "the University will undertake research or studies only if the scientific results can be published or otherwise promptly disseminated,"[8] there was unlikely to be a problem.

When Dong and her colleagues finally decided that the company's scientific concerns were spurious delaying tactics and that they should publish, the university, now with a new lawyer, was faced with a difficult choice. The university knew the financial stakes had risen because of an impending takeover of Boots, and they had to consider "the possibility of significant damages the company might claim by virtue of publication of the article."[9] Extensive negotiation failed to change the university's opinion that the contract superseded any general right of a member of the faculty to publish, or considerations of science or the public health.

Boots/Knoll

At this time the pharmaceutical manufacturing arm of Boots was indeed being considered for purchase, and information on

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the comparative bioequivalence of its most important drug, Synthroid, might affect its price. In March 1995, the company was bought by BASF AG, for $1.4 billion, and is now part of their Knoll Pharmaceutical subsidiary. In May 1995, *JAMA* and a number of other journals received a letter from Dr Gilbert Mayor at Boots/Knoll, who had been monitoring the work of Dong et al, disparaging both the study and Dr Dong, and saying that the journals should "be concerned about publishing [the paper]." Meanwhile, Boots/Knoll had hired firms of investigators to look, among other things, into possible conflicts of interest on the part of the UCSF researchers (of which they had none).

Unable to publish their paper and receiving calls from their acquaintances asking about the firms' inquiries, Dong and her colleagues were further mortified when Mayor et al,[10] employees of Boots/Knoll, not only published the results of the study by Dong et al in a 16-page article without any acknowledgment to the people who did the study, but did so in a reanalysis that reached the opposite conclusion and threw doubt on the work at UCSF. Indeed, the article contains a table showing 18 "major study limitations." Using the UCSF data, Mayor et al agreed that bioequivalence of all the preparations was the same, but if correction was made for baseline values (something Dong et al did not do because they thought it inappropriate, partly as it produced negative values for levothyroxine), the preparations were "therapeutically inequivalent." The effect would, of course, be at the same time to strengthen the position of Synthroid and make it impossible for any journal to publish Dong's paper. The article by Mayor et al was published in a new journal, the *American Journal of Therapeutics*, of which Mayor was an associate editor.

Publicity

The issue came to the attention of the public when, on April 25, 1996, the *Wall Street Journal* published a meticulously researched account of the story, written by Ralph King. The Boots/Knoll position was best summarized by Carter Eckert, president of Boots/Knoll, who was quoted as saying: "I stopped a flawed study that would have put millions of patients at risk."[4]

Food and Drug Administration

On August 26, 1994, the FDA wrote to Boots (letter from A. M. Reb to R. F. King) saying that an article published in 1992 by 2 Boots researchers, Berg and Mayor,[11] on work done at IBF Research Corporation, Scarborough, Ontario, to support the position that Synthroid was pharmacokinetically superior to other preparations was misleading and should not be disseminated by Boots. This article showed that in normal volunteers studied over 48 hours (the half-life of levothyroxine is 7.6 days), there was a difference in absorption between Levoxine (now Levoxyl) and Synthroid.

Boots replied (letter from K. F. King to A. M. Reb, September 20, 1994), arguing that the study by Berg and Mayor[11] was designed not to test bioequivalence but to identify bio*in*equivalence. And a later letter from Knoll (letter from B. A. Buhler to P. C. O'Brien, July 12, 1995) quoted the Berg and Mayor article as saying that to determine bioequivalence "would require a more complex design involving chronic administration in a well-controlled hypothyroid population with the measurement of several endpoints, including thyroid-stimulating hormone." The Knoll letter further stated that "Knoll can state unequivocally that it is aware of no study that has been published or even conducted that satisfies these criteria," though the Berg and Mayor article cited 4 published ones the authors considered to be deficient. For the first time the company mentioned the unpublished work done by Dong et al, which Mayor and the company had known about for 3 years before the Berg and Mayor article came out. The letter cited it as the "upcoming" paper by Mayor et al,[10] and dismissed the work on which it was based as worthless.

Despite this, on November 7, 1996, the FDA wrote to Knoll concluding that Knoll had violated the Federal Food, Drug, and Cosmetic Act, 21 USC §331(a) by misbranding Synthroid (letter from M. Baylor-Henry to R. Ashworth). The FDA letter continues: "[T]he endpoints evaluated were the rate and extent of absorption over a relatively short period of time (less than one half-life) following supra-therapeutic doses of levothyroxine sodium [in normal volunteers]. . . . [T]he authors noted that to show similarity, 'a more complex design involving chronic administration in a well-controlled, hypothyroid population with the measurement of several endpoints' [11] would be required."

The letter noted that Knoll was in possession of the results of the study by Dong et al, which the company had not disclosed. The FDA wrote that the article by Dong et al was "a study with just such a more complex design involving administration of thyroid replacement products in a hypothyroid population with the measurement of several endpoints, including thyroid stimulating hormone." And, of course, the manuscript written by Dong et al reached opposite conclusions: namely, that Synthroid was bioequivalent with the other preparations.

Knoll Changes Its Mind

Under pressure from the FDA, and perhaps realizing that the public perception was so negative, Knoll began negotiations with the university. Eventually, this resulted in the current president of Knoll, Carter Eckert, and a board member, Louis Sullivan, MD (former secretary of the US Department of Health and Human Services), meeting with the chancellor of UCSF on November 25, 1996. Knoll agreed not to block publication of the manuscript by Dong et al, while still insisting that its conclusions were not supported by the data.

JAMA is now publishing the manuscript set into proof 2 years ago[1]; none of the content has been changed. *JAMA*'s mission is the public health, and we try hard to select the best papers we are sent. We do not claim that we are publishing a perfect study, just one of the best, made as good as expert review can make it. Experience has taught us that there are very few studies in which some reviewers cannot find flaws, and so it may be here. For example, though mean values of thyrotropin (TSH), the important long-term measure, were similar, individual values differed. Because this may make a difference to individual patients when switching therapy, some clinicians may feel that bioequivalence might not be the clinically relevant parameter when switching, as opposed to starting, therapy. However, it is our belief that this is a good study carried out by highly competent workers following a sensible design that tried to answer an important question. It is hard to believe that the sponsors would have made such extraordinary efforts to delay and block publication of the

y for such a very long time and for such an extraordinary ber of specious reasons if the results had shown Syd to be better.

the same time, we are publishing a letter from Knoll gizing for blocking the manuscript,[12] and another obg to its conclusions,[13] as well as rebuttals from Dong et Given that Knoll has already made an extraordinary mptive strike by publishing its lengthy criticisms of the y by Dong et al at a time when it looked as though the would never see the light of day, we do not think Knoll res more space.

t Are the Lessons?

r Researchers and Faculty.—Even if researchers have approached by sponsors, investigators should not as- that the sponsors will encourage publication of unfa- ble results and should never allow sponsors veto power. ong was naive, but faculty members are the last line of se against industry interference, and she and her col- es deserve credit for standing up for their academic s.

ven that this is an issue basic to their freedom to publish, eaction of faculty at UCSF has been mixed. Many seem ve considered, reasonably enough, that Dr Dong had ght this upon herself and her colleagues by foolishly g the contract and did not realize it could be challenged. I believe that other considerations have been at work. faculty, perhaps hoping for commercial success, might imagined the view from the commercial side of the fence sympathized with the company. Or perhaps they were ied lest Dong and her coworkers might, by their stance, spoiled things for others hoping for pharmaceutical com- sponsorship and fearing that potential sponsors would iven to friendlier universities or to commercial drug- g shops.

answer starts with the realization that when some- like this happens, everyone loses, from researcher, to or, to patient. But none stands to lose more than the y and the university. When it is revealed that its faculty e bullied and kept quiet by their sponsor, yet the uni- y has failed to back them fully on this basic issue, the rsity's reputation inevitably suffers. When there is no y, the faculty is seen as willing to cede its freedoms.

the University.—All academic research institutions d forbid such clauses. But the problem would never have had the university set up a system to screen them out. niversity, handicapped by its faculty's signature on this ctive clause, investigated charges against, and cleared, esearchers, while encouraging them to publish. Then, wed by the amount of money they thought might be at the university suddenly switched its position and told esearchers they would be at great personal jeopardy if were to publish because the university would not defend

re are 2 views of the clause in the contract giving the ny veto power. One, the narrower, holds that Dr Dong, ut permission of the university and against its regula- signed her publication rights away. She was bound by tter of the contract, and any attempt to get out of it have been legally doomed. In this view, the university advise against publication. If the researchers had gone against its advice, the university would be freed from its statutory duty to indemnify and defend its faculty, and the researchers would have been on their own. This is the view that prevailed.

The other view, and that taken by the UCSF attorney who originally advised Dr Dong, was that when the company approached her they knew she did not work at a commercial drug-testing laboratory, but at a university, where she had a duty to publish, and where a high premium was placed on publication. The restrictive clause was incompatible with university regulations and the purpose of university research and was at odds with the purpose of the rest of this research contract.

The university, well aware of the importance of publication and the refusal of Boots/Knoll to consent to it, could have taken the case to court by filing for a motion for declaratory judgment, whereby a judge would be asked to rule on the meaning of the contract, particularly the reasonableness of the restrictive clause. With a ruling in their favor, Dong et al would have been free to publish. However, UCSF apparently failed to threaten to do so to Knoll's legal counsel, and when UCSF put this idea to the researchers, the plan died because the faculty was under the impression that this would require them to engage in a lengthy court battle and because the faculty was still afraid of being left to fend for themselves in any suit after publication.

In my view, an academic principle of the highest priority was at stake and recognized as such in the university's policies, and this principle should have been immediately and staunchly defended, notwithstanding the language of the contract. If the university had advised publication and stood behind its faculty, I doubt whether any suit would have resulted, if only because of the consequent adverse publicity to the company.

A university must above all things support the rights of its faculty. Indeed, California law requires UCSF to defend its employees, of whom Dong was one. The failure to do so seriously threatens academic freedom by creating an impression that the university will not back its faculty's right to publish or even to use results for other purposes, for example, teaching. This should be pondered by all segments of the institution if it is intent on encouraging academic-industry partnerships. Pharmaceutical companies come to researchers because they wish to form mutually beneficial cooperative relationships in developing and testing their products. And they come to places like UCSF because of its extraordinarily high reputation, hoping that some of the prestige of the university and its researchers will carry through to influence the FDA and the prescribers. Commercial sponsors are most likely to take their business elsewhere when the best people leave. And if the university, lawyers, and faculty cannot be trusted to defend faculty on such a key issue, why should they feel confident about staying?

For the Company.—I am relieved that the company president has said, in response to a highly critical editorial in *Science*,[16] that Knoll is "committed to strong industry academic partnerships."[17] A skeptic might ask whether the company's change of heart came in order to appease the FDA after the company had successfully delayed the bad news several years to maintain the market position of Synthroid and to increase the purchase price of Boots. Nevertheless, I congratulate them on belatedly seeing that neither academics nor the public are likely to commend their heavy-handed

tactics. I suggest that it is in the long-term interests of companies intending to sponsor research to be careful not to include such restrictive clauses if they wish to attract the best investigators.

Companies should realize that even if, as in the present instance, they select researchers whose results have favored the company's product in the past, the results may go against them. Sponsors must understand that researchers at universities have a duty to publish and a self-interest in publication. It may seem that the short-term interests of a company will be served by suppression of the results, but the public revelation of bullying tactics and spurious charges will ultimately damage the name of the sponsor in the eyes of the profession, the FDA, and the public.

For the FDA.—Thyroid preparations were grandfathered in by the 1938 Food, Drug, and Cosmetic Act, which required demonstration of safety, and the 1962 amendment, which required that drugs be shown to be effective. As is the case with other preparations of levothyroxine, Synthroid, introduced in 1958, could reasonably be regarded as a reformulation. The FDA has the authority to designate important pre-1938 drugs that have been reformulated as "new" drugs and require a New Drug Application (NDA). The FDA has taken this course in the cases of, for example, theophylline, phenytoin, quinidine, and digoxin. With levothyroxine, the issue is not so much safety and efficacy, but the requirement that its bioavailability be demonstrated. This itself would require specific standards to be set for levothyroxine, which would then allow bioequivalence to be measured and therefore generic substitution. One advantage of pursuing the NDA route is that it would finally let the practitioner and the public know whether substitution with cheaper formulations was appropriate and would dispel the confusion surrounding present claims of bioequivalence. It is, however, an arduous route to take merely to straighten this out for a drug that is good and one relied upon by millions.

A simpler and possibly more fruitful approach to setting standards for both bioequivalance and clinical interchangeability might be for scientific organizations with the best expertise in this area, such as the American Association of Pharmaceutical Scientists, the American Society for Clinical Pharmacology and Therapeutics, and the American Thyroid Association, to establish guidelines by consensus, which they could then publish for the benefit of all.

For Professional Societies.—The research community is getting progressively more entangled with industry, as became evident to me when I found it hard to find thyroid experts to review the paper who did not have financial ties with Boots/Knoll. This is a reflection, perhaps, of the extraordinary market dominance of Synthroid and, associated with this, the munificent scale of research and educational grants given by Boots/Knoll. But there is an inverse side which is dependence. Recently, for example, the American Thyroid Association, which receives more than 60% of its commercial sponsorship from Knoll, had the courage to debate whether to write to Knoll to allow publication of the paper. Obviously, the members could not debate its merits as it was unpublished, and the senior author of the manuscript by Dong et al, Dr Greenspan, did not attend the meeting, partly because the gag clause in the contract forbade him from discussing it. The motion to write the letter was narrowly defeated. At stake was the crucial ethical issue of suppression of a manuscript coauthored by one of its most distinguished members. An outsider is left with the sad impression that the ability of the association to influence these events by speaking with moral authority was weakened by its heavy dependence on money from Knoll.

Having said this, I would point out that other specialty societies supported by Knoll have failed to address the issue at all. And the American Thyroid Association, at the same meeting, voted to write to pharmaceutical companies to indicate that clauses restricting publication be removed from contracts; to write to their members advising them to avoid such clauses; and to write to the FDA requesting appropriate guidelines for bioequivalence studies. The association has also taken steps to make itself more independent of corporate sponsorship: an essential prerequisite for maintaining the public trust.

But the fact is that though all of us believe we are personally uninfluenced by money or gifts, that is not how others see it. If academic societies wish to retain any credibility, they should consider making sure that no individual sponsor can contribute, for example, more than 5% of the total, and, for example, rely more on charging their members realistic dues. Meanwhile, if academics wish to be credible as objective authorities, they should be cautious when they accept speaker's fees and travel advances from individual companies, lest they be accused of conflict.

Institutions and researchers worry that research money will go to more compliant places in a race for the ethical bottom. The answer to this is for prestigious societies such as the Association of American Medical Colleges and the Association of American Universities, which work by moral persuasion, to set up standards for such contracts. I strongly recommend that they do this, and soon.

For Journals.—This has been an awkward time for *JAMA*. We put in a lot of work on the paper, only to see it suddenly withdrawn at the last moment. But when the news broke, we were constrained from discussing it because of the rules against discussing unpublished papers. We were then shocked when the reanalysis of "our" paper appeared in print.[10] A journal's job is to select the best, publish it, and then let the criticism come in, but certainly not to publish results hijacked from those who did the work. I believe that editors of the journal publishing the paper by Mayor et al should examine their policies carefully.

Is This Common?

The Synthroid case, where publication was delayed about 7 years, seems an extreme case. However, in this issue of THE JOURNAL, we publish a paper from Blumenthal et al[18] on withholding of research results by researchers. These authors found that almost 20% of 2100 life science faculty reported delay of over 6 months in the publication of their research results. Of 410 respondents to their survey who reported such delay, in 28% it was "to slow dissemination of undesired results." It is not clear whether such an unacceptable delay came from the scientists themselves or from industry sponsors. Blumenthal et al conclude that withholding is not widespread. Perhaps. But if "undesired results" are withheld by only about 5% of all researchers, the fears induced by the increased part industry is playing in the funding of research are not dispelled. And before we decide the danger is past, workers at Carnegie-Mellon University reported

that in their sample of university-industry research centers, 35% of the signed agreements allowed the sponsor to delete information from publication, 53% allowed publication to be delayed, and 30% allowed both.[19]

The ethical dilemma in which researchers may put themselves is also not trivial. In 1995, Dr Nancy Olivieri published an optimistic article on the effects of an oral iron-chelation agent.[20,21] As her trials proceeded, however, she became disturbed by increasing evidence of the agent's lack of effectiveness. She found an increase in hepatic iron in those on the oral therapy, despite good compliance over 2 years, and she was concerned about possible danger to patients. She had signed a confidentiality agreement with her sponsors, the makers of the drug. She decided she had to break confidentiality by reporting her results at a meeting.[22,23] The manufacturers disagreed with her interpretation of the results and tried unsuccessfully to block her presentation. Because she now feels that she risks litigation for having made her presentation, she would not, on the advice of her attorney, speak with me.

Rosenberg,[24] sounding the alarm, makes the point that secrecy in research is increasing and gives 4 examples from his personal experience. He writes: "The goals of medical research are clear: to prevent human suffering and premature death from disease.... Deliberately withholding useful information ... is a violation of this principle." As I have pointed out before,[25] a major problem in medicine is failure to publish the results of studies that show no advantage to the intervention under study, so that treatments tend to be based on biases in favor of the new. I take Chalmers' position[26] that it is unethical not to publish such negative results. The Olivieri case, hinging as it does on the interpretation of data about the safety of a therapy, shows that this is not just a theoretical position.

Rosenberg[24] concludes, as do I, that scientists should never sign any agreements that give their sponsors veto power over publication.

Marshall[27] has recently described the battle in genome research between those who wish to lock up results by delaying publication and those, including sponsors both governmental and commercial, who see a wider societal good in putting gene sequences promptly into the public domain. Marshall notes that, for example, withholding DNA sequence data on pathogens could cost human lives, but is "commonplace." It is too early to see who will win, but unless the scientific community gives its strong support and approval to sponsors who forbid secrecy, we will all suffer the consequences.

Conclusion

We are proud to publish the article by Dong and her colleagues. We believe it is good work, not merely because it passed peer review by more than the usual number of experts, but because it has also passed careful and prolonged scrutiny by the university in response to widely disseminated allegations of scientific defects and ethical violations. We are also confident in the work because of the university's finding that none of the allegations had the slightest merit and because they came from those who had most to gain if the work was discredited. Now that the thyroid storm has passed, clinicians and third-party payers finally have the information they need to best serve their patients.

Coda

There is nothing new about commercial sponsorship of research, a fact brought home to me when I was privileged to attend the June 1996 meeting of the International Committee of Medical Journal Editors (the Vancouver Group) in the Council Room in the Trent Building of the University of Nottingham in England. As we editors discussed the implications of the suppression of the paper by Dong et al, we did so under the portrait of the man who would become Baron Trent (1850-1931) and who had given the land and the money for the Trent Building to be built in 1928. Lord Trent, who founded the chain of retail chemists (pharmacies) that have made his name a household word in the United Kingdom, started off life as Jesse Boot. I wondered whether Boot would have been prouder of the research his company had sponsored or of the skill with which his company had protected the interests of its shareholders.

Drummond Rennie, MD

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INTERNATIONAL GUIDELINES FOR ETHICAL REVIEW OF EPIDEMIOLOGICAL STUDIES

INTRODUCTION

These Guidelines are intended for investigators, health policy-makers, members of ethical review committees, and others who have to deal with ethical issues that arise in epidemiology. They may also assist in the establishment of standards for ethical review of epidemiological studies.

The Guidelines are an expression of concern to ensure that epidemiological studies observe ethical standards. These standards apply to all who undertake any of the types of activity covered by the Guidelines. Investigators must always be held responsible for the ethical integrity of their studies.

Epidemiology is defined as the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems.

Epidemiology has greatly improved the human condition in the present century. It has clarified our understanding of many physical, biological and behavioural dangers to health. Some of the knowledge obtained has been applied to the control of environmental and biological threats to health, such as diseases due to drinking polluted water. Other epidemiological knowledge has become part of popular culture, leading to changed values and behaviour, and thus has led to improved health: examples include attitudes towards personal hygiene, tobacco smoking, diet and exercise in relation to heart disease, and the use of seat-belts to reduce the risk of traffic injury and death.

Epidemiological practice and research are based mostly on observation, and require no intervention more invasive than asking questions and carrying out routine medical examinations. Practice and research may overlap, as, for example, when both routine surveillance of cancer and original research on cancer are conducted by professional staff of a population-based cancer registry.

Epidemiological research is of two main types: observational and experimental:

Three types of observational epidemiological research are distinguished: *cross-sectional studies* (also known as surveys), *case-control studies*, and *cohort studies*. These types of study carry minimal risk to study subjects. They involve no intervention other than asking questions, carrying out medical examinations and, sometimes, laboratory tests or x-ray examinations. The informed consent of subjects is normally re-

quired, although there are some exceptions — for example, very large cohort studies conducted exclusively by examining medical records.

A *cross-sectional* study (survey) is commonly done on a random sample of a population. Study subjects are asked questions, medically examined, or asked to submit to laboratory tests. Its aim is to assess aspects of the health of a population, or to test hypotheses about possible causes of disease or suspected risk factors.

A *case-control* study compares the past history of exposure to risk among patients who have a specified condition (cases) with the past history of exposure to this risk among persons who resemble the cases in such respects as age and sex, but do not have the specified condition (controls). Differing frequency of past exposure among cases and controls can be statistically analysed to test hypotheses about causes or risk factors. Case-control studies are the method of choice for testing hypotheses about rare conditions, because they can be done with small numbers of cases. They generally do not involve invasion of privacy or violation of confidentiality. If a case-control study requires direct contact between research workers and study subjects, informed consent to participation in the study is required; if it entails only a review of medical records, informed consent may not be required and indeed may not be feasible.

In a *cohort study*, also known as a longitudinal or prospective study, individuals with differing exposure levels to suspected risk factors are identified and observed over a period, commonly years, and the rates of occurrence of the condition of interest are measured and compared in relation to exposure levels. This is a more robust research method than a cross-sectional or case-control study, but it requires study of large numbers for a long time and is costly. Usually it requires only asking questions and routine medical examinations; sometimes it requires laboratory tests. Informed consent is normally required, but an exception to this requirement is a retrospective cohort study that uses linked medical records. In a retrospective cohort study, the initial or base-line observations may relate to exposure many years earlier to a potentially harmful agent, such as x-rays, a prescribed drug or an occupational hazard, about which details are known; the final or end-point observations are often obtained from death certificates. Numbers of subjects may be very large, perhaps millions, so it would be impracticable to obtain their informed consent. It is essential to identify precisely every individual studied; this is achieved by methods of matching that are built into record linkage systems. After identities have been established to compile the statistical tables, all personal identifying information is obliterated, and therefore privacy and confidentiality are safeguarded.

An experiment is a study in which the investigator intentionally alters one or more factors under controlled conditions to study the effects of doing so. The usual form of epidemiological experiment is the *randomized controlled trial*, which is done to test a preventive or therapeutic

regimen or diagnostic procedure. Such experiments involving human subjects should be regarded as unethical unless there is genuine uncertainty about the regimen or procedure and this uncertainty can be clarified by research.

Usually in this form of experiment, subjects are allocated at random to groups, one group to receive, the other group not to receive, the experimental regimen or procedure. The experiment compares the outcomes in the two groups. Random allocation removes the effects of bias, which would destroy the validity of comparisons between the groups. Since it is always possible that harm may be caused to at least some of the subjects, their informed consent is essential.

Epidemiology is facing new challenges and opportunities. The application of information technology to large data-files has expanded the role and capacity of epidemiological studies. The acquired immunodeficiency syndrome (AIDS) epidemic and its management have given epidemiological studies new urgency; public health authorities are using population-screening studies to establish prevalence levels of human immunodeficiency virus (HIV) infection for purposes of monitoring and restricting the spread of infection. Ahead lie entirely new challenges, such as those arising from the conjunction of molecular and population genetics.

PREAMBLE

The general conduct of biomedical studies is guided by statements of internationally recognized principles of human rights, including the Nuremberg Code and the World Medical Association's Declaration of Helsinki, as revised (Helsinki IV). These principles also underlie the Proposed International Guidelines for Biomedical Research Involving Human Subjects, issued by the Council for International Organizations of Medical Sciences in 1982. These and similar national codes are based on the model of clinical medicine, and often address interests of "patients" or individual "subjects". Epidemiological research concerns groups of people, and the above codes do not adequately cover its special features. Proposals for epidemiological studies should be reviewed independently on ethical grounds.

Ethical issues often arise as a result of conflict among competing sets of values, such as, in the field of public health, the conflict between the rights of individuals and the needs of communities. Adherence to these guidelines will not avoid all ethical problems in epidemiological studies. Many situations require careful discussion and informed judgement on the part of investigators, ethical review committees, administrators, health-care practitioners, policy-makers, and community representatives. Externally sponsored epidemiological studies in developing countries merit special attention. A framework for the application

of these guidelines is set by the laws and practices in each jurisdiction in which it is proposed to undertake studies.

The purpose of ethical review is to consider the features of a proposed study in the light of ethical principles, so as to ensure that investigators have anticipated and satisfactorily resolved possible ethical objections, and to assess their responses to ethical issues raised by the study. Not all ethical principles weigh equally. A study may be assessed as ethical even if a usual ethical expectation, such as confidentiality of data, has not been comprehensively met, provided the potential benefits clearly outweigh the risks and the investigators give assurances of minimizing risks. It may even be unethical to reject such a study, if its rejection would deny a community the benefits it offers. The challenge of ethical review is to make assessments that take into account potential risks and benefits, and to reach decisions on which members of ethical review committees may reasonably differ.

Different conclusions may result from different ethical reviews of the same issue or proposal, and each conclusion may be ethically reached, given varying circumstances of place and time; a conclusion is ethical not merely because of what has been decided but also owing to the process of conscientious reflection and assessment by which it has been reached.

GENERAL ETHICAL PRINCIPLES

All research involving human subjects should be conducted in accordance with four basic ethical principles, namely *respect for persons, beneficence, non-maleficence,* and *justice.* It is usually assumed that these principles guide the conscientious preparation of proposals for scientific studies. In varying circumstances, they may be expressed differently and given different weight, and their application, in all good faith, may have different effects and lead to different decisions or courses of action. These principles have been much discussed and clarified in recent decades, and it is the aim of these Guidelines that they be applied to epidemiology.

Respect for persons incorporates at least two other fundamental ethical principles, namely:

a) *autonomy*, which requires that those who are capable of deliberation about their personal goals should be treated with respect for their capacity for self-determination; and

b) *protection of persons with impaired or diminished autonomy*, which requires that those who are dependent or vulnerable be afforded security against harm or abuse.

Beneficence is the ethical obligation to maximize possible benefits and to minimize possible harms and wrongs. This principle gives rise to

norms requiring that the risks of research be reasonable in the light of the expected benefits, that the research design be sound, and that the investigators be competent both to conduct the research and to assure the well-being of the research subjects.

Non-maleficence ("Do no harm") holds a central position in the tradition of medical ethics, and guards against avoidable harm to research subjects.

Justice requires that cases considered to be alike be treated alike, and that cases considered to be different be treated in ways that acknowledge the difference. When the principle of justice is applied to dependent or vulnerable subjects, its main concern is with the rules of *distributive justice*. Studies should be designed to obtain knowledge that benefits the class of persons of which the subjects are representative: the class of persons bearing the burden should receive an appropriate benefit, and the class primarily intended to benefit should bear a fair proportion of the risks and burdens of the study.

The rules of distributive justice are applicable within and among communities. Weaker members of communities should not bear disproportionate burdens of studies from which all members of the community are intended to benefit, and more dependent communities and countries should not bear disproportionate burdens of studies from which all communities or countries are intended to benefit.

General ethical principles may be applied at individual and community levels. At the level of the individual (*microethics*), ethics governs how one person should relate to another and the moral claims of each member of a community. At the level of the community, ethics applies to how one community relates to another, and to how a community treats each of its members (including prospective members) and members of other groups with different cultural values (*macroethics*). Procedures that are unethical at one level cannot be justified merely because they are considered ethically acceptable at the other.

ETHICAL PRINCIPLES APPLIED TO EPIDEMIOLOGY

Informed Consent

Individual consent

1. When individuals are to be subjects of epidemiological studies, their informed consent will usually be sought. For epidemiological studies that use personally identifiable private data, the rules for informed consent vary, as discussed further below. Consent is informed when it is given by a person who understands the purpose and nature of the study, what participation in the study requires the person to do and to risk, and what benefits are intended to result from the study.

2. An investigator who proposes not to seek informed consent has the obligation to explain to an ethical review committee how the study would be ethical in its absence: it may be impractical to locate subjects whose records are to be examined, or the purpose of some studies would be frustrated — for example, prospective subjects on being informed would change the behaviour that it is proposed to study, or might feel needlessly anxious about why they were subjects or study. The investigator will provide assurances that strict safeguards will be maintained to protect confidentiality and that the study is aimed at protecting or advancing health. Another justification for not seeking informed consent may be that subjects are made aware through public announcements that it is customary to make personal data available for epidemiological studies.

3. An ethical issue may arise when occupational records, medical records, tissue samples, etc. are used for a purpose for which consent was not given, although the study threatens no harm. Individuals or their public representatives should normally be told that their data might be used in epidemiological studies, and what means of protecting confidentiality are provided. Consent is not required for use of publicly available information, although countries and communities differ with regard to the definition of what information about citizens is regarded as public. However, when such information is to be used, it is understood that investigators will minimize disclosure of personally sensitive information.

4. Some organizations and government agencies employ epidemiologists — who may be permitted by legislation or employees' contracts to have access to data without subjects' consent. These epidemiologists must then consider whether it is ethical for them, in a given case, to use this power of access to personal data. Ethically, they may still be expected either to seek the consent of the individuals concerned, or to justify their access without such consent. Access may be ethical on such grounds as minimal risk of harm to individuals, public benefit, and investigators' protection of the confidentiality of the individuals whose data they study.

Community agreement

5. When it is not possible to request informed consent from every individual to be studied, the agreement of a representative of a community or group may be sought, but the representative should be chosen according to the nature, traditions and political philosophy of the community or group. Approval given by a community representative should be consistent with general ethical principles. When investigators work with communities, they will consider communal rights and protection as they would individual rights and protection. For communities in which collective decision-making is customary, communal leaders can express the collective will. However, the refusal of individuals to participate

in a study has to be respected: a leader may express agreement on behalf of a community, but an individual's refusal of personal participation is binding.

6. When people are appointed by agencies outside a group, such as a department of government, to speak for members of the group, investigators and ethical review committees should consider how authentically these people speak for the group, and if necessary seek also the agreement of other respresentatives. Representatives of a community or group may sometimes be in a position to participate in designing the study and in its ethical assessment.

7. The definition of a community or group for purposes of epidemiological study may be a matter of ethical concern. When members of a community are naturally conscious of its activities as a community and feel common interests with other members, the community exists, irrespective of the study proposal. Investigators will be sensitive to how a community is constituted or defines itself, and will respect the rights of underprivileged groups.

8. For puposes of epidemiological study, investigators may define groups that are composed of statistically, geographically or otherwise associated individuals who do not normally interact socially. When such groups are artificially created for scientific study, group members may not readily be identifiable as leaders or representatives, and individuals may not be expected to risk disadvantage for the benefit of others. Accordingly, it will be more difficult to ensure group representation, and all the more important to obtain subjects' free and informed consent to participate.

Selective disclosure of information

9. In epidemiology, an acceptable study technique involves selective disclosure of information, which seems to conflict with the principle of informed consent. For certain epidemiological studies non-disclosure is permissible, even essential, so as to not influence the spontaneous conduct under investigation, and to avoid obtaining responses that the respondent might give in order to please the questioner. Selective disclosure may be benign and ethically permissible, provided that it does not induce subjects to do what they would not otherwise consent to do. An ethical review committee may permit disclosure of only selected information when this course is justified.

Undue influence

10. Prospective subjects may not feel free to refuse requests from those who have power or influence over them. Therefore the identity of the investigator or other person assigned to invite prospective subjects to participate must be made known to them. Investigators are expected to explain to the ethical review committee how they propose to neutralize such apparent influence. It is ethically questionable whether subjects

should be recruited from among groups that are unduly influenced by persons in authority over them or by community leaders, if the study can be done with subjects who are not in this category.

Inducement to participate

11. Individuals or communities should not be pressured to participate in a study. However, it can be hard to draw the line between exerting pressure or offering inappropriate inducements and creating legitimate motivation. The benefits of a study, such as increased or new knowledge, are proper inducements. However, when people or communities lack basic health services or money, the prospect of being rewarded by goods, services or cash payments can induce participation. To determine the ethical propriety of such inducements, they must be assessed in the light of the traditions of the culture.

12. Risks involved in participation should be acceptable to subjects even in the absence of inducement. It is acceptable to repay incurred expenses, such as for travel. Similarly, promises of compensation and care for damage, injury or loss of income should not be considered inducements.

Maximizing Benefit

Communication of study results

13. Part of the benefit that communities, groups and individuals may reasonably expect from participating in studies is that they will be told of findings that pertain to their health. Where findings could be applied in public health measures to improve community health, they should be communicated to the health authorities. In informing individuals of the findings and their pertinence to health, their level of literacy and comprehension must be considered. Research protocols should include provision for communicating such information to communities and individuals.

Research findings and advice to communities should be publicized by whatever suitable means are available. When HIV-prevalence studies are conducted by unlinked anonymous screening, there should be, where feasible, provision for voluntary HIV-antibody testing under conditions of informed consent, with pre- and post-test counselling, and assurance of confidentiality.

Impossibility of communicating study results

14. Subjects of epidemiological studies should be advised that it may not be possible to inform them about findings that pertain to their health, but that they should not take this to mean that they are free of the disease or condition under study. Often it may not be possible to extract from pooled findings information pertaining to individuals and their families, but when findings indicate a need of health care, those concerned should be advised of means of obtaining personal diagnosis and advice.

When epidemiological data are unlinked, a disadvantage to subjects is that individuals at risk cannot be informed of useful findings pertinent to their health. When subjects cannot be advised individually to seek medical attention, the ethical duty to do good can be served by making pertinent health-care advice available to their communities.

Release of study results

15. Investigators may be unable to compel release of data held by governmental or commercial agencies, but as health professionals they have an ethical obligation to advocate the release of information that is in the public interest.

Sponsors of studies may press investigators to present their findings in ways that advance special interests, such as to show that a product or procedure is or is not harmful to health. Sponsors must not present interpretations or inferences, or theories and hypotheses, as if they were proven truths.

Health care for the community under study

16. The undertaking of an epidemiological project in a developing country may create the expectation in the community concerned that it will be provided with health care, at least while the research workers are present. Such an expectation should not be frustrated, and, where people need health care, arrangements should be made to have them treated or they should be referred to a local health service that can provide the needed care.

Training local health personnel

17. While studies are in progress, particularly in developing countries, the opportunity should be taken to train local health workers in skills and techniques that can be used to improve health services. For instance, by training them in the operation of measuring devices and calculating machines, when a study team departs it leaves something of value, such as the ability to monitor disease or mortality rates.

Minimizing Harm

Causing harm and doing wrong

18. Investigators planning studies will recognize the risk of causing harm, in the sense of bringing disadvantage, and of doing wrong, in the sense of transgressing values. Harm may occur, for instance, when scarce health personnel are diverted from their routine duties to serve the needs of a study, or when, unknown to a community, its health-care priorities are changed. It is wrong to regard members of communities as only impersonal material for study, even if they are not harmed.

19. Ethical review must always assess the risk of subjects or groups suffering stigmatization, prejudice, loss of prestige or self-esteem, or economic loss as a result of taking part in a study. Investigators will inform ethical review committees and prospective subjects of perceived

risks, and of proposals to prevent or mitigate them. Investigators must be able to demonstrate that the benefits outweigh the risks for both individuals and groups. There should be a thorough analysis to determine who would be at risk and who would benefit from the study. It is unethical to expose persons to avoidable risks disproportionate to the expected benefits, or to permit a known risk to remain if it can be avoided or at least minimized.

20. When a healthy person is a member of a population or sub-group at raised risk and engages in high-risk activities, it is unethical not to propose measures for protecting the population or sub-group.

Preventing harm to groups

21. Epidemiological studies may inadvertently expose groups as well as individuals to harm, such as economic loss, stigmatization, blame, or withdrawal of services. Investigators who find sensitive information that may put a group at risk of adverse criticism or treatment should be discreet in communicating and explaining their findings. When the location or circumstances of a study are important to understanding the results, the investigators will explain by what means they propose to protect the group from harm or disadvantage; such means include provisions for confidentiality and the use of language that does not imply moral criticism of subjects' behaviour.

Harmful publicity

22. Conflict may appear between, on the one hand, doing no harm and, on the other, telling the truth and openly disclosing scientific findings. Harm may be mitigated by interpreting data in a way that protects the interests of those at risk, and is at the same time consistent with scientific integrity. Investigators should, where possible, anticipate and avoid misinterpretation that might cause harm.

Respect for social mores

23. Disruption of social mores is usually regarded as harmful. Although cultural values and social mores must be respected, it may be a specific aim of an epidemiological study to stimulate change in certain customs or conventional behaviour to lead through change to healthful behaviour — for instance, with regard to diet or a hazardous occupation.

24. Although members of communities have a right not to have others impose an uninvited "good" on them, studies expected to result in health benefits are usually considered ethically acceptable and not harmful. Ethical review committees should consider a study's potential for beneficial change. However, investigators should not overstate such benefits, in case a community's agreement to participate is unduly influenced by its expectation of better health services.

Sensitivity to different cultures

25. Epidemiologists often investigate cultural groups other than their own, inside or outside their own countries, and undertake studies in-

itiated from outside the culture, community or country in which the study is to be conducted. Sponsoring and host countries may differ in the ways in which, in their cultures, ethical values are understood and applied — for instance, with regard to autonomy of individuals.

Investigators must respect the ethical standards of their own countries and the cultural expectations of the societies in which epidemiological studies are undertaken, unless this implies a violation of a transcending moral rule. Investigators risk harming their reputation by pursuing work that host countries find acceptable but their own countries consider offensive. Similarly, they may transgress the cultural values of the host countries by uncritically conforming to the expectations of their own.

Confidentiality

26. Research may involve collecting and storing data relating to individuals and groups, and such data, if disclosed to third parties, may cause harm or distress. Consequently, investigators should make arrangements for protecting the confidentiality of such data by, for example, omitting information that might lead to the identification of individual subjects, or limiting access to the data, or by other means. It is customary in epidemiology to aggregate numbers so that individual identities are obscured. Where group confidentiality cannot be maintained or is violated, the investigators should take steps to maintain or restore a group's good name and status. Information obtained about subjects is generally divisible into:

Unlinked information, which cannot be linked, associated or connected with the person to whom it refers; as this person is not known to the investigator, confidentiality is not at stake and the question of consent does not arise.

Linked information, which may be:

- anonymous, when the information cannot be linked to the person to whom it refers except by a code or other means known only to that person, and the investigator cannot know the identity of the person;
- non-nominal, when the information can be linked to the person by a code (not including personal identification) known to the person and the investigator; or
- nominal or nominative, when the information is linked to the person by means of personal identification, usually the name.

Epidemiologists discard personal identifying information when consolidating data for purposes of statistical analysis. Identifiable personal data will not be used when a study can be done without personal identification — for instance, in testing unlinked anonymous blood samples for HIV infection. When personal identifiers remain on records used for a study, investigators should explain to review committees why this is necessary and how confidentiality will be protected. If, with the con-

sent of individual subjects, investigators link different sets of data regarding individuals, they normally preserve confidentiality by aggregating individual data into tables or diagrams. In government service the obligation to protect confidentiality is frequently reinforced by the practice of swearing employees to secrecy.

Conflict of interest

Identification of conflict of interest

27. It is an ethical rule that investigators should have no undisclosed conflict of interest with their study collaborators, sponsors or subjects. Investigators should disclose to the ethical review committee any potential conflict of interest. Conflict can arise when a commercial or other sponsor may wish to use study results to promote a product or service, or when it may not be politically convenient to disclose findings.

28. Epidemiological studies may be initiated, or financially or otherwise supported, by governmental or other agencies that employ investigators. In the occupational and environmental health fields, several well-defined special-interest groups may be in conflict: shareholders, management, labour, government regulatory agencies, public interest advocacy groups, and others. Epidemiological investigators may be employed by any of these groups. It can be difficult to avoid pressures resulting from such conflict of interest, and consequent distorted interpretations of study findings. Similar conflict may arise in studies of the effects of drugs and in testing medical devices.

29. Investigators and ethical review committees will be sensitive to the risk of conflict, and committees will not normally approve proposals in which conflict of interest is inherent. If, exceptionally, such a proposal is approved, the conflict of interest should be disclosed to prospective subjects and their communities.

30. There may appear to be conflict when subjects do not want to change their behaviour and investigators believe that they ought to do so for the sake of their health. However, this may not be a true conflict of interest, as the investigators are motivated by the subjects' health interests.

Scientific objectivity and advocacy

31. Honesty and impartiality are essential in designing and conducting studies, and presenting and interpreting findings. Data will not be withheld, misrepresented or manipulated. Investigators may discover health hazards that demand correction, and become advocates of means to protect and restore health. In this event, their advocacy must be seen to rely on objective, scientific data.

ETHICAL REVIEW PROCEDURES

Requirement of ethical review

32. The provisions for ethical review in a society are influenced by economic and political considerations, the organization of health care and research, and the degree of independence of investigators. Whatever the circumstances, there is a responsibility to ensure that the Declaration of Helsinki and the CIOMS International Guidelines for Biomedical Research Involving Human Subjects are taken into account in epidemiological studies.

33. The requirement that proposals for epidemiological studies be submitted to independent ethical review applies irrespective of the source of the proposals — academic, governmental, health-care, commercial, or other. Sponsors should recognize the necessity of ethical review and facilitate the establishment of ethical review committees. Sponsors and investigators are expected to submit their proposals to ethical review, and this should not be overlooked even when sponsors have legal power to permit investigators access to data. An exception is justified when epidemiologists must investigate outbreaks of acute communicable diseases. Then they must proceed without delay to identify and control health risks. They cannot be expected to await the formal approval of an ethical review committee. Nevertheless, in such circumstances the investigator will, as far as possible, respect the rights of individuals, namely freedom, privacy, and confidentiality.

Ethical review committees

34. Ethical review committees may be created under the aegis of national or local health administrations, national medical research councils, or other nationally representative health-care bodies. The authority of committees operating on a local basis may be confined to one institution or extend to all biomedical studies undertaken in a defined political jurisdiction. However committees are created, and however their jurisdiction is defined, they should establish working rules — regarding, for instance, frequency of meetings, a quorum of members, decision-making procedures, and review of decisions, and they should issue such rules to prospective investigators.

35. In a highly centralized administration, a national review committee may be constituted to review study protocols from both scientific and ethical standpoints. In countries with a decentralized administration, protocols are more effectively and conveniently reviewed at a local or regional level. Local ethical review committees have two responsibilities:

— to verify that all proposed interventions have been assessed for safety by a competent expert body, and
— to ensure that all other ethical issues are satisfactorily resolved.

36. Local review committees act as a panel of investigators' peers, and their composition should be such as can ensure adequate review of the study proposals referred to them. Their membership should include epidemiologists, other health practitioners, and lay persons qualified to represent a range of community, cultural and moral values. Committees should have diverse composition and include representatives of any populations specially targeted for study. The members should change periodically to prevent individuals from becoming unduly influential, and to widen the network involved in ethical review. Independence from the investigators is maintained by precluding any member with a direct interest in a proposal from participating in its assessment.

Ethical conduct of members of review committees

37. Ethical review committee members must carefully guard against any tendencies to unethical conduct on their own part. In particular, they should protect the confidentiality of review-committee documents and discussions. Also, they should not compel investigators to submit to unnecessary repetition of review.

Representation of the community

38. The community to be studied should be represented in the ethical review process. This is consistent with respect for the culture, the dignity and self-reliance of the community, and the aim of achieving community members' full understanding of the study. It should not be considered that lack of formal education disqualifies community members from joining in constructive discussion on issues relating to the study and the application of its findings.

Balancing personal and social perspectives

39. In performing reviews, committees will consider both personal and social perspectives. While, at the personal level, it is essential to ensure individual informed and free consent, such consent alone may not be sufficient to render a study ethical if the individual's community finds the study objectionable. Social values may raise broad issues that affect future populations and the physical environment. For example, in proposals for the widespread application of measures to control intermediate hosts of disease organisms, investigators will anticipate the effects of those measures on communities and the environment, and review committees will ensure that there is adequate provision for the investigators to monitor the application of the measures so as to prevent unwanted effects.

Assuring scientific soundness

40. The primary functions of ethical review are to protect human subjects against risks of harm or wrong, and to facilitate beneficial studies. Scientific review and ethical review cannot be considered separately: a study that is scientifically unsound is unethical in exposing subjects to risk or inconvenience and achieving no benefit in knowledge. Nor-

mally, therefore, ethical review committees consider both scientific and ethical aspects. An ethical review committee may refer technical aspects of scientific review to a scientifically qualified person or committee, but will reach its own decision, based on such qualified advice, on scientific soundness. If a review committee is satisfied that a proposal is scientifically sound, it will then consider whether any risk to the subject is justified by the expected benefit, and whether the proposal is satisfactory with regard to informed consent and other ethical requirements.

Assessment of safety and quality

41. All drugs and devices under investigation must meet adequate standards of safety. In this respect, many countries lack resources to undertake independent assessment of technical data. A governmental multidisciplinary committee with authority to co-opt experts is the most suitable body for assessing the safety and quality of medicines, devices and procedures. Such a committee should include clinicians, pharmacologists, statisticians and epidemiologists, among others; for epidemiological studies, epidemiologists occupy a position of obvious significance. Ethical review procedures should provide for consultation with such a committee.

Equity in the selection of subjects

42. Epidemiological studies are intended to benefit populations, but individual subjects are expected to accept any risks associated with studies. When research is intended to benefit mostly the better off or healthier members of a population, it is particularly important in selecting subjects to avoid inequity on the basis of age, socioeconomic status, disability or other variables. Potential benefits and harm should be distributed equitably within and among communities that differ on grounds of age, gender, race, or culture, or other variables.

Vulnerable and dependent groups

43. Ethical review committees should be particularly vigilant in the case of proposals involving populations primarily of children, pregnant and nursing women, persons with mental illness or handicap, members of communities unfamiliar with medical concepts, and persons with restricted freedom to make truly independent choices, such as prisoners and medical students. Similar vigilance is called for in the case of proposals for invasive research with no direct benefit to its subjects.

Control groups

44. Epidemiological studies that require control (comparison) or placebo-treated (i.e., non-treated) groups are governed by the same ethical standards as those that apply to clinical trials. Important principles are that:

(i) the control group in a study of a condition that can cause death, disability or serious distress should receive the most appropriate currently established therapy; and

(ii) if a procedure being tested against controls is demonstrated to be superior, it should be offered promptly to members of the control group.

A study will be terminated prematurely if the outcome in one group is clearly superior to that in the other, and all subjects will be offered the better treatment. Research protocols should include "stopping rules", i.e., procedures to monitor for, and act upon, such an event. Investigators must continually bear in mind the potential benefits of the study to the control group, and the prospect of improved health care from applying the findings to the control group.

Randomization

45. Trials in which the choice of regimen or procedure is determined by random allocation should be conducted only when there is genuine uncertainty about differences in outcome of two or more regimens or procedures. Where randomization is to be used, all subjects will be informed of the uncertainty about optimum regimens or procedures, and that the reason for the trial is to determine which of two or more is in the subjects' best interests. Informing subjects about such uncertainty can in itself arouse anxiety among patients, who may already be anxious for other reasons; therefore, tact and delicacy are required in communicating the information. Ethical review committees should ascertain whether investigators refer explicitly to informing subjects about this uncertainty, and should enquire what will be done to allay subjects' anxiety about it.

Random allocation also can cause anxiety: persons chosen for, or excluded from, the experimental regimen or procedure may become anxious or concerned about the reasons for their being chosen or excluded. Investigators may have to communicate to members of the study population some basic concepts about application of the laws of chance, and reassure them that the process of random allocation is not discriminatory.

Provision for multi-centre studies

46. When participation in a multi-centre study is proposed according to a common protocol, a committee will respect different opinions of other committees, while not compromising on the application of the ethical standards that it expects investigators to observe; and it will attempt to reconcile differences so as to preserve the benefits that only a multi-centre study can achieve. One way of doing so could be to include in the common protocol the necessary procedures. Another would be for the several committees to delegate their review functions to a joint committee of the centres collaborating in the study.

Compensation for accidental injury

47. Some epidemiological studies may inadvertently cause harm. Monetary losses should be promptly repaid. Compensation is difficult when it is not appropriate to make monetary payments. Breach of con-

fidentiality or insensitive publication of study findings, leading to loss of group prestige, or to indignity, may be difficult to remedy. When harm results from a study, the body that has sponsored or endorsed the study should be prepared to make good the injury, by public apology or reparation.

Externally sponsored studies

48. Externally sponsored studies are studies undertaken in a host country but initiated, financed, and sometimes wholly or partly carried out by an external international or national agency, with the collaboration or agreement of the authorities or the host country.

Such a study implies two ethical obligations:

The initiating agency should submit the study protocol to ethical review, in which the ethical standards should be no less exacting than they would be for a study carried out in the initiating country.

The ethical review committee in the host country should satisfy itself that the proposed study meets its own ethical requirements.

49. It is in the interest of the host country to require that proposals initiated and financed externally be submitted for ethical approval in the initiating country, and for endorsement by a responsible authority of the same country, such as a health administration, a research council, or an academy of medicine or science.

50. A secondary objective of externally sponsored studies should be the training of health personnel of the host country to carry out similar study projects independently.

51. Investigators must comply with the ethical rules of the funding country and the host country. Therefore, they must be prepared to submit study proposals to ethical review committees in each country. Alternatively, there may be agreement to the decision of a single or joint ethical review committee. Moreover, if an international agency sponsors a study, its own ethical review requirements may have to be satisfied.

Distinguishing between research and programme evaluation

52. It may at times be difficult to decide whether a particular proposal is for an epidemiological study or for evaluation of a programme on the part of a health-care institution or department. The defining attribute of research is that it is designed to produce new, generalizable knowledge, as distinct from knowledge pertaining only to a particular individual or programme.

For instance, a governmental or hospital department may want to examine patients' records to determine the safety and efficacy of a facility, unit or procedure. If the examination is for research purposes, the proposal should be submitted to the committee that considers the ethical features of research proposals. However, if it is for the purpose of programme evaluation, conducted perhaps by staff of the institution

to evaluate a therapeutic programme for its effects, the proposal may not need to be submitted to ethical review; on the contrary, it could be considered poor practice and unethical not to undertake this type of quality assurance. The prospect of benefit or avoidance of harm to patients may constitute an ethical value that outweighs the risk of breaching the confidentiality of former patients whose medical records are liable to be inspected without their consent.

If if is not clear whether a proposal involves epidemiological study or routine practice, it should be submitted to the ethical review committee responsible for epidemiological protocols, for its opinion on whether the proposal falls within its mandate.

Information to be provided by investigators

53. Whatever the pattern of the procedure of ethical review, the investigator must submit a detailed protocol comprising:

— a clear statement of the objectives, having regard to the present state of knowledge, and a justification for undertaking the investigation in human subjects;
— a precise description of all proposed procedures and interventions, including intended dosages of drugs and planned duration of treatment;
— a statistical plan indicating the number of subjects to be involved;
— the criteria for terminating the study; and
— the criteria determining admission and withdrawal of individual subjects, including full details of the procedure for obtaining informed consent.

Also, the protocol should:

→ include information to establish the safety of each proposed procedure and intervention, and of any drug, vaccine or device to be tested, including the results of relevant laboratory and animal research;
→ specify the presumed benefits to subjects, and the possible risks of proposed procedures;
→ indicate the means and documents proposed to be used for eliciting informed consent, or, when such consent cannot be requested, state what approved alternative means of obtaining agreement will be used, and how it is proposed to protect the rights and assure the welfare of subjects;
→ provide evidence that the investigator is properly qualified and experienced, or, when necessary, works under a competent supervisor, and that the investigator has access to adequate facilities for the safe and efficient conduct of the research;
→ describe the proposed means of protecting confidentiality during the processing and publication of study results; and
→ refer to any other ethical considerations that may be involved, and indicate that the provisions of the Declaration of Helsinki will be respected.

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WORLD MEDICAL ASSOCIATION DECLARATION OF LISBON

ON

THE RIGHTS OF THE PATIENT

Adopted by the 34th World Medical Assembly
Lisbon, Portugal, September/October 1981

and amended by the 47th General Assembly
Bali, Indonesia, September 1995

PREAMBLE

The relationship between physicians, their patients and broader society has undergone significant changes in recent times. While a physician should always act according to his/her conscience, and always in the best interests of the patient, equal effort must be made to guarantee patient autonomy and justice. The following Declaration represents some of the principal rights of the patient which the medical profession endorses and promotes. Physicians and other persons or bodies involved in the provision of health care have a joint responsibility to recognize and uphold these rights. Whenever legislation, government action or any other administration or institution denies patients these rights, physicians should pursue appropriate means to assure or to restore them.

In the context of biomedical research involving human subjects – including non therapeutic biomedical research – the subject is entitled to the same rights and consideration as any patient in a normal therapeutic situation.

PRINCIPLES

1. Right to medical care of good quality

a. Every person is entitled without discrimination to appropriate medical care.

b. Every patient has the right to be cared for by a physician whom he/she knows to be free to make clinical and ethical judgements without any outside interference.

c. The patient shall always be treated in accordance with his/her best interests. The treatment applied shall be in accordance with generally approved medical principles.

d. Quality assurance always should be a part of health care. Physicians, in particular, should accept responsibility for being guardians of the quality of medical services.

e. In circumstances where a choice must be made between potential patients for a particular treatment which is in limited supply, all such patients are entitled to a fair selection procedure for that treatment. That choice must be based on medical criteria and made without discrimination.

f. The patient has the right of continuity of health care. The physician has an obligation to cooperate in the coordination of medically indicated care with other health care providers treating the patient. The physician may not discontinue treatment of a patient as long as further treatment is medically indicated, without giving the patient reasonable assistance and sufficient opportunity to make alternative arrangements for care.

2. Right to freedom of choice

a. The patient has the right to choose freely and change his/her physician and hospital or health service institution, regardless of whether they are based in the private or public sector.

b. The patient has the right to ask for the opinion of another physician at any stage.

3. Right to self-determination

a. The patient has the right to self-determination, to make free decisions regarding himself/herself. The physician will inform the patient of the consequences of his/her decisions.

b. A mentally competent adult patient has the right to give or withhold consent to any diagnostic procedure or therapy. The patient has the right to the information necessary to make his/her decisions. The patient should understand clearly what is the purpose of any test or treatment, what the results would imply, and what would be the implications of withholding consent.

c. The patient has the right to refuse to participate in research or the teaching of medicine.

4. The unconscious patient

a. If the patient is unconscious or otherwise unable to express his/her will, informed consent must be obtained whenever possible, from a legally entitled representative where legally relevant.

b. If a legally entitled representative is not available, but a medical intervention is urgently needed, consent of the patient may be presumed, unless it is obvious and beyond any doubt on the basis of the patient's previous firm expression or conviction that he/she would refuse consent to the intervention in that situation.

c. However, physicians should always try to save the life of a patient unconscious due to a suicide attempt.

5. The legally incompetent patient

a. If a patient is a minor or otherwise legally incompetent the consent of a legally entitled representative, where legally relevant, is required. Nevertheless the patient must be involved in the decision making to the fullest extent allowed by his/her capacity.

b. If the legally incompetent patient can make rational decisions, his/her decisions must be respected, and he/she has the right to forbid the disclosure of information to his/her legally entitled representative.

c. If the patient's legally entitled representative, or a person authorized by the patient, forbids treatment which is, in the opinion of the physician, in the patient's best interest, the physician should challenge this decision in the relevant legal or other institution. In case of emergency, the physician will act in the patient's best interest.

6. Procedures against the patient's will

Diagnostic procedures or treatment against the patient's will can be carried out only in exceptional cases, if specifically permitted by law and conforming to the principles of medical ethics.

7. Right to information

a. The patient has the right to receive information about himself/herself recorded in any of his/her medical records, and to be fully informed about his/her health status including the medical facts about his/her condition. However, confidential information in the patient's records about a third party should not be given to the patient without the consent of that third party.

b. Exceptionally, information may be withheld from the patient when there is good reason to believe that this information would create a serious hazard to his/her life or health.

c. Information must be given in a way appropriate to the local culture and in such a way that the patient can understand.

d. The patient has the right not to be informed on his/her explicit request, unless required for the protection of another person's life.

e. The patient has the right to choose who, if anyone, should be informed on his/her behalf.

8. Right to confidentiality

a. All identifiable information about a patient's health status, medical condition, diagnosis, prognosis and treatment and all other information of a personal kind, must be kept confidential, even after death. Exceptionally, decendants may have a right of access to information that would inform them of their health risks.

b. Confidential information can only be disclosed if the patient gives explicit consent or if expressly provided for in the law. Information can be disclosed to other health care providers only on a strictly "need to know" basis unless the patient has given explicit consent.

c. All identifiable patient data must be protected. The protection of the data must be appropriate to the manner of its storage. Human substances from which identifiable data can be derived must be likewise protected.

9. Right to Health Education

Every person has the right to health education that will assist him/her in making informed choices about personal health and about the available health services. The education should include information about healthy lifestyles and about methods of prevention and early detection of illnesses. The personal responsibility of everybody for his/her own health should be stressed. Physicians have an obligation to participate actively in educational efforts.

10. Right to dignity

a. The patient's dignity and right to privacy shall be respected at all times in medical care and teaching, as shall his/her culture and values.

b. The patient is entitled to relief of his/her suffering according to the current state of knowledge.

c. The patient is entitled to humane terminal care and to be provided with all available assistance in making dying as dignified and comfortable as possible.

11. Right to religious assistance

The patient has the right to receive or to decline spiritual and moral comfort including the help of a minister of his/her chosen religion.

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