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Concerning the HHS Inspector General Reports on Institutional Review Boards
(OEI-01-97-00191-93)
June 11, 1998

Since these reports find that "the System," referring to Institutional Review Boards (IRBs), is "in jeopardy," it is clear to us that the health and safety of thousands of human experimental subjects are also in jeopardy since the protection of people in these experiments is the most important function of the IRB system. Although these reports conclude that there are not "widespread abuses of human research subjects," the increasingly large number of violations found by FDA investigators in IRB-approved informed consent documents, the dangerous lack of on-site inspections for HHS-funded research by NIH's Office of Protection from Research Risks (OPRR), the rise of for-profit IRBs--much of whose work is to monitor research done by for-profit clinical trials companies--and many other problems documented in these reports believe the conclusion of "no widespread abuse." This conclusion seems particularly inappropriate as no systematic search for abuses was conducted nor were known abuses examined.

<u>**The most alarming findings of the Inspector General's Reports are:**</u>

1. Unsafe workload of IRBs: According to the Inspector General's Report, "at the sites we visited, the [IRB] meetings typically lasted about 2 ½ hours and included an average of 18 initial [research proposal] reviews, 9 expedited reviews, 43 protocol amendments, and 21 adverse event reports." The report cites other studies finding that the average academic medical center IRB was reviewing 297 proposals a year. It is clear that adequate time is not being devoted to this difficult task. Worse, there is "minimal" attention spent by the IRBs on monitoring the research after it has begun to see if the study's conduct is consistent with the approved protocols.

2. Massive number of informed consent violations: According to the report, the FDA annually does site visits to only about 200 of the 1,500 to 1,700 IRBs involved in overseeing research which includes FDA-regulated products. These investigations are mainly not done for cause and therefore it can be assumed that the sites inspected in a given year are representative of the larger universe of IRBs. In FY1997, there were a total of 74 informed consent deficiencies found at the 210 IRBs visited. Since 210 is 210/1,500 or only 14% of all of the IRBs, it is reasonable to project that in 1997 there were a total of 528 informed consent deficiencies (74/14%). Of the inspection findings deemed by FDA to be "most serious", there were 8 in FY 97 among the 210 IRBs inspected which projects to a total of 56 for the whole country in that one year alone.

3. Misleading advertisements to recruit patients to join experiments: 60 newspaper or public transportation advertisements were examined to estimate the extent to which the line between treatment and research was being blurred. People are lured into experiments by emphasizing treatment instead of research: "the mention of research is either placed at the end of a long list of benefits or is embedded in language so enticing that the inevitable risks of research are easily overlooked....The danger of these advertisements is that subjects may come to a research study with misconceptions....They may be motivated by the promise of free treatment, free screening or extra money." One ad illustrating this stated: "Do you have asthma? If you qualify for any of our asthma studies, you can: learn to care for your asthma, receive free medication, receive up to $1,730!"

4. New conflict of interest problems with "Independent" (For-profit) IRBs: Because a progressively larger fraction of research undertaken in order to get drugs and medical devices approved is done by for-profit drug and device testing companies which are not part of university medical centers, there has been a proliferation of "independent" IRBs to service them. Although they are "independent" of an academic research institution, as for-profit entities they are quite dependent on pleasing their customers (the for-profit research companies) and their owners. The Inspector General study found that "some IRB officials are concerned that an independent, for-profit IRB might compromise its review process to advance the financial well-being of the firm. Such concerns are heightened to the extent that corporate-equity owners or employees serve on the IRB review boards and are sustained to some extent by the fact that reviewers are paid for their services." An additional problem involves the fact that most of these are nationwide and therefore do not have local representation and input from the localities where the trials are being conducted.

5. Inadequate oversight of IRBs by FDA or OPRR: As mentioned above, only 210 out of 1,500 to 1,700 IRBS which review studies involving FDA-regulated products are inspected by the FDA in a given year. Thus, it may be five or more years between inspections, during which hundreds or more studies will have been approved by the IRB with no on-site oversight. OPRR does even fewer on-site inspections of IRB monitoring functions, mainly employing phone and paper investigations. "Only rarely does OPRR go on-site. Between 1990 and April 1996, OPRR conducted only 18 compliance visits...[there were] no on-site visits between April 1997 and February 1998 because of staffing problems." Thus, with thousands of NIH-funded human experiments being monitored by IRBs, there is dangerously little oversight by the OPRR which is, in another example of conflict of interest, part of NIH.

6. Little evaluation of real effectiveness of IRBs: According to the Inspector General's Report, "officials [of IRBs] reported that during the past year they seldom visited the research site. Although many would like to, none oversees the informed consent process or solicits feedback from subjects." One IRB member said "he reviews the continuing review summaries during the board meeting to see if a patient has died. If no patient has died, then he generally will not raise questions."

Inadequacies of Inspector General Investigations

There is an enormous amount of important information and recommendations in these reports but there are two areas of investigation which would have been useful to include:

1. Failure to interview subjects of human experiments: Since IRBs themselves do not find out if informed consent was really obtained (see #6 above), relying on a review of the document content instead of finding out if patients actually understand the nature of the experiment in which they agreed to participate, it would have been useful to interview a representative sample of patients in trials, particularly those who had finished trials.

2. Failure to assess differences between boards based on review of a standardized protocol or to collect data on differences between IRBs in rejection rates or rates of requiring serious modifications in protocols: In the United Kingdom, studies have shown that ethical review committees, the equivalent of IRBs, differ greatly in the way they approach and criticize a standardized protocol. Rather than collecting such systematic data, the Inspector General reports depend primarily on site visits and qualitative information. Such data would be very instructive in better training and education of IRB members. Data examining the extent to which the rate of rejection or serious modification of studies reviewed by IRBs differed from one IRB to the next might focus on conflicts of interest or other problems with the training and education of IRB members. It would also set standards by which IRBs could be objectively compared.

Recommendations beyond those made by the Inspector General

1. Funding for more adequate review by IRBs: This should be done as an automatic predetermined portion of academic overhead for clinical trials. In other words, since academic centers are getting funded to do the trials, a sufficient portion of this overhead should go to assuring that a much more rigorous review of the research, initially and while the trial is underway, is done.

2. Change in composition of IRBs including much more attention to conflicts of interest, especially at for-profit IRBs: Despite recommendations dating back 25 years that scientists from outside the institution and non-health professional lay persons should be included in IRBs,[1] this need, especially the outside scientist element, is not being adequately addressed. Given the strong institutional bias to say yes to the possible flow of money, it is particularly important to temper the institutional enthusiasm with these more disinterested parties.

The idea of a for-profit IRB is appalling. It is one thing for a loyal academic to say yes to a research proposal which will benefit his or her institution but another for the IRB member, possibly an executive or a major stockholder in the IRB, to personally gain from approving research proposals. The policy for HHS-funded research reviews by for-profit IRBs is to exclude IRB equity owners from participating in the review process, but there is no such policy for industry-sponsored studies which are to be submitted to the FDA. If it is not possible to abolish for-profit IRBs, at least this extreme conflict of interest for the approval of studies of drugs, devices and other FDA-regulated products should be ended. This conflict of interest also facilitates the phenomenon of IRB-shopping, in which sponsors take a protocol rejected at one IRB (perhaps a University IRB as in a recent case mentioned in congressional testimony [2]) and take it instead to a for-profit IRB which has every incentive to approve the protocol lest it gain a reputation as "too strict" and therefore lose business.

3. Regulation by the FDA of advertising done by clinical trials units: As discussed under finding #3 above, patients can easily be lured into participating in human experiments by the misleading advertising discussed in the Inspector General's Report. The FDA should expand its regulation of IRBs to include the recruiting materials such as advertisements and these materials should also be part of the materials received by the IRBs. Combined with misleading information in the informed consent forms, the result may be for patients to participate in an experiment without adequate informed consent.

4. Requirements for a central registry of all trials and that the results of all trials be made public within one year of completion. In a recent article entitled, *Are Research Ethics Committees Behaving Unethically? Some Suggestions for Improving Performance and Accountability,* British researchers concluded that the committees were behaving unethically "by endorsing new research which is unnecessary and by

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[1] Barber B, Lally JA, Makarushka JL, Sullivan D. Research on Human Subjects. Russell Sage Foundation, New York. 1973.

[2] Wilfond B. Testimony before the House Subcommittee on Human Resources, Committee on Government Reform and Oversight, U.S. House of Representatives, May 8, 1997.

acquiescing in biased underreporting of research which they have approved." [3] They concluded that research ethics committees should:

a/ Require systematic reviews of existing research before approving research;

b/ Require that a summary of relevant systematic reviews be made available to potential participants;

c/ Require registration of clinical trials at inception as a condition of approval [national registry];

d/ Require a commitment by investigators to make the results publicly accessible as a condition of approval; and

e/ Audit the reporting of results of research previously approved by them. (IRB monitoring of publication is critical to avoid publication bias or debacles such as Knoll Pharmaceutical's suppression of the levothyroxine equivalency study.[4])

5. Analysis of close votes at IRBs to see if and why those protocols got approved.

6. Retrospective analyses of IRB meetings which approved trials now considered unethical.

7. Remove OPRR from NIH because of conflict of interest: As long as OPRR is part of the institutional block diagram and under the control of the NIH, over whose research it is supposed to exert independent control, it is highly unlikely that it will be able to fulfill its important mission. It should be moved outside of the NIH but still within HHS.

8. Implementing as mandatory for IRBs some of the strategies discussed in *Institutional Review Boards: Promising Approaches (OEI-01097-00190)* : With the growing number of research applications, it seems reasonable at the present time to put a limit on the number of applications a given IRB can review per year. IRBs should also be required to provide some educational outreach to faculty and students, at a minimum including a lecture series on ethics, including lectures on recent controversies and new directions in ethics. We were particularly impressed with the

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[3] Savulescu J, Chalmers I, Blunt J. Are research ethics committees behaving unethically? Some suggestions for improving performance and accountability. *British Med J* 1996; 313:1390-3.

[4] Rennie D. Thyroid storm. *JAMA* 1997; 277:1238-43.

computer-assisted monitoring of research activity at the University of California, San Diego which determined that fully 10% of recent publications by faculty members had not received IRB approval; this monitoring function, which is rapid and inexpensive, should also be made mandatory. Periodic informed consent audits by third parties, as conducted at the University of Texas Health Sciences Center, should also be required, as should the presence of a bioethicist on the IRB.