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HEADLINE: Patients or Profits? Clinical testing a hot topic in search for new medications

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BODY:

Overweight?'

'Worried about forgetfulness? Trouble recalling information? Difficulty in planning and organizing?'

'Are you experiencing irritability? Loss of energy? Anxiety? Trouble sleeping? A diminished sex drive?'

If you answer yes to any of these questions, asked in provocative newspaper and radio ads, you're fair game for a **clinical trial.**

Answer the ads and you'll be invited to come down for testing. If you pass and agree to volunteer, you'll be given an experimental drug and interviewed for eight or nine weeks.

But don't expect to get treatment for your condition. Many of these trials are conducted by independent clinics whose physicians are paid by drug manufacturers just to test experimental drugs, not to treat patients.

Changing reasons

In the past, **clinical trials** were funded by government bodies or nonprofit foundations to find treatments or cures for medical conditions or to advance our understanding of disease. Today that's not always the case.

Sometimes, the ads deliberately use general language because researchers are looking for people who are clinically ill, but not yet diagnosed, said Barry Make, a physician and researcher at National Jewish Hospital, even if 'they don't know they have a chronic disease.'

And other times, the ads' language is broad because an investigator is interested in enrolling as many patients as possible in a trial, interested less in the patients than in the potential profits paid per enrollee.

Over the last 10 years, privately funded **clinical trials** have become a huge, and hugely profitable, industry. At least a dozen such clinics are doing business in the Denver area, advertising for guinea pigs to test weight-loss drugs, antidepressants and drugs that treat memory loss.

Critics say they are driven less by humanitarian interests than by drug companies eager to bring potentially profitable new products to the market.

In short, if you volunteer for a **clinical trial,** you may find yourself less a patient under treatment than a human guinea pig trying out a new drug.

Research centers that focus on anti-depressants make no bones about turning away prospective volunteers who are suicidal or whose depression is linked to alcohol or drug abuse, or to a heart attack.

They want healthy volunteers whose depression is severe enough to require medication, but not debilitating.

Call the number listed on the Feiger Health Research Center's advertisement, for example, and the recording emphasizes the center has been 'instrumental in the development of dozens of new medications' and that 'we continue to be selected by pharmaceutical companies' to investigate new antidepressant treatments.

Clear-cut message

'This is the wrong place to go for psychotherapy; we do not take people who are in dire straits or who have a severe illness,' said physician Alan D. Feiger, president of the Feiger Health Research Center in Wheat Ridge, who conducts three to five **clinical trials** a year. Each trial is divided into cycles, with new groups of volunteers (and some returning volunteers who did well on the tested drug) replaced every nine weeks.

'We evaluate prospective volunteers very, very carefully. We do see patients who've been on antidepressants, and frankly, if someone's doing well on the antidepressant, we don't think it's a good idea to take them off it. We are looking for people who don't have access to care, or for whom their antidepressant isn't working.'

Most of the volunteers participate in a nine-week study. If the volunteers do well on the tested medication, Feiger said, he gives them the option of remaining on it for a year. Among the drugs Feiger researched is Efexor, a new anti-depressant that was favorably compared to Prozac, the leading antidepressant, in trial results published last February in The Journal of Affective Disorders.

Changed in the '90s

In past years, medical research has led to enormous advances in scientific knowledge, often prolonging and saving lives. Traditionally, that research came from **clinical trials** and investigations that were, almost exclusively, the province of a few medical university and teaching-hospital researchers. Then, researchers typically received a flat per-patient fee for their work, paid by their employer-institutions, which were paid by the pharmaceutical companies and by government grants.

That changed in the 1990s, when managed-care companies pressured the pharmaceutical industry to keep down drug prices. Manufacturers responded by developing new products to expand their market share and maintain profits.

As competition for new drugs increased, turnaround time became more important. Researchers once spent 10 to 20 years or more leisurely studying the safe dosage, side effects and effectiveness of a new drug. Now, researchers typically spend a year on phase 1 testing, two years on phase 2 tests, and three to five years on phase 3 tests and post-market trials, according to PhRMA at the Tufts Center for the Study of Drug Development. Depending on luck and successful results, a new drug can be on the market in as little as seven years.

When academic researchers, accustomed to lengthy investigations, didn't increase the pace and turn-around time of their work, the drug companies began recruiting private-practice physicians to do research. Investigator grants average $ 43,000 per study, according to one online physicians' listing service, Clinmark Dotcom.

The result: The number of doctors conducting drug studies nearly tripled, according to a New York Times computer analysis of drug study forms submitted annually to the Food and Drug Administration. In 1990, 4,307 doctors were involved in **clinical trials.** By 1997, **clinical trials** had evolved into a multibillion dollar industry, with 11,662 doctors conducting drug studies. No one keeps track of how many patients are involved in **clinical trials,** according to Colorado Medical Society.

Is this a good thing? Not necessarily, says Centura oncologist David Shimm, a Denver physician who

has written extensively about the pitfalls of current **clinical trial** investigations.

'The issue is, first, whether patients are receiving inappropriate, and even harmful care,' Shimm said. 'For example, imagine a patient with pain from terminal cancer. The concern is that the patient is being offered participation in a **clinical trial,** instead of being given radiation and/or pain medication.'

By subtly or not-so-subtly wording the advertisement to attract patients, the researcher may also be convincing him or her to choose the trial over conventional treatment. The investigator's payoff: a per-patient premium paid by the drug manufacturer.

Pharmaceutical companies routinely pay physician researchers a fee for each patient in a study. That fee ranges from $ 1,100 per patient to more than $ 4,000 per patient. The actual costs per patient typically are $ 1,500 or less, Shimm says. So, for a **clinical trial** involving 80 patients and a pharmaceutical company's payment of $ 2,670 per patient, for example, a researcher could clear a profit of $ 1,170 per patient, or about $ 93,600.

The patient, however, may not understand that he or she is bypassing treatments already proven effective to test an unknown - and maybe ineffective - drug. In early stage (phase 1) trials, the only thing being tested is the drug's safety, or in Shimm's words, 'how much of it you can take before it poisons or kills you.'

Physician Jennifer Hone, an endocrinologist who specializes in treating patients with diabetes and participates in **clinical trials,** is less cynical about the process. If physicians didn't make money by conducting them, she asks, 'why would they bother?'

The six or seven drug trials she conducts help keep her practice open, she said.

'It's a reasonable source of income, and I was about to go out of business by taking care of people, often poor people, with chronic diseases.

'If there's a responsible physician involved in the trial,' she stresses, 'it's an opportunity for patients to be part of cutting-edge therapy that they might not otherwise have access to. It's an opportunity for physicians, if they're being ethical, to get experience with a new medicine or therapy, or whatever's being tested.'

Independent reviewing

Still, critics like Shimm say that the pharmaceutical manufacturers who sponsor **clinical trials** are less interested in patients than in the research data those patients can provide. For that reason, independent review boards are set up to monitor **clinical trials.** Those that receive government funding follow strict guidelines set up by independent review boards at universities or hospitals.

'For every trial we do at National Jewish, we have to file conflict-of-interest statements that answer questions like, is the drug company paying you for anything other than the study, do they take you out to dinner? Do you have any stock holdings in the company?' said Barry Make, a physician and researcher at National Jewish Hospital. 'We have to disclose all that. Now companies are under pressure to produce a lot of new medications, and they want the drugs to be investigated quicker. They may not have all the safeguards in place that they should.'

Private **clinical trial** centers also have review boards, but government officials complain they review too many studies without closely inspecting them, or they are more interested in representing the interests of pharmaceutical companies than in solid research.

'The private review boards are supposed to conduct reviews, just like the universities',' Shimm said.

'I doubt the privates do even as good a job as the universities. And even universities don't do so well.'

Case in point: A year ago, Werner Bezwoda, a medical researcher then affiliated with the University of Witwatersrand in Johannesburg, South Africa, reported promising results when treating late-stage breast cancer patients with a combination of high-dose chemotherapy and blood-stem-cell transplants.

Results repudiated

By the end of the year, Bezwoda's claims collapsed. The results from his clinical investigation were based on fabricated data, sloppy research and such a disregard for protocol that there was no evidence of patients' **consent** for trial enrollment.

Congressional representatives are trying to curb such abuses by requiring that private trials meet the same stringent guidelines used for government-funded trials.

U.S. Rep. Diana DeGette of Denver is drafting legislation that would address that problem.

The bill will establish uniform standards for review boards, private and government-funded; improve federal oversight and review of **clinical trials;** and clarify informed-**consent** language. The bill is necessary, said DeGette senior policy analyst Bruce Lesley, because standardized guidelines 'will uniformly protect people.'

'Yes, there are dangers in **clinical trials,**' said Hone. 'Yes, people should be careful about being participants. Yes, physicians should NEVER pressure a patient to participate in a study and should not assume that the patient understands that it really IS voluntary. And that it should not, in any way, influence the relationship between the doc and the patient.'

It shouldn't influence that relationship, agrees Shimm, but does it, anyway? 'A 'research institute' physician's primary relationship is with the pharmaceutical company,' he explained, not with the patient. 'For the actively practicing physician enrolling patients into a **clinical trial,** there is a real conflict of loyalty, although most would indignantly deny this.'

Check it out

If you're tempted to

enroll in a **clinical trial,**

do your homework first,

advises Barry Make, a

researcher at the

ational Jewish Hospital.

Then you're

less likely to fall prey

to an unscrupulous in-

vestigator more interest-

ed in cash on the hoof -

signing up as many patients

as possible for the per-head reimbursement - than in weeding out legitimate patients. His advice:

Check with your own physician first. Does your doctor think this is a reasonable study, based on your medical condition? Your doctor should be aware if you're participating in a study, particularly if it involves medications or other alternatives that can physiologically affect you.

Carefully read the informed **consent** form. Does it outline all the risks and benefits that may be associated with this trial? If you're not sure, ask. Be wary of an informed **consent** form that's written in jargon you can't readily understand.

Do you feel comfortable with the investigator(s) and researcher(s) as well as the director of the study? Do you feel that all of your questions are being answered thoroughly and competently? A knowledgeable staff is important. You should feel that staffers are doing their best to address your concerns. Don't forget to ask: 'Is there anything else I should know or be aware of?'

Is the principal investigator - the study's director - a physician with a valid and current medical license?

Ask if the drug or product manufacturer is reimbursing the study investigators above and beyond the study's expenses. Be blunt: How much, per study participant, does the investigator receive? The National Institutes of Health typically reimburse investigators about $ 1,500 per study participant, but independent investigators often receive twice that or more - far beyond the actual cost of the study.

Be an informed participant. Ask the investigator if the medicine or treatment in the study is the best option, considering your personal circumstances. Ask the investigator to spell out all the risks and downsides of participating in the study. If he or she brushes aside the risks and seems overeager to recruit you, think twice about participating in the study.

-Claire Martin

How experimental drugs are tested in humans

In **clinical trials,** experimental drugs are tested in at least three stages:

Phase 1: Primarily assesses the drug's safety. How is the drug absorbed? Metabolized? Excreted? What side effects show up as the dosage is increased? Initial testing is typically conducted with 20 to 100 healthy volunteers, usually paid for participating. A phase 1 **clinical trial** typically takes several months or more. About 70 percent of experimental drugs pass phase 1 tests, according to CenterWatch, a **clinical trial** industry organization.

Phase 2: Testing for efficacy. One group of patients receives the experimental drug, while a second 'control' group receives a placebo or traditional treatment. In a blind trial, neither researcher nor patient knows who's getting the experimental drug. A phase 2 study lasts several months to several years. Only about a third of experimental drugs pass phase 1 and phase 2 testing.

Phase 3: The experimental drug is tested on a larger group (several hundred to several thousand patients) in trials that are both randomized and blind. A phase 3 study typically lasts several years, with 70 to 90 percent of the drugs finally submitted for Food and Drug Administration approval.

Late Phase 3/Phase 4: The drug is compared with other drugs already on the market, mostly for the purpose of marketing, but also to determine a drug's long-term effectiveness and impact, and to determine its cost-effectiveness.

-Claire Martin

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Human Research Subjects Protections

Q. What are you announcing today?

A: We are announcing several new efforts designed to improve human research subject safety, to further strengthen government oversight of all medical research, and to reinforce clinical researchers' responsibility to follow federal guidelines.

We are taking the following steps:

- **Education and Training.** HHS will undertake an aggressive effort to improve the education and training of clinical investigators, IRB members, and associated IRB and institutional staff. NIH, FDA and the Office of Protections from Research Risks (OPRR) will work closely together to ensure that all clinical investigators, research administrators, IRB members and IRB staff receive appropriate research bioethics training and human subjects research training. Such training will be a requirement of all clinical investigators receiving NIH funds and will be a condition of the NIH grant award process and of the OPRR assurance process.

- **Informed Consent.** NIH and FDA will issue specific guidance on informed consent, clarifying that research institutions and sponsors are expected to audit records for evidence of compliance with informed consent requirements. For particularly risky or complex clinical trials, IRBs will be expected to take additional measures, which, for example, could include third-party observation of the informed consent process. The guidance will also reassert the obligation of investigators to reconfirm informed consent of participants upon the occurrence of any significant trial-related event that may affect a subject's willingness to participate in the trial.

- **Improved Monitoring.** NIH will now require investigators conducting smaller-scale early clinical trials (Phase I and Phase II) to submit clinical trial monitoring plans to the NIH at the time of grant application, and will expect investigators to share these plans with IRBs. The NIH already requires investigators to have such plans and they also require large scale (Phase III) trials to have Data and Safety Monitoring Boards (DSMBs). For research on medical products intended to be marketed, FDA will also issue guidelines for DSMBs that will delineate the relationship between DSMBs and IRBs, and define when DSMBs should be required, when they should be independent, their responsibilities, confidentiality issues, operational issues and qualified membership.

- **Conflict of Interest.** NIH will issue additional guidance to clarify its regulations regarding conflict of interest, which will apply to all NIH-funded research. HHS will also hold public discussions this summer to find new ways to manage conflicts of interest so that research subjects are appropriately informed, and to further ensure that research results are analyzed and presented objectively. In addition, these public discussions also will focus on clarifying and enhancing the informed consent process. Based on these public forums, NIH and FDA will work together to develop new policies for the broader biomedical research community, which will require, for example, that any researchers' financial interest in a clinical trial be disclosed to potential participants.

- **Civil Monetary Penalties.** HHS will pursue legislation to enable FDA to levy civil monetary penalties for violations of informed consent and other important research practices—up to $250,000

per clinical investigator and up to $1 million per research institution. HHS will propose While FDA can currently issue warning letters or impose regulatory sanctions that halt research until problems are rectified, financial penalties will give the agency additional tools to sanction research institutions, sponsors and researchers who do not follow federal guidelines. As an interim step, NIH, OPRR and FDA will work more closely together to enforce and target existing penalties.

Q. Why are you doing this?

A: Clinical research has become increasingly complex in recent years and has been accompanied by an increase in new ethical and conflict-of-interest considerations.

Recent reports of gene transfer trials with insufficient human subject protections and apparent financial conflicts of interest have clarified the urgency and importance of additional steps in protecting human research subjects and crystallized the new pressures facing medical researchers, research institutions and IRBs.

It is critical that the integrity of human subjects research be maintained, and it is vitally important that we ensure that research institutions and their clinical investigators and IRBs fully understand their oversight responsibilities for protecting human subjects in research.

Q. These recommendations don't seem very significant. Do you really think they will make a difference?

A: The actions we are announcing today are important steps in enhancing the system of protections for human subjects in research and can be implemented quickly. It is critical that the integrity of human subjects research be maintained, and it is vitally important that we ensure that research institutions and their clinical investigators and IRBs fully understand their oversight responsibilities for protecting human subjects in research.

Q. The informed consent provisions look really weak. Why aren't you doing more?

A. This is a shared responsibility, and we believe the actions we're taking now are a solid first step. But we also want to hear the recommendations of the National Bioethics Advisory Commission on June 8, and we want to consult with universities and academic medical centers. This is a joint responsibility.

Q. Why don't you just overhaul the whole system with new regulations?

A: The actions we are announcing today are important steps in enhancing the system of protections for human subjects in research and can be implemented quickly. Before we consider even broader steps, such as new regulatory actions, it is important that we have input from research institutions, clinical investigators, IRB members and staff, and the public on approaches to further enhancements for human subject protections.

This summer HHS will conduct extensive public discussions regarding conflicts of interest associated with clinical trials. The primary objective of these discussions is to find ways to ensure that all real or potential conflicts of interest are identified promptly and are managed in such a way that human research subjects are neither misled nor coerced in any way.

HHS will host a conference on August 15-16 to showcase best practices in human subject protections and to begin development of new guidance on identifying and managing financial conflicts of interest related to research institutions and their clinical investigators and IRB members.

Q. So much of what NIH and FDA do to oversee the protection of human research subjects seems duplicative. Why doesn't just one agency oversee this issue?

FDA and NIH play important and complementary roles in overseeing health research and protecting the rights of people enrolled in clinical trials. FDA must approve all clinical trials aimed at testing a new drug or medical device, and NIH has developed important patient safety guidelines that must be followed in any research the agency funds.

However, the line between university-funded research (primarily funded by NIH and governed by NIH guidelines) and industry-funded research (aimed at bringing a product to market and governed by FDA guidelines) is becoming increasingly blurred. University researchers may receive public as well as private funding – or they may be stockholders in small biotechnology startups themselves. For example, recent reports of several gene transfer trials with insufficient protections have clarified the urgency of this effort and highlighted the new pressures facing biomedical researchers, their institutions and IRBs.

As a result, researchers -- even in academic settings -- are now faced with financial pressures that create new kinds of ethical and conflict-of-interest considerations. IRBs may be struggling to find members who do not have ties to pharmaceutical, device and biotech industries to ensure that unbiased, open discussion can take place before granting protocol approval. And clinical trial recruitment tactics are becoming more questionable as researchers face increased competition to enroll patients in their trials.

Because of these new complexities in research, NIH and FDA are working even more closely together, conferring with one another, for example, to develop appropriate guidance for their respective research communities that addresses new and evolving needs.

Q. Don't these actions put more workload on the IRBs, which you say are already overworked and stretched to their limits?

A. No. In fact, we have already taken steps to reduce the workload of IRBs so they can focus more of their effort on monitoring human subjects protections in clinical trials and less time on paperwork and other administrative activities. OPRR is streamlining its requirements for research institutions, thereby making more resources available for monitoring and education. In addition, NIH has issued new guidance allowing grant applicants to defer IRB review of proposed research protocols until after completing the initial phase of NIH peer review but before final funding approval. Previously, NIH asked for IRB review and approval to be included with all grant applications, even though fewer than half of all applications submitted to NIH are actually funded.

Q. Why are these actions happening so late? The HHS Inspector General issued a report in June 1998 making numerous recommendations to enhance protections, but you've done virtually nothing since then.

A. NIH and FDA are committed to ensuring the protection of patients in clinical trials and, as the IG report noted, both agencies "have been actively addressing human subject protections" since 1998, and even before. There has been a rise in the enforcement of federal requirements including a major increase in inspections and surveillance. Numerous educational outreach activities to promote greater understanding of patient protection efforts have already taken place and will continue.

Also following the issuance of the report, the Advisory Committee to the Director of NIH examined the role of OPRR and recommended in June 1999 that OPRR be relocated in the Office of the Secretary to elevate its stature and effectiveness. The committee also recommended that an independent advisory council be established to provide broad scientific and ethical guidance to OPRR in its oversight role.

Secretary Shalala has accepted the committee's recommendation and will soon be relocating OPRR to the Office of Public Health and Science within the Office of the Secretary.

It's also important to remember that pace of change in medical research is very rapid, with new conflict of interest issues we weren't facing two or three years ago. We are constantly exploring new and effective ways to enhance systems to strengthen patient protections without unduly burdening IRBs or stifling important clinical research. Patient protection is priority number one and we encourage all IRBs, researchers, and patients to join with us in working to ensure that patients have the protections they need to make informed decisions about trials and are adequately protected during trials.

Q. The President asked you on February 8th to expedite your review of gene transfer guidelines and regulations -- to determine whether the current informed consent requirements need to be strengthened. Why did it take so long?

A. The President asked us to look at gene transfer trials specifically, which we did. In March we announced two new initiatives: gene transfer research sponsors will now be required to routinely submit monitoring plans in advance to FDA; and NIH and FDA will conduct a continuing series of gene transfer safety symposia.

Our review of gene transfer trials crystallized the broader issues for us, so we broadened our focus to examine the issues of human subject protections in the more general context of all clinical research. Because the number of research projects and study volunteers has been increasing and because clinical research has become increasingly complex, it is critical that the integrity of research be maintained. Recently reported problems in human subject protections have occurred because some of the basic oversight rules were not followed and IRB oversight was uneven.

The actions we are announcing today are important steps in enhancing the system of protections for human subjects in research and can be implemented quickly. Before we consider even broader steps, such as new regulatory actions, it is important that we have input from research institutions, clinical investigators, IRB members and staff, and the public on approaches to further enhancements for human subject protections.

Q. Will these new initiatives help avoid another Jessie Gelsinger incident?

A. FDA's investigation suggests that the main problems with the study in which Jesse Gelsinger participated stemmed from lapses in informed consent, and the fact that he was enrolled when he shouldn't have been, given the approved protocol. We believe all of these initiatives will help, especially the requirement for formal data safety and monitoring plans.

Research institutions and their clinical investigators and IRBs have ultimate responsibility for ensuring effective protections of human subjects in medical research, primarily through the IRB review process. Current federal regulations require IRBs to conduct continuing review of approved research at regular intervals. This requirement is in addition to an IRB's responsibility for protocol review and informed consent review prior to the start of a study.

The steps we are announcing today will further enhance the system of protections for human subjects in research, but the ultimate responsibility for protecting human research subjects lies with research investigators, institutions and IRBs.

Q. Do you think gene transfer research is safe, or not?

A. The vast majority of serious adverse events, including deaths, reported in human gene transfer research

A. We haven't yet had a chance to review the language of the Mica bill. Human research subject protections are a top priority for the department, and we would certainly want to work with members of Congress on civil money penalties and other issues that would lead to enhanced protections of human research subjects in clinical trials. Updating the Common Rule is cumbersome, since it requires concurrence of 17 agencies, and we are open to discussing legislative options for doing so.

Q. Why are you not requiring accreditation of IRBs, as the Department of Veterans Affairs just recently announced?

A. To require accreditation, one must have a third-party organization that has the competence and resources to determine compliance with HHS standards, based on inspections of IRBs' structure and performance. At this time, HHS has not generated such standards nor has it identified one or more potential accreditors. However, the Public Responsibility in Medicine and Research (PRIM&R) organization, which has coordinated numerous educational activities on research subject protections, is investigating the financial and logistical requirements for assuming that responsibility as an accrediting agent for HHS. Nevertheless, IRB accreditation is not something that will occur in the near future.

Q. Isn't the real problem that participants in clinical trials have no idea of the conflicts of interest when they enroll in these trials?

A. That's certainly part of the problem, and the IG has been very helpful in how we think about addressing this issue. IRBs do have the authority to require disclosure of potential conflicts of interest to patients. This is an area where universities and the federal government need to work together, and it will definitely be part of our recommendations after our public consultation this summer. Based on these public forums, NIH and FDA will work together to develop new guidance for the broader medical research community, which will require that any researchers' financial interest in a clinical trial be disclosed both to potential participants and to federal officials.

Q. What do you think about Harvard relaxing its conflict of interest guidelines?

A. I think they're moving in the wrong direction. Universities have a real responsibility here, and we hope they'll be more stringent, not less.

Q. I understand the IG is just finishing a report on recruitment. How will these initiatives address those concerns?

A. The actions we are announcing today are important steps in enhancing the system of protections for human subjects in research, and they address the recommendations of this report. Some contemporary recruitment practices may put potential subjects at unnecessary risk—a risk could be reduced to a minimal level if IRBs were uniformly diligent in their oversight of recruitment practices.

One of our key actions announced today focuses on taking aggressive efforts to improve the education and training of clinical investigators, IRB members, and associated IRB and institutional staff and will issue additional guidance to research institutions to clarify their role in carrying out their responsibilities for protecting human research subjects, including recruitment practices.

It is critical that the integrity of human subjects research be maintained, and it is vitally important that we ensure that research institutions and their clinical investigators and IRBs fully understand their oversight responsibilities for protecting human subjects in research.

have been due to the natural progression of the patient's underlying serious disease, and not due to the investigational gene transfer product. Of all serious adverse events reported to NIH, about nine percent were considered to have been possibly associated and unexpected. To our knowledge, there has been only one instance, at the University of Pennsylvania, in the 10-year history of human gene transfer research in which the investigational gene transfer product clearly appeared to be a cause of the participant's death.

Like all experimental therapies, gene transfer has great potential and great risk. The question is, ultimately, do the potential benefits outweigh the risks? To my mind, gene transfer has great potential—particularly in areas like cancer, where the alternative is chemotherapy, and severe immunodeficiency, where the alternative is bone marrow transplants.

Q. It's been nearly a year since you announced that OPRR would be elevated to the Office of the Secretary, but it hasn't happened yet. What's taking so long?

A: Transferring OPRR to the Office of the Secretary actually has involved several steps because of overlapping recommendations from a report of an advisory panel to the director of NIH. OPRR has historically provided both human subject and animal welfare protection. A second review group determined it was preferable to transfer only the human subject protection function as the office was elevated to the Office of the Secretary. Additionally, an external independent management consultant performed a resources and organizational review and has presented their report on how best to achieve OPRR's goals in this new environment. Lastly, time has been spent working to hire a new director for the transferred OPRR. Once these steps are complete, the transfer will occur.

Q. How will moving OPRR to the Office of the Secretary level and renaming it help improve protections for human subjects?

A: As the number of research projects and study volunteers has increased, it is critical that the office have appropriate stature and effectiveness in carrying out its oversight responsibilities. Moving OPRR to the Office of the Secretary will put it in a position to more effectively exercise a leadership role in the research community on issues relating to the protection of human subjects. Locating OPRR at the Departmental level also will permit OPRR to forge new alliances with the components within HHS and with other federal agencies that support human research. I believe OPRR will become a powerful forum for exploring and addressing the challenging issues involved in protecting research subjects.

Q. Why haven't you made any decisions on the new head of OPRR, or the resource needs of that office?

A. I hope to be making an official announcement shortly. While we are looking at the resource needs of the office, neither Dr. Satcher nor I want to make any final decisions without the input of the new director.

Q. Why is it taking so long to establish the new advisory committee on protection from research risks? What's the timetable for action?

A: Forming the advisory committee is another element of the multi-step process. The advisory committee will be chartered under the Federal Advisory Committee Act and will provide advice to the Secretary, Assistant Secretary for Health, director of the soon-to-be-established Office of Human Research Protections and other senior officials. We anticipate that within the next 45 days that we will be publishing a Federal Register notice that announces the formation of the committee and includes a solicitation of public nominations of individuals to be considered for appointment.

Q. Do you support the Mica bill on the Common Rule?

Q. I understand the IG is just finishing a report on FDA oversight. How will these initiatives address those concerns?

A. Again, the actions we are announcing today are important steps in enhancing the system of protections for human subjects in research. FDA has always been committed to protecting individuals from possible abuse or harm in clinical research trials and to ensuring that potential participants fully understand the benefits and risks of experimental treatment.

In fact, clinical trial subjects are most frequently put at unreasonable risk because of deviations from approved protocols. That is why FDA is increasing its surveillance of clinical trials as well as its efforts to inform and educate the clinical trial community. FDA also continues to enforce its regulations designed to protect patients. Its investigators inspect approximately 600 clinical investigators annually, as well as 250 to 300 IRBs every year.

Finally, HHS will pursue legislation to enable FDA to levy civil monetary penalties to enforce good research practices. While FDA can currently issue warning letters or impose regulatory sanctions that halt research until problems are rectified, financial penalties will give the agency additional tools to sanction IRBs, sponsors and researchers who do not follow federal guidelines. As an interim step NIH, OPRR and FDA will work more closely together to enforce and target existing penalties.

Q. How will an expansion in training requirements for all clinical investigators funded by the NIH help improve protections of human subjects? When will this begin? How will NIH ensure that this training requirement is being met?

Training and education are first order requirements to ensure that clinical investigators have a consistent and complete understanding of their responsibilities. This training requirement will ensure that all clinical investigators have the requisite knowledge of the human subjects regulations, regulatory requirements, clinical trial design and appropriate trial monitoring. Such training will improve the safety of research subjects enrolled in NIH funded clinical trials.

Next steps:

NIH-funded institutions will have to develop a training course, or use one of the many already existing training courses available; NIH will list these on its website. Grant applicants will have to report in their grant applications that they have fulfilled this training requirement with the October receipt-date for research grant applications.

NIH will notify NIH-funded institutions about this new requirement, through the web-based NIH Guide to Grants and Contracts, by June 1.

It is expected that institutions will take further steps to enhance such training.

Q. How will expanding the requirements for monitoring all trials help improve protections for human subjects? How will NIH notify grantees about this requirement?

This new requirement for submitting Phase I and Phase II clinical trial monitoring plans to the NIH will improve the safety of participants in clinical trials by ensuring close monitoring.

The NIH and the NIH Initial Review Group (IRG) will review clinical trial monitoring plans, and any concerns or comments must be addressed satisfactorily before a trial can begin. Clinical trial monitoring plans should address, as applicable, issues such as the experience and training of the monitors, the process

by which the monitors will verify that the rights and well-being of human subjects are protected; that the conduct of the trial is in accordance with the protocol, regulatory requirements, and good clinical practices; and that data reporting (including safety reporting to IRB, FDA, and NIH, as applicable) is accurate and complete. The plan should include a summary and an organizational chart identifying each individual responsible for oversight of clinical studies and his or her duties.

Since 1979, NIH has required oversight and monitoring of all intervention studies to ensure the safety of participants and the validity and integrity of the data. This requirement was reissued in 1998, along with a additional requirement that all Phase III clinical trials include a Data and Safety Monitoring Board (DSMB).

Next Steps:

NIH will notify grantee institutions of this new requirement by June 1. Clinical trial monitoring plans will be required in grant applications coming into NIH for the October receipt-date for research grant applications.

Q. How will this guidance on the individual responsibilities of the various parties involved in clinical research help improve protections for human subjects?

This should ensure that all entities (scientists, IRB and DSMB members, and NIH staff overseeing clinical studies) involved in clinical trials clearly understand their responsibilities for protecting human subjects. It will also enhance communication and sharing of information between DSMBs and IRBs. All entities (some multi-site studies are overseen by multiple IRBs at different institutions) will be notified in a timely manner of important data flowing to the DSMBs from ongoing studies. This will enhance discussion, for example, about aggregate data about adverse events and will greatly inform decision-making regarding safety.

Next Steps: NIH will distribute the guidance to all involved entities at institutions (IRB members, DSMB members, and principal investigators) by June 1. NIH staff overseeing clinical studies will also receive the guidance.

Q. How will increasing "not for cause" site visits to research institutions help improve protections for human subjects?

Such "not for cause" site visits are important for several reasons. First, they allow NIH to identify potential problems early on and work with institutions to fix the problem together. Secondly, they help NIH assess whether institutions, in general, understand NIH guidance. In general, "not for cause" site visits allow NIH to be proactive instead of reactive, addressing the potential for problems to occur rather than waiting for a problem to arise. Three such site visits—to monitor compliance with NIH policies on human-subject protections—have been conducted so far, and a total of 10 are projected this year.

Q. How will the additional comprehensive training session and regional workshops for IRBs help improve protections for human subjects?

Effective human subject protections depend on a thorough understanding and appreciation of protection requirements by research investigators and IRBs. This grass roots, front line training is the best way to ensure effective protection of human research subjects.

Q. What action is FDA taking to help ensure that informed consent is properly obtained in emergencies?

On March 30, FDA published draft guidance for Institutional Review Boards, sponsors of human research, and clinical investigators concerning how to conduct emergency research ethically and according to federal regulations designed to protect patients while allowing important research to move ahead.

Obtaining informed consent in emergency research presents unique challenges since potential subjects are often not able to provide consent as it is traditionally understood.

Q. When will this guidance be available?

FDA published the draft guidance March 30, with a 60-day comment period. The agency expects the final guidance to be published next fall.

Q. Why is this guidance important for protecting patients?

The guidance will help IRBs, sponsors, and clinical investigators better understand their obligations to disclose information about their research to the community from which research subjects will be drawn. The guidance will also help ensure that communities are consulted about this research so that it can be conducted in accordance with community standards.

Q. What is involved in FDA's guidance on Data Safety and Monitoring Boards?

FDA's guidance to Data Safety and Monitoring Boards will describe such issues as the relationship between DSMBs and IRBs and define when DSMBs should be required, their responsibilities, composition, when they should be independent, confidentiality issues, statistical methodology, and operational issues.

Q. When will this guidance be ready?

We expect to issue a draft guidance within several months, after which there will be an opportunity for public comment before final guidelines are published.

Q. How will this guidance help protect patients?

DSMBs will receive clinical trial data at set intervals. Because they generally receive "unblinded" data, they can review the data and spot trends. DSMBs can stop a trial if an "arm" of the trial shows a great benefit from a product being studied. Likewise, the trial could be stopped if it poses undue risks to patients.

DSMBs could also help protect patients by making their reports, which now go to sponsors, also available to IRBs.

Q. How much money could an institution be fined using civil monetary penalties?

The amount of potential fines will depend on the law that provides this authority to FDA.

Q. Are FDA regulations forcing companies to perform clinical trials overseas?

A. Over the years some have expressed concern that FDA's high standards for conducting clinical trials was driving research abroad. Others have criticized FDA for accepting data from foreign trials, where research subjects might not enjoy the same protections.

Through the International Conference on Harmonization (ICH), standards for clinical trials are being harmonized at a uniformly high level. This collaborative process has brought about new international guidelines that are consistent with US regulations that ensure the integrity of the data collected and provide protection for human subjects through written informed consent procedures.

Commensurate with the increasing number of trials done abroad, FDA is increasing the number of foreign inspections it performs each year. In 1999, FDA did 65 foreign inspections compared to 22 done in 1995.

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BYLINE: Abbey S. Meyers

BODY:

The highly publicized death in September of an 18-year-old patient in a **clinical trial** at one of the largest academic gene therapy centers in the world--the University of Pennsylvania's Institute for Human Gene Therapy--has spurred a host of investigations and recriminations. It has also prompted some people to ask a question we shall never be able to answer for sure: If Jesse Gelsinger had known that monkeys had died from the therapy before it was given to humans and that several previous participants had suffered serious toxic reactions to the kind of treatment he was volunteering to undergo, would he have agreed to take part in the trial?

More generally, can we be certain that participants in the proliferating number of experiments being conducted in other centers around the country have been given the information they need before agreeing to participate?

My experience as a former member of the National Institutes of Health advisory committee that oversees gene therapy research suggests that the likely answer to both those questions is no. Gelsinger's untimely death has exposed the shortcomings in the system we have developed to protect patients. Some researchers seem to view the process of informing patients about experiments as a necessary hindrance in their race for scientific glory--and financial reward. Gelsinger's story is viewed by many as an aberration. I believe, however, that it may fit a pattern. Some researchers--not all--don't take seriously enough the need for informed **consent,** despite the abuses of the past.

Certainly, many of the greatest triumphs of the past 100 years were the accomplishments of medical researchers who tamed rheumatic fever, eradicated smallpox and polio and discovered the magical potency of antibiotics to win countless victories over disease and death.

But for every story of medical success there is a darker one of medical abuse: the Nazi experiments on defenseless minorities; the Tuskegee experiment in which African American men with syphilis were purposely denied medical treatment for decades by American physicians; and numerous unethical experiments on the mentally retarded and mentally ill who were confined to U.S. institutions. History teaches that we should be cautious about allowing researchers to pursue their investigations without government oversight and regulation to ensure that their research will be meaningful and patients will be adequately protected.

The Nuremberg trials revealed the full horror of medical experiments conducted by Nazi scientists during World War II--and created the political resolve in industrialized countries to establish rules that would protect **human subjects** in all future clinical experiments. In the United States, this code of conduct for scientific research became known as the "Common Rule," and it was last revised by the federal government in 1981.

The Common Rule requires that all patients--or their legal guardians--who volunteer to participate in

clinical trials be fully informed about the details of the experiment. They must have a complete understanding of the risks (even the possibility of unknown dangers) as well as the potential benefits of the experiment. For example, in an early (Phase I) **clinical trial,** which is conducted solely for the purpose of determining the safety (not the effectiveness) of a treatment, volunteers must be told that they should not expect any personal benefit from the experiment, although the knowledge that scientists will gain from the trial is likely to help other patients in the future. In essence, the motivation for participation must be altruistic--a desire to help humanity, not a desire to help oneself.

The National Research Act of 1974 led to legal protections for all volunteers who participate in medical and psychological research that involve federal funds. The responsibility for ensuring that these rules are obeyed is assigned to an institutional review board (IRB) located at every facility in the United States that conducts research on humans, as long as the institution receives federal money. Privately funded research is not affected. The IRB must ensure that each experiment is scientifically and ethically sound, and must monitor its progress to ensure that patients' rights are adequately protected. Unfortunately, IRBs have been overburdened and underfunded. In recent months, the federal government has stopped all human research at several universities--including Duke University Medical Center, Rush-Presbyterian-St. Luke's Medical Center in Chicago, and West Los Angeles Medical Center--because their IRBs were failing to comply with patient protection rules.

These sorts of shortcomings are particularly troubling in the swiftly moving field of gene therapy. If the example of Gelsinger is anything to go by--and the closings of these other medical centers suggests it is--patients are not being fully and truthfully informed before being asked to give their **consent** to participate.

Unlike the infamous experiments that led to the adoption of the Common Rule, modern gene therapy research is primarily funded by private companies, not the government. That's an important distinction. While government-funded academics must share information about their experiments, corporate funding often requires scientists to keep information secret: Companies often insist that releasing research information may provide an advantage to their competitors. If they release news, it is often carefully tailored good news, while the bad news remains hidden in the "trade secret" closet.

The result is that many people have the mistaken impression that gene therapy is already curing people (so far, however, there have been no documented cures), and pin false hopes on the technology. Cancer patients, for example, will often demand admission into a gene therapy trial because it represents their "last chance" to be cured. It is worth noting that the great majority of gene therapy experiments are not conducted on genetic diseases, which are too rare to encourage investment capital, but on cancer, primarily because investors sense that a potential treatment for cancer will be more profitable.

Gene therapy has always been a controversial area of science, because it has the potential to change the essence of the human race. In recognition of this, the government assigned the Recombinant DNA Advisory Committee (RAC) at the National Institutes of Health (NIH) the task of overseeing development of the technology. Composed of volunteer scientists, expert bioethicists, consumer advocates and others who discuss each trial at quarterly public meetings, the RAC created rules called "Points to Consider." Gene therapy researchers must obey these rules if any patients in the trial are treated at a hospital that receives federal funds. But trials sponsored by private companies do not have to obey the rules if patients do not use facilities receiving federal funds.

There have been a number of problems with putting those rules into effect. When members of the RAC have complained that an informed **consent** document is inaccurate or misleading, they are reminded that only the local IRB has authority to dictate the words in the document. Not even the Food and Drug Administration has any authority over the wording. (The agency focuses solely on science, not ethics, so it cannot demand that a doctor disclose to patients in a trial that he or she owns shares in the sponsoring company and thus stands to benefit financially from the product being tested.) The sole authority for approving informed **consent** documents--the local IRB--is not required to have any members who are knowledgeable about the technology that they are reviewing.

Members of an IRB (mostly staff of the institution) are usually keenly aware of the need to attract

government and industry research grants, and often are unwilling to be too demanding when asked to revise informed **consent** documents. It sometimes appears that IRBs are more concerned about protecting their institutions' liability concerns than about protecting patients.

In 1994, the RAC's Working Group on Informed **Consent** strengthened the Points to Consider rules and spelled out exactly what each **consent** document should address. Of course it is a challenge to make the highly technical work of modern research scientists comprehensible to patients, but the Points to Consider set up some straightforward rules: They require that informed **consent** documents must be written in understandable language and they state that any adverse effects seen in animal studies and patients who previously participated in the experiment must be disclosed. Nevertheless, researchers and IRBs largely continue to ignore these rules. The FDA, which does not have any bioethicists on its staff, continues to approve new trials with inadequately worded informed **consent** documents.

In recent years, the RAC's authority over gene therapy research has also lessened. In 1996, Harold Varmus, as director of the NIH, withdrew the RAC's authority to approve gene therapy protocols, which greatly diminished its oversight. Today, the RAC is left with only moral suasion, especially with regard to informed **consent** documents.

After Jesse Gelsinger died from multiple-organ failure, brought on by the infusion of genetically altered cold viruses into his diseased liver, the FDA found some glaring violations. The informed **consent** document Gelsinger signed was very different from the documents the RAC had reviewed, and even different from the so-called "final" document that the FDA had seen. Information about the deaths of monkeys in the pre-clinical studies had been deleted, and there was no mention of several serious adverse events experienced by patients who preceded Gelsinger in this trial. As a result, all seven of the University of Pennsylvania's gene therapy studies were recently suspended.

Some of these problems were undoubtedly peculiar to this trial. But the oversight system failed to prevent serious violations of patient protection rules. Gelsinger's death shows that we must take a closer look at these guidelines. After all, gene therapy is only one of many burgeoning biomedical advances. Soon xenotransplantation, stem cells, cloning, in-utero transplants, fetal gene transfers and many as-yet unimaginable giant steps in medicine will be approaching the clinic.

Next week, as a result of the investigations into Gelsinger's death, there will be congressional hearings on gene therapy trials. Now is the time to build the political resolve to fix this problem, before more tragedies occur. We should not allow the Gelsinger case to stop the progress of gene therapy research. The research must move forward with the appropriate patient protections firmly in place to ensure that all **clinical trial** volunteers are fully informed before they are asked to give their **consent.**

Abbey Meyers, the founder and president of the National Organization for Rare Disorders, was a member of the National Institute of Health's Recombinant DNA Advisory Committee's (RAC) Gene Therapy Subcommittee from 1989 to 1992, and a member of the full RAC from 1993 to 1996.

Even Before Nuremberg

The Nuremberg Code of 1947 is usually referred to as the prototype for regulations regarding informed **consent,** but debate over medical experimentation goes back to 19th-century Prussia. In 1898, a University of Breslau professor of venereology named Albert Neisser injected serum from syphilitic

patients (most of whom were prostitutes) into patients being treated for other conditions. The patients were not informed about the injections nor asked for their **consent.** When some of them contracted syphilis, Neisser denied his trials were the cause. But news of his experiment prompted a public outcry.

Berlin psychiatrist Albert Moll was one of the few academic physicians who did not side with Neisser at the time. He collected evidence from 600 cases of unethical, non-therapeutic research on humans and called for a new practice: informed **consent.** Neisser was fined for his actions by the Prussian Royal Disciplinary Court, according to a 1996 account by the British Medical Association.

After the court's action, the Prussian government formed a commission to study the matter further. In 1900, Prussian hospitals and clinics were ordered to perform medical interventions only for diagnosis, healing and immunization-- unless "the **human subject** was a minor or not competent for other reasons" or if the subject "had not given his or her unambiguous **consent"** after "proper explanation of the possible negative consequences" of the intervention. Unfortunately, the directive was not legally binding, which could account for its lack of historical impact.

Thirty years later, the Nazi government issued legal guidelines, based on a doctrine of informed **consent,** that were meant to minimize risk for **human subjects.** The wording was remarkably similar to informed **consent** documents today. The guidelines obviously did not keep Nazi doctors from performing unethical experiments on concentration camp prisoners during World War II. The ethical regulations in human medical research--and the doctrine of informed **consent** that came about as a result of the Nuremberg trials--were the ones with staying power.

Cases

Judgment calls about how and when to pursue informed **consent** are often controversial. Examples in the news during the late 1990s:

* At a hospital in Philadelphia, doctors treating a 31-year-old man with a particular type of benign brain tumor recommended an untested variation on the usual course of radiation. They did not get the man's **consent;** he suffered an incapacitating stroke after the treatment. The neurosurgeons had not sought experimental status for the procedure, nor had they submitted their proposal to a hospital review board until they had treated several other patients, more than a year later. A malpractice suit against the doctors and the hospital is set for trial in mid-February.

* One hundred severely injured trauma victims admitted to emergency rooms across the country were unwitting participants in a drug company's **clinical trial** for a new blood substitute intended to aid patients in hemorrhagic shock. The product was used to treat 52 patients categorized as having a high expected mortality rate due to their injuries; 24 died, leading the manufacturer to stop the trial. Under government rules, the trial was legal; an FDA waiver allowed the drug company to test its product on trauma victims who are unconscious or otherwise unable to give **consent.** The hospitals conducting such trials are supposed to notify their communities well in advance. A similar trial using the same blood substitute is ongoing in European hospitals.

GRAPHIC: Illustration, jean-francois allaux for The Washington Post

LANGUAGE: ENGLISH

Department of H ealth and Human Services. We have Dr. Gary Ellis, acting director of the Office of Protection from Research Risks.

We have Daniel Michels, and he is the director of Enforcement of the Office of Regulatory Affairs of the Food and Drug Administration.

This is an investigation and oversight subcommittee of Congress. We will sw ear you in just a minute. All of our witnesses appear under oath. Furthermore, i f you have any lengthy statements or documentation that you'd like to have made part of the record, upon request through the chair and with the concurrence of t he minority, that will be granted.

Those are basically the rules and the way we'll proceed today.

Without objection, Mr. Kucinich has moved that the record be left open for additional comments or submissions for two week. So ordered.

REP. KUCINICH: Thank you, Mr. Chairman.

REP. MICA: We now will proceed. If the witnesses would stand and be sworn. Raise your right hand.

Do you solemnly swear that the testimony you're about to give before this s ubcommittee of Congress is the whole truth, and nothing but the truth?

WITNESSES: I do.

REP. MICA: The witnesses answered in the affirmative.

We'll now hear first from the deputy inspector general for Evaluation and I nspection, George Grob. He has submitted a rather lengthy findings for the subco mmittee, and Mr. Kucinich moves, without objection, that they be made part of th e record. So ordered. So we will have your complete testimony in here.

We'd like each of our witnesses today to try to limit their oral presentati ons to five minutes if possible. I know we have two that are making presentation s I think with this panel, and we will submit any additional data or testimony u pon request.

With that, let me recognize George Grob, deputy inspector general for Evalu ation and Inspections. You're recognized, sir.

MR. GEORGE GROB: Thank you, Mr. Chairman and Mr. Kucinich.

The system which was designed to protect the human subjects of research

has inherent vulnerabilities, most of which remain even after the best efforts of o ur department to address them. To understand why this is the case, we must go ba ck to their origins.

They were gradually developed after the second world war in response to res earch atrocities that came to life during the second world war and other trouble some research experiments that arose shortly thereafter.

In 1966, the surgeon general issued the Human Subject Policy for the Depart ment of Health, Education and Welfare, and in 1974, the National Research Act re quired reviews by institutional review boards for all research sponsored by the Department of Health, Education and Welfare. In 1991, those procedures were adop ted by 15 other federal departments in what has come to be known as the "common rule."

These and other developmental events during that period were among the priv ate days of American science with respect to protection of human subjects. Howev er, during this same period, research exploded in size, in complexity, in number s and the amounts of money spent. The institutional review boards were overwhelm ed and left behind. Vulnerabilities suddenly emerged, at first unnoticed. Later we begun to notice them.

In 1995, at the request of the Food and Drug Administration, we conducted a study of the unauthorized marketing of investigational medical devices, and dur ing the course of this report we stumbled upon some problems with the institutio nal review boards and other systems designed to protect the human subjects of th is research.

For example, in one experiment, a researcher was authorized to implant 75 i nvestigational devices for surgery, reported to the investigational review board that 37 had been implanted. We found that 264 had, in fact, been implanted.

We found other discrepancies in the surgery reports of other investigators. Fifteen devices were implanted during the six-week period in which the research had been suspended by the institutional review board. We found changes not made to the research protocols requested by the boards and reported as having been m ade. We found informed consent forms missing, in some cases, consent forms obtai ned after the surgery was performed and other similar results.

As a result of stumbling upon these kind of findings, we decided that a mor e systematic look was required at the institutional review boards and other syst ems designed to protect human subject research. And based on that work, we publi shed in June of '98 a more comprehensive review that provided an early warning o f troubles and vulnerabilities in the system.

To get a better sense of the problems that the institutions were facing at the time, let me just rattle off some of the circumstances that made it more dif ficult for them to do their jobs.

When they began this work in the '60s and '70s, most research consisted of research at a single site; today it's mostly multi-site across the country, some times even the world. It used to involve a single investigator; now it involves hundreds of investigators. It used to be a small cohort of subjects; now it's th ousands. Most funding came from government offices; now a lot of it comes from c ommercial sponsors. A lot of it used to be done at teaching hospitals; now it's done at clinics, doctor offices and in other settings. There's been a rise of pa tient consumerism and demands for access to investigational procedures, drugs an d device and new types of research have emerged.

In 1978, there were about 500 institutions with institutional review boards ; now there is somewhere between 3,000 and 5,000 of them. They used to review an average of 43 proposals a year; now it's up to about 300. The adverse event rep orts are flooding their offices, in some cases being stored in boxes on the floo r without being reviewed. In one case we found a couple hundred of these reports coming in per month at one of the institutional review boards.

With such a change in circumstances, the institutional review boards were n ot able to keep up. They had insufficient resources. They've been unable to stay on top of the research that's being performed, so that while they might give a review of the proposals before the research starts, they can seldom look beyond that. We found insufficient training and little evaluation in oversight, and we made corresponding recommendations, which have already been cited in the opening statement.

Recently, the department has attempted to deal with these problems, and it' s taken a number of steps, which Mr. Raub will summarize for you. I particularly want to point out the stepped-up enforcement that NIH has been doing. Recently, 10 on-site visits were made and 7 institutions had their research suspended. I think the sentinel effect of these efforts has been very strong and has sent a w ave through the research community, indicating that improper processes will not be tolerated.

But fundamental vulnerabilities remain, and we're reminded too often of the consequences of this. I know that departmental officials are engaged intently i n addressing these vulnerabilities and our own work is continuing. But I would l ike to add to my statement here a note that the solutions don't depend entirely on the department. The companies which sponsor research, the investigators, the universities and medical centers, their institutional review boards, they're all involved, and they're responsible too.

The talent, energy, creativity and dedication is what fueled the boom in re search that overwhelmed the human subject protection system.

These same forces now need to be directed to bring it back into balance.
REP. MICA: Thank you. Does that conclude your opening statement?

Mr. Grob: Yes.

REP. MICA: Let me now recognize, if I may, Dr. William Raub, who's the depu ty assistant secretary for Science Policy, the Office of Secretary of Health and Human Services.

You're recognized, sir. Welcome DR. WILLIAM RAUB: Good afternoon, Mr. Chairman and members of the subcommit tee. I am William Raub, deputy assistant secretary for Science Policy at the Dep artment of Health and Human Services. I'm accompanied today by Gary Ellis, direc tor of the NIH Office for the Protection of Research Risks, and Daniel Michels, Director of Enforcement at the Food and Drug Administration. Thank you for this opportunity to testify regarding the protection of human research subjects.

For more than 50 years, HHS and its predecessors have led the nation and th e world in protecting human research subjects from unnecessary risks. Our approa ch is rooted in the Nuremberg Code whose principles have been adopted, reinforce d and built upon in a succession of policies culminating in the current federal regulations governing research with human subjects.

HHS led the way in developing the core of these regulations, the so-called "common rule," which has been promulgated by 17 different departments and indepe ndent agencies. In addition, FDA has carefully tailored its regulations for the products-oriented clinical research it oversees so that they harmonize with the common rule.

The primary foci for implementing these regulations are the institutional r eview boards or IRBs. They are responsible for reviewing proposed research proto cols and associated informed consent statements before subjects are recruited an d clinical research begins. No covered project may commence without IRB'd approv al.

Further, IRBs are responsible for continuing review; that is, oversight of approved research projects throughout their life cycle. If in the course of cont inuing review the responsible IRB were to find cause for concern regarding the s afety of research subjects, the IRB could halt the project temporarily or perman ently or otherwise require the investigators to take

whatever protective or corr ective actions it deems appropriate.

Two types of IRBs exist-- IRBs operated by research institutions, such as a cademic health centers and IRBs that operate as private entities. Two HHS compon ents share responsibility for overseeing IRBs, the OPRR and the FDA. OPRR overse es IRBs operated by HHS awardee institutions. FDA oversees IRBs that review clin ical research related to the products it regulates, irrespective of whether that research is ongoing at HHS awardee institutions or other sites.

HHS is very concerned that the effectiveness of IRBs is in jeopardy. Althou gh the inspector general's investigation did not reveal either significant insta nces of actual harm to research subjects or evidence for any widespread pattern of outright IRB failure, we must not let that be cause for complacency.

Many IRBs face unacceptably large workloads with too little time and too fe w resources to do their job properly. The fact that instances of actual harm to research subjects have been few and far between is a credit to the extraordinary dedication and prudent decision making of IRB members and the commitment of inv estigators to the integrity of their work.

In the wake of the June 1998 reports by the inspector general, OPRR and FDA stepped up the pace of their inspections. Taken together, their findings reinfo rced the conclusion that the IRB system is under considerable strain. Moreover, for several institutions the OPRR and FDA inspections led to partial or complete suspension of clinical research at those sites until the institutions' deficien cies were corrected, often only after major revamping of the IRB structure and c ommitment of substantial additional resources by the research institution. These examples make clear that we must intensify our work to strengthen human subject s' protection before more and more serious failures ensue.

An imminent organizational change within HHS will do much to facilitate our intensified efforts. Last year, acting on the results of the study commissioned by the director of the National Institutes of Health, Secretary Shalala determi ned that the human subjects component of the OPRR should be elevated to the Offi ce of Public Health and Science within the Office of the Secretary. Further, the secretary directed the assistant secretary for Health to carry out a national s earch to fill the position and to assess the resource requirements for the new o ffice, to be called the Office of Human Research Protection. Further, she author ized the creation of a public advisory committee to help guide the new office sp ecifically and the department overall.

We agree with the inspector general that the creation of the Office of Huma

n Research Protection and its associated advisory committee presents "a new oppo rtunity to exert federal leadership in protecting human research subjects."

At the same time, we urge research institutions to strengthen their local e fforts to protect human research subjects in accord with the inspector general's recommendations. In particular, we urge research institutions to give their IRB s the standing and resources they need to do their job, especially during the co ntinuing review phase.

Human subjects protection is a shared responsibility among the federal gove rnment, research institutions, IRBs, investigators and sponsors. HHS is committe d to doing its part, and we will continue to expect others to do theirs.

My full statement describes the series of actions by HHS agencies in recent years to enhance protection of human research subjects. We view these steps as a strong beginning but concur with the inspector general that much more remains to be done.

With your permission, Mr. Chairman, I will submit my full statement for the record.

REP. MICA: Without objection, so ordered.

DR. RAUB: On behalf of Secretary Shalala and my senior HHS colleagues, I as sure the subcommittee that HHS is firmly committed to protecting human research subjects and to working actively with the research community to achieve that end . We believe that the inspector general has provided a timely wake-up call for e veryone involved. Thank you, Mr. Chairman.

REP. MICA: Thank you for your testimony.

I'm pleased now to recognize the gentleman from Maryland, Mr. Cummings, for his opening statement.

REP. ELIJAH CUMMINGS (D-MD): Thank you very much, Mr. Chairman.

Conducting safe clinical trials of breakthrough medicines and treatments ar e critical if we are to win the war against disease and physical ailment. I can think of nothing more noble than putting your life on the line for the good of h umanity. Our soldiers do it on the battlefield, and human research subjects do i t in the hospitals. While both groups put their lives in danger, we must do ever ything we can to minimize the risk.

Today we are here to discuss what can be done to ensure the highest level o f safety possible for those who consent to enroll in clinical trials.

The death last September of Jesse Gelfinger and subsequent revelations of t hree other deaths in a gene therapy experiment last year, sponsored by Harvard m edical school, has raised serious questions about care and oversight procedures. Jesse's father, Paul, told a Senate panel earlier this year that researcher s did not disclose that laboratory monkeys died following a procedure similar to the one done on his son or that several earlier human subjects sustained seriou s liver damage.

After the boy's death, the National Institutes of Health sent letters to re searchers, reminding them that they must report serious adverse events to the NI H and the Food and Drug Administration. NIH subsequently received a flood of fil ings disclosing nearly 700 previously unreported incidents of problems arising f rom gene therapy experiments.

I think this is simply unacceptable. Seven hundred unreported incidents put s too many lives at risk. We must do better, and we will. Something is failing i f 700 incidents were unreported. If a real estate company withheld that many pro blems with their properties, they would be out of business.

Today we will hear from those who carry out the mission of oversight at the Department of Health and Human Services and the Food and Drug Administration. I 'm eager to hear how they plan to address these oversight problems. And, Mr. Cha irman, again, I thank you for holding this hearing.

REP. MICA: Thank you, Mr. Cummings.

Mr. Cummings also moves that the statement by Mr. Waxman, the ranking membe r of the full committee, be submitted for the record. Without objection, so orde red.

And I believe we just had those two witnesses who had statements at this ti me; is that correct? And the others are available for answering questions.

Well, we're start with some questions that I have, and I'm going to address these first to Mr. Grob, deputy inspector general for Evaluation and Inspection I guess sort of a basic question to start out with is, what do you consider to be the reasons for HHS' failure to implement that 1998 recommendation?

MR. GROB: I think Mr. Raub could probably address it better than I can, but I'm willing to speculate.

REP. MICA: Well, you did a review here. Maybe you can tell the

subcommittee what the basic problems are, one, two three.

MR. GROB: I think the basic problems are that the institutional review boar ds are simply overwhelmed, and they're not able to carry out their responsibilit ies, particularly the oversight of research that is ongoing. I think once the re search starts, they don't have the ability to stay on top of it; and I think tha t the problems occur at that level.

REP. MICA: We heard a description of this human research, and some of these activities started off in fairly isolated context, and numbers of universities or whoever was doing it, and it's exploded.

It sounds like it's difficult for the department to get its hands around it , and then we have several agencies involved here, but we have the element of re sponsibility to the public.

I may be jumping the gun a little bit, but maybe we should look at restruct uring this whole thing or some other procedure to, gain, keep up with the sheer volume that you described.

Do you have an opinion about that?

MR. GROB: I think it's time to think in those terms. I don't know that marg inal changes around the edges will really be able to do it.

I think the fundamental structure was a good idea, and it worked when it st arted, and it worked for a while. But I just think the research took off, it bec ame far more complicated; and in a way, it's almost as if the IRBs, figuratively , were still using manual typewriters trying to keep up with the power notebooks for the research.

It's just something that--it's a different world today, and I don't think t hat system has kept pace with the world. So I think it's a fair thing to say tha t we might need to look at different structures.

REP. MICA: A complete reorganization of the approach.

What about HHS? Is this a priority on their scale? The other thing too is C ongress has also raised questions about what's going on in the oversight as we v iew agency responsibility. It appears that there's been minor action and a lot o f inaction. I believe too we had testimony that many things could be done withou t a lot of cost, some improvements without a great deal of cost.

Maybe you could tell me, first, does this appear to be a priority, have the y gotten their attention, and then why haven't they instituted some things that were basic that could be done without a great deal of cost?

MR. GROB: It's my feeling right now that certainly there's an intense effor t being made in the department to address these things-- the problems that have been raised. I think the publicity of the troubling cases and just a general des ire to do it right, the congressional hearings, the interest of the science in t he department are all there; it's all coming to a head. I think the interest is there now, and I do expect to see some substantial changes coming down the pike. As far as things that can be done fairly quickly, I think training and educ ation could be done pretty well and fairly quickly. The National Institutes for Health, for example, on their own have developed training which they require the ir researchers to follow. They've put it up on the web. They've got some trainin g courses that they've made available. What's lacking is a requirement for the t raining and requirement for any particular standards of training. But the resour ces seem to be there.

If they require all of their researchers, as they do, for example, take the course that's on the web, it seems to me that all of the grantees could take th at course on the web as well and to avail themselves of the resources.

So I think that education and training of the researchers and of board memb ers could be done pretty fast if there were a requirement to do it.

REP. MICA: In '98, you came out with a list of specific recommendations for improvement. Has HHS developed a schedule or time frame or given you any implem entation schedule?

MR. GROB: I haven't seen a time schedule like that that went recommendation by recommendation with a time schedule.

REP. MICA: Let me just ask you a quick question now.

Of course, every agency comes to members of Congress, and they always say j ust give me more resources, and we can handle our job. But we had recommendation s that had been made that folks testified to that could be implemented with fair ly low cost and things that could be done to improve oversight, operation and fu nction.

I have two questions for Mr. Raub. One, what's the status of those low-cost things that could be done within budget? And then secondly, you have already su bmitted your '00-01 budget. What kind of requests for additional resources or pe rsonnel were included in the secretary's request?

DR. RAUB: Thank you, Mr. Chairman.

With respect to the overall question, we've taken the recommendations of th e inspector general to heart and have, in fact, undertaken some substantial

effo rts. As I indicate in my prepared statement, we think that, while substantial, t hey're nowhere near enough, and we will continue to intensify that effort.

Among the things we've done within the available resources are the followin g. I indicated the stepped-up investigations and inspections both by the OPRR an d the FDA.

REP. MICA: That's what was referred to from 1 to 10?

DR. RAUB: Well, it's a lot more than that. My opening statement was, of cou rse, within the five minutes. But there have been increases in the number of non on-site reviews that the NIH has made, and FDA has made about a 50 percent incr ease in the number of site visits.

REP. MICA: Is that adequate?

DR. RAUB: No, we need more.

REP. MICA: So those are some things you started. I'm sorry, Mr. Raub, conti nue.

DR. RAUB: And along that line, just continuing Mr. Grob's thought there, wh ile the returns on those investigations have been disappointing in the sense of identifying some widespread pattern of problems and have led to enforcement acti ons, those enforcement actions have a secondary effect in the sense of promoting compliance elsewhere, indicated by the inspector general as a sentinel effect. So we believe that the expenditure of those funds dealing with individual p roblems has, in fact, had a positive effect in terms of making the larger commun ity sensitive to the need for more attention and more investment of resources in these activities.

REP. MICA: When we had the hearing last time, was there one instance of sus pension reported, one or two? Since that time, what's the status? Usually enforc ement would indicate that there's some penalty or there's some suspension of fun ds taken place. What's taken place in that regard?

DR. RAUB: I'll comment generally, and then if I might ask Dr. Ellis and Mr. Michels if they want to add some detail to it.

But, in essence, the thrust of the suspensions is not only to stop the acti vity and put an immediate protection in place, but more important, to require ce rtain remedial actions on the part of the institutions to ensure that the proble ms are solved and the protections are in place. And that's been a pattern on the se various one.

REP. MICA: But my question dealt with have there been any suspension of fun ds since the last hearing or penalty of actions? Remedial actions are fine, but I want to see--usually if somebody gets a penalty, then it does have an effect d own the line on others to sort of straighten up their act.

DR. RAUB: Let me ask my colleagues to address that.

REP. MICA: Identify yourself for the record, please.

DR. GARY ELLIS: My name is Gary Ellis, director of the Office for Protectio n From Research Risks and chairman of the Interagency Human Subjects Committee. For research that is funded by the Department of Health and Human Services, the ultimate penalty is a cessation of funding for future research.

REP. MICA: And my question was, have there been any since the last time? Now, what we've discovered is there are more problems that we anticipated. We just heard the inspector general talk about finding a pattern of problems far in excess of what, I think, we even expected. And then we've heard that we were taking some enforcement actions; that was part of the corrective pattern.

My question is, what type of enforcement action?

DR. ELLIS: Well, since the June 1998 hearing and the inspector general repo rt, OPRR has evaluated the protection of human subjects at a couple dozen instit utions. There have probably been about 10 site visits during that period. In vir tually every case we've made findings of shortcomings with regard to the human s ubject regulations and required remedial action.

In a few noteworthy cases at the Duke University Medical Center in May 1999 , and just a small number of other institutions, we've actually ordered an inter ruption research. At Virginia Commonwealth University in January 2000, as with D uke, we ordered an interruption research. These are extreme cases and an extreme action was taken, the interruption research.

REP. MICA: So in two cases?

DR. ELLIS: There were other cases where we imposed restrictions, but we did n't have the suspension that you note? The Food and Drug Administration took an action at-- REP. MICA: Was it the suspension of the program or suspension of funding or both?

DR. ELLIS: Suspension of the program. The Food and Drug Administration took action at the University of Colorado Health Sciences Center, and Dan might want to talk about that.

REP. MICA: Identify yourself for the record.

MR. DANIEL MICHELS: Yes, sir. I'm Daniel Michels, director of the Office of Enforcement at FDA.

I think you've put your finger on an important issue from the standpoint th at the action available to both our organizations is an extreme one; that is, th e authority to shut down an operation in its entirety. The threat of that most f requently causes either a voluntary shut down before we need to deal with that o r else, certainly, a great deal of willingness to do the right thing and get bac k on the right track.

One of the things that we are exploring is the possibility of asking the Co ngress for intermediate remedies that might be less than throwing the atom bomb, if you will, to deal with these situations.

REP. MICA: You don't feel that you have the authority to do that?

MR. MICHELS: That is correct in this particular instance. But I want to rei nforce--and I think that Representative made the point very eloquently. Too ofte n the IRBs are underfunded. The willingness to do the right thing is there, but they do not have the resources and support to do it. And our taking enforcement action will result hopefully in that kind of funding somewhere downstream, but w e would much rather see education happen first--do the right job the first time- -in a well-funded situation.

REP. MICA: Mr. Cummings, I have additional questions? Do you want me to yie ld to you at this time and come back for a second round? Is that okay or do you want me to proceed?

REP. CUMMINGS: No, I'll ask a few.

REP. MICA: All right. I'll recognize Mr. Cummings, and I do have an additio nal round of questions.

REP. CUMMINGS: I was just wondering, just following up on what the chairman just asked about, what kind of sanctions would you like to see, would you like to have the authority to use?

MR. MICHELS: Unfortunately, the thinking is a little bit early on this. One of the things that we've thought about is civil money penalties. But again, fin ding an organization which is poor already doesn't seem to be a very good option . If we could find something more prescriptive, that is, more targeted, to the p articular problem that an institution has, rather than simply shutting down the whole engine, we would be possibly better off than we are now.

But that's the be st I can do for you at the moment.

REP. CUMMINGS: Why would an organization, when threatened with a shut down, voluntarily shut down as opposed to, say, straightening up the matter. I know y ou said sometimes they do, but sometimes they just go on and shut down. What kin d of situations would cause that?

MR. MICHELS: Well, the recognition that something major needs to happen. An d rather than having the terms dictated, if you will, by the regulatory agency, they see the light and say, okay. Before that letter of shut down is received, " here's our plan; this is what we're going to do. In the meantime, we're going to suspend some or all of our operation as a signal of good faith."

As a regulator, I wouldn't be necessarily too thrilled to see somebody make some offers without doing something immediate and protecting those folks that a re at risk.

REP. CUMMINGS: Right.

Mr. Ellis, in 1998 I think you told the subcommittee that your office was p ursuing about 70 opening investigations.

DR. ELLIS: That's correct, sir.

REP. CUMMINGS: How many of those cases have been closed?

DR. ELLIS: That's something I'd have to get back to you on. A large number remain open. Today we actually have 163 open investigations.

REP. CUMMINGS: So in two years the number of open investigations have more than doubled?

DR. ELLIS: That's correct. Some of the 70 to which you refer have closed, b ut many more have opened since then.

REP. CUMMINGS: Why do you think that is? I mean, that's a lot of cases. I m ean, when you look at 70, some have been close and now you're up to 163. Why is that?

DR. ELLIS: We are receiving more complaints. The issue of protecting of hum an subjects and research has been featured in the press. Our complaints come fro m citizens. They come from research institutions themselves, from employees at r esearch institutions that see things they don't like, in some cases from human s ubjects who feel that they have been wronged or harmed in some way.

Our office was not all that prominent, perhaps hard to find, and now it's e asier to find for complainants. That's my best explanation.

REP. CUMMINGS: How many employees do you have doing the investigations on a nimal and human subject research?

DR. ELLIS: Our office was recently split, so the animal welfare staff are n ow in a different office. But with regard to human subject investigations, we ha ve two full-time equivalent investigators; actually, a full-time physician, a ha lf-time physician and a half-time attorney handling 163 cases.

REP. CUMMINGS: And how many do you think you need to do an adequate job? DR. ELLIS: One could work through the arithmetic of what a serious caseload would be for a high-level professional. The Public Health Service Act requires what they call a "prompt resolution" of the cases. We could work out the arithme tic. If we took "prompt" to mean six months, let's say, how many cases an indivi dual can move and get six months closure--something I could calculate for you. REP. CUMMINGS: That's okay.

Is there a statutory requirement to report adverse events to your office? DR. ELLIS: There's a regulatory requirement that pertains to research funds that are conducted by 17 departments and agencies that's been in place for year s. Institutions must report unanticipated problems involving risks to subjects o thers. That's one kind of report. A second kind of report is any suspension or t ermination of institutional review board approval. And the third type of report is any serious deviation or noncompliance with the regulation. The answer's yes. REP. CUMMINGS: And those reports that you just talked about, do you know ho w many you've received over the last year?

DR. ELLIS: In 1999, we received 187 reports of that type from I think about 87 institutions.

REP. CUMMINGS: Mr. Raub, back in December, Dr. Art Lawrence testified befor e us in a hearing we held in New York; and at that time, Dr. Lawrence assured us that the Office of Protection from Research Risks would be moved to the Office of the Secretary, and a new director would be selected by March 2000.

It's now May. Can you tell us where we are on that?

DR. RAUB: Yes, sir. The department is close to completing those actions, bu t it has taken somewhat longer than the original estimates. I am hopeful, as is Assistant Secretary Satcher, that the appointment of a director for the new offi ce of Human Research Protections is imminent we hope in the next few weeks or at least the announcement of that appointment. And with that

then, the formalizati on of the move of the office from NIH to the Office of the Secretary and the est ablishment of the new advisory committee.

REP. CUMMINGS: Well, while in New York, Dr. Lawrence also testified, and he even introduced a letter from Dr. Satcher, which said that the advisory panel w ould be created, which would be responsible for human subject research protectio n.

Is that the advisory panel you were just talking about?

DR. RAUB: Yes, it is.

REP. CUMMINGS: And how do you see that as helping this problem, the appoint ment of that panel?

DR. RAUB: Well, first of all, we see the relocation of the office as giving it the higher visibility in terms of the Office of the Secretary and an undersc oring of the secretary's commitment to this.

Second, as part of the move, the secretary directed Assistant Secretary Sat cher to commission a study of resources along the lines of the question that you were just addressing to Mr. Ellis. And that study--as I understand it is either complete or near so--will be an important factor in the future budgeting decisi ons for this office.

The advisory committee is intended to ensure that we have a public, high-le vel and highly qualified group of individuals--Ron Brodlee (sp)--from the resear ch community and the interested general public who can provide a continuing foru m of advice and criticism for the department as we move to set priorities and do what we can to ensure that these human subjects protections are in place.

We have not had that kind of forum before in the department, and we think i t's much needed; and I'm optimistic as to what it will be able to provide for us .

REP. CUMMINGS: Now, right now you have to go through part of the processes that you use the Federal Register?

DR. RAUB: For what, sir?

REP. CUMMINGS: For the advisory panel.

DR. RAUB: The advisory panel will be created under the terms of the Federal Advisory Committee Act, and those actions have been taken in terms of securing the necessary slot and authorization to do it. Most likely

what we will do is an nounce in the Federal Register the functions and other expectations for the comm ittee, and as we do with many other advisory groups, invite nominations of membe rs from interested members of the public; and then put together a recommended sl ate or alternative slate for consideration by Dr. Satcher and the secretary.

REP. CUMMINGS: Thank you.

REP. MICA: Thank you, Mr. Cummings.

I didn't get the answer when I yielded to Mr. Cummings of the second part o f my question-- the number of personnel that have been requested in '00-01? Agai n, we've identified that there's the problem that some of the answer is more per sonnel and more resources.

Can you tell me the request for additional slots?

DR. RAUB: Sir, I don't have those figures with me, but I'd be pleased--
REP. MICA: Does anybody have them?

DR. RAUB: I'd be pleased to provide them for the record.

REP. MICA: Mr. Ellis, do you? You said you could calculate. You know, this isn't something that just snuck up on us today; it's a problem we've known about , and one of the ways that we resolve is by applying the necessary resources, pu tting the request through the process.

And nobody knows what we have requested? Maybe somebody could slip somebody a paper with a magic number on it? No?

And you don't have a recommendation to the subcommittee about what kind of resources it would take?

DR. RAUB: Again, I don't have the budget figures with me. I'd be glad to pr ovide them for the record, sir.

REP. MICA: Mr. Grob described a situation that, again, it seems to be a thi ng out of control-- the sheer number where there are federal dollars involved in this human experimentation and money going into that within this large universe outside of commercial activity. I think you spoke to some of that.

What are we looking at as far as percentages in each of these areas of expe rimentation, federally funded and non-federally funded? Would you care to ventur e a guess, Mr. Grob?

MR. GROB: I don't know about the exact numbers. Certainly, we're talking

ab out billions of dollars in both cases. An easy way to think of it is, most of th e commercially funded research that we're talking of in here would be that that' s connected with the proposed drugs, medical devices that are overseen by the Fo od and Drug Administration. So their entire workload of oversight would be the c ommercially funded; whereas, the National Institutes of Health would be those th at are funded by our department. Now, of course, there's these other departments that also fund on the federal level their research.

So I'd say it's billions and billions but what the exact amounts are, I can 't tell you.

MR. YESSIAN: Mr. Chairman, I would add that some of the major medical--my n ame is Mark Yessian, and I'm the regional inspector general.

At some of the major medical centers that we visited and talked to, about h alf the applications that the IRBs are getting are coming from commercial sponso rs these days, so that helps put it in a little perspective.

REP. MICA: Another question that was raised at the last hearing and continu es to be a concern is the problem now with commercial activities and other inter ests in this whole operation-- the conflict of interest. I think there was a rec ent Los Angeles Times article that alleged the U.S. government's top diabetes re searcher help guide $150-million federal study involving Resolin while serving a s a paid consultant for the drug manufacturer, which is the Warner-Lambert compa ny.

What's the federal government's policy regarding outside employment and con flicts of interest, Mr. Raub?

DR. RAUB: There are several elements to that. First off, the changes in the nature and the patterns of financial relationship are one of those changing ele ments that Mr. Grob and his colleagues had mentioned. It's a quite different sit uation then say 20 years ago.

A major impetus for that have been some statutory changes designed to promo te the commercialization of publicly-funded research. And for the many highly de sirable results of that, it has created a pattern of relationships where not onl y do some of the universities and academic health centers, for example, receive a substantial amount of funding from the private sector--some on the order of ha ve as Mr. Yessian indicates--we also have instances where some of the university professors also have either stock holdings or even serve as corporate officials for some of the private organizations, some of which may be sponsoring the rese arch.

A major element already in place related to that is a public health service

regulation that requires all of the entities funded by the agencies of the publ ic health service--that is the universities and other recipients of awards--to h ave in place a policy and a system to identify actual or apparent conflicts of i nterest that might affect the scientist's participation and to take such steps t hat are necessary to manage those conflicts, in some instances removing the conf lict, in others putting certain safeguards in place.

One of the areas where we will be intensifying our effort is trying to find ways to ensure that as those procedures relate to human subjects protection, so me of the kinds of safeguards we have in place will be those against both the po tential coercion of subjects in research as well as guarding against things that would create less than full objectivity in the way experiments are designed, pa tients are recruited or results are presented. This will be a continuing challen ge for the entire research community.

REP. MICA: Is it necessary for additional legislation, corrective legislati on, to deal with a new set of emerging conflicts and circumstances?

DR. RAUB: In my judgment, sir, no. The public health service regulation to which I referred and a companion regulation that the Food and Drug Administration has dealing with reporting of financial confli cts of interest give us a considerable set of tools to use here. I believe the t ask will be building on those tools and using them more effectively. I'm sure th e department won't hesitate to propose legislation if it concludes that's necess ary, but we don't think so now.

REP. MICA: I don't want to pick anybody out, but in this case I just cited, this individual served as a paid consultant to the drug manufacturer, and it wa s, I believe, a Dr. Eastman who had this employment as a consultant. And it appe ars to be a conflict of interest.

Do you know if you all investigated this particular arrangement to see if t here was a conflict of interest?

DR. RAUB: I don't know the full details, sir. I know that an investigation was carried out at the NIH. I don't know that it is completed, and we can provid e a report for that to the subcommittee.

REP. MICA: Well, I'd like to know because if you feel that we don't need ad ditional laws and you have at least the authority to proceed, we want to make ce rtain that there is some attention to the problem of a conflict of interest that has been raised to us.

I have other cases here, and I won't be able to get into all of them. And w e could submit some of them for questions to you. But it appears that some of th e problems we've had--now, conflict of interest is one thing; maybe we

picked th at up through the media. But we're also--and I think you all have testified that you're picking up problems that have resulted sometimes even in death in these experimentation cases where there hasn't been--and I think we're going to have w itnesses--the full disclosure about oversight, about the proper functioning of t he review process, which is a big concern to us.

We have an agency. And maybe it is short on some resources, but, in fact, w e are told that it is somewhat dysfunctional and even no- cost or low-cost recom mendations have not been instituted. So I have to cite these as major concerns o f the committee.

And then we have another area now, this growing area of a commercial activi ty. And we don't have the handle because we don't have the federal funds into th e activity, and FDA has some responsibility, but there's some instances here in which there appear to be a gap, which is another problem.

Did you want to comment on that briefly, Mr. Grob?

MR. GROB: We don't know the extent of that, but it's probably small but gro wing where there is research that's going on that's not connected with any propo sal for federal approval of a drug or device that is simply being done by a rese archer there and are not the result of a federal grant. And in those cases there are no requirements for institutional review boards or for some of these other protections. Just simply good practice would call for it. But the extent to whic h it's happening and type of controls over that are just sort of an area that's just not well known or understood at this time.

REP. MICA: What's interesting too is there's so many new research technique s and biogenetic--I mean, they just go on and on about things that are happening almost on a daily basis that the law is not keeping up with. I'm wondering if w e really need to take a closer look at some of these gaps and, again, have in pl ace some mechanism to deal with this in the future.

Mr. Michels.

MR. MICHELS: Yes, sir. Thank you, Mr. Chairman.

I just wanted to clarify that the Food and Drug Administration is working i n the area of, if you will, noncommercial research from the standpoint that ther e are requirements from time to time, notwithstanding to market the product, if it is being used as an experimental agent on people, it should be covered by an investigational application.

I think what is maybe troublesome to some folks is the zone in between, whe re a clinical investigator may also be the entrepreneur who is intending to ulti mately develop the product for him or herself, rather than working as an

employe e or agent for a major pharmaceutical house, for example.

The roles have become very blurred here, and we also are puzzling over wher e we need to be drawing the line. I would suggest, again, we go back to the prin ciple that was laid out very early in your hearing today. And that is, we need t o be educating all of the scientists--be they clinical investigators, the resear chers, the IRBS--as to what the requirements are. Minimize their impact so that the right decisions are made on behalf of the subjects being exposed.

REP. MICA: Thank you.

I'm not going to give you an opportunity to respond because we have a vote out and less than four minutes to get to the floor. I'm going to excuse the pane l. We're going to submit some specific questions on cases, Mr. Ellis.

But I tell you, Mr. Raub, we've got to do something to get into place some of these recommendations. Mr. Cummings discussed some of the foot-dragging and s ome of the things in simple appointments, getting people in place, making low-co st or no-cost recommendations. We have got to do something.

If necessary, I'll hold another hearing and call everybody back, and we'll subpoena the secretary, if we have to, to get something moving in this area.

But without objection, we will submit to you further questions and ask for your written response.

We'll stand in recess for approximately 15 minutes until the conclusion of the next vote.

(Recess.) REP. MICA: I'd like to call the subcommittee back to order.

I want to go ahead and proceed. We have our second panel before us at this point. Unfortunately, there may be a vote in the full committee. There's been a full committee hearing going on while we're conducting this subcommittee hearing , and we may need to recess at some point if a vote is called in that body.

Our second panel today consists of Mr. Richard Curtin, and he, I believe, w as a human subject in one of these research experiments. We also have Charles R. McCarthy, and he is a senior research fellow at the Kennedy Institute of Ethics at Georgetown University. And then we also have Dr. Robert Amdur, and Dr. Amdur is the associate professor and associate chair of Clinical Affairs at the Depar tment of Radiology and Oncology at the University of Florida. I get to see someo ne from my alma mata here. If we

could just get a president now, we'd be in good shape. That's an inside matter.

I'd like to welcome all three of our panelists this afternoon.

Let me go ahead and explain the ground rules. I think you're all new witnes ses. We do swear in our witnesses. This is an investigation; it's an oversight s ubcommittee of Congress. I'll swear you in in just a minute.

I'm going to ask you to limit your oral testimony to five minutes, and then upon request we'll put in any full statements or additional information in the record deemed appropriate upon request through the chair.

With that, I will swear you in. If you'd stand, please. Raise your right ha nd.

Do you solemnly swear that the testimony you're about to give before this s ubcommittee of Congress is the whole truth, and nothing but the truth?

WITNESSES: I do.

REP. MICA: Witnesses answered in the affirmative. I welcome the witnesses, and I think we'll call on Richard Curtin, who was involved in one of these resea rch projects. He's from Fall Church, Virginia.

Welcome, sir; and you're recognized.

MR. RICHARD CURTIN: Thank you, sir.

I'd like to thank this subcommittee for inviting me to appear today, but I have to admit that I'm surprised to find myself in the position where I'm being so critical of genetic research.

I have a masters degree in human genetics. And 25 years ago, I was working with the director of NIH in an effort to convince the Congress to go ahead with funding for cutting-edge DNA research.

By September of 1998, I was introduced to a different aspect of genetics re search when my daughter, Alison (sp), received a Virginia twin study sponsored b y Virginia Commonwealth University. The study consisted of a 25-page questionnai re asking hundreds of questions about a person's medical history. When I looked through the questionnaire, I was surprised to find that 176 of these questions i nvolved not only my daughter's medical history but also the medical history of h er mother, her brother and me. In other words, she was being asked to comment up on the medical history for the entire family.

I was further shocked by the bizarre nature of some of these questions. For example, the study asked if any of us had suffered from depression, infertility , alcoholism or schizophrenia. It asked if Alison's brother and I had abnormal g enitalia, sperm abnormalities or low sperm count. And it asked if Alison's mothe r had any diseases of the genital tract or if were menstrual periods were unusua lly long or strong.

Nowhere in the study package were the words "informed consent" ever mention ed, and this package was addressed strictly to my daughter. I was outraged that a federally funded project would attempt to violate my family's privacy in this manner.

I immediately wrote to the principal investigator of this study and also to the chairman of the institutional review board. All I asked him to do was to re move the columns for the other family members and to send separate questionnaire s to each of us. I realized that this would have cost him more and it might have cut down on the response rate, but the database would have been more accurate, and it also would avoided the problem with informed consent.

The chairman of the institution review board, he just didn't bother to resp ond at all. The principal investigator, she responded, but her response was so d emeaning and so arrogant that it probably would have better off if she hadn't re sponded either.

It became very clear to me that the concerns I raised were not going to be addressed to my satisfaction by the people at Virginia Commonwealth, so I filed a complaint with OPRR.

OPRR concluded that the internal controls for the protection of research su bjects at the university were so inadequate that all federally funded research h ad to be shut down until proper controls could be put into place. The sum total of this action was 1,100 research projects were suspended.

With the chair's permission, I'd like to enter into the record a summary li st that I prepared listing 19 deficiencies that OPRR listed from its investigati on at Virginia Commonwealth University.

REP. MICA: Without objection, that will be made part of the record. Proceed .

MR. CURTIN: Rather than addressing the legitimacy of the deficiencies found at Virginia Commonwealth, the leadership of the genetics research community dec ided to take a different path. They went on the attack. They went after OPRR. I' m especially offended by the positions taken by two of their main leaders, Dr. E dward McCabe (sp), chairman of the Secretary's

Advisory Committee on Genetic Tes ting and Dr. Francis Collins (sp), Director of the National Human Genome Researc h Institute at NIH.

These gentlemen have argued in writing that, even within a family, once a p iece of medical information becomes known to one other person within that family , there is no longer any expectation of privacy, and there is no need for any re searcher to bother getting informed consent of the family members.

A have a little anecdote also about this time. My daughter was home for Chr istmas vacation, and she asked me if I would call the University of Virginia reg istrar to find out one of her grades. So I made the phone call, and obviously I wasn't Alison; and I explained to the registrar's office that I was her father, and they would not release the grade to me because it's a violation of her priva cy, despite the fact that she was my dependent and I was paying the tuition, the y wouldn't tell me her grade.

But the people of the Virginia twin study fully expected her to go around a nd tell the most intimate nature of medical history of not only herself, which I wouldn't mind her doing, but of every other member of her family.

I've been involved with this issue now for 20 months, and I've reached five basic conclusions. One, the public cannot rely upon individual researchers bein g geared to the rules and regulations that go along with the acceptance of feder al funding. When a research protocol does not go as planned initial reaction of the researchers seem to be, covered it up.

Number two. The public cannot rely upon institutional review boards to ensu re that guidelines are followed that experiments are scientifically and ethicall y sound. Basically, I don't believe that colleagues at the same institution can be trusted to critically review and police each other's work. If I criticize you r work today, what's going to happen when I come in front of the IRB tomorrow. Three. The statute of staffing and funding levels at the Office of Protecti on for Research Risks have been designed to ensure that OPRR will not be too eff ective. We've already gone into this and other speakers have mentioned this. And to me, it's very, very clear that OPRR has been treated as proverbial step-chil d within the NIH family.

Four. The research community, in my opinion, is in a state of denial regard ing the trouble they'vc been in. They have allowed a regulatory vacuum to exist and trust gap to develop. And now others are rushing in to fill this vacuum and to close this gap. A community strategy of stonewalling, covering up and attacki ng will not, I don't believe be successful in the long-run.

Five. From potential solutions, it's obvious that OPRR needs to be upgraded

. But you also have to be realistic, how much can a centralized office here in W ashington do when the research is so decentralized?

In my opinion, therefore, the quickest, least expensive and possibly most e ffective course of action is for each researcher to realize the violations of gu idelines and regulations will have very serious consequences. If the probability of getting caught is going to be low, then the consequence of getting caught sh ould be very severe.

One of the members asked earlier, what other penalties do we possibly have? I have a suggestion. I suggest that a principal investigator who fails to file a timely and accurate adverse event report might be suspended from the project f or one year. Allow the project to continue so that the benefits of the research aren't lost, but let it continue under someone else's leadership.

REP. MICA: Excuse me. I'm going to have to recess the hearing for approxima tely 10 minutes. We do have a vote in the other committee. We'll continue when I return.

(Recess.) REP. MICA: We'll call the subcommittee back to order. I apologize for the d elay, but all members of the full committee were summoned to get back here.

Let's see. We had Mr. Curtin who was interrupted as he had some closing rem arks, I believe.

So if you would sum up your testimony? Mr. Curtin, you're recognized.

MR. CURTIN: Yes, sir.

Just finishing up. Two possible penalties to suggest. One, as I was mention ing before, suspension of a principal investigator while his project still goes on. A second possible penalty would be making that principal investigator unable to compete for future grants or contracts for a certain period of time. Those a re just two suggestions. I don't think it's that hard to find penalties.

And that's the end. I want to thank you for the opportunity to express my c oncerns and my opinion. And I'd like to submit a more lengthy statement for the record.

REP. MICA: Without objection, your entire statement will be welcomed and in cluded as part of the record. And we did leave the record open for a period of t wo weeks. And we'll come back for questions a little bit later.

I'll now recognize Mr. Charles R. McCarthy, and he's a senior research fell ow--a most patient one--at the Kennedy Institute of Ethics at Georgetown

Univers ity.

MR. CHARLES R. MCCARTHY: Mr. Chairman, thank you. I'm honored to be able to testify before you today. I think the matters on which you're deliberating are of extraordinary importance, and I hope we can make some contribution to protect ing human subjects.

Your staff asked me to comment just on one aspect of the inspector general' s report, namely recommendations concerning utilization of data and safety monit oring boards to supplement the word or IRBs. So I focus my attention almost excl usively on that issue.

I will summarize here very quickly. I have submitted a longer statement for the record.

REP. MICA: Without objection, that entire statement will be entered in the record.

MR. MCCARTHY: And I would like to modify even that a little. Since I submit ted it, I have spent some time in the library and found references to a number o f other sources that make recommendations identical to or similar to the ones th at I'm making today. So I will add those, and if I may submit those as well?

REP. MICA: Without objection, and within the time limit that have been anno unced go ahead.

MR. MCCARTHY: As it's been noted earlier in the hearing, institutional revi ew boards were initiated by the public health service in 1966. It is not so well known that in the late '60s--and I can't give you a specific year--the National Heart Institute, now the National Heart, Lung and Blood Institute, at NIH created an additional kind of oversight body to look at very large multi-centered trials to collect and an alyze data, particularly adverse event data, in those trials. So the data and sa fety monitoring boards, while nowhere near as well known, are, indeed, almost as old and as honorable as the IRBs.

During the '70s, Dr. Robert Gordon, who was, at least for a time, the direc tor of the Clinical Center at NIH and Dr. Curtis Menard (sp) from Johns Hopkins University spent a great deal of time refining and defining the work of data and safety monitoring boards.

And as the funding patterns for NIH grants changed from single grants that were made to single investigators in a single institution to multi-centered tria ls where there might be anywhere from 5 to 50 or even 100 different centers carr ying out the same kind of protocol.

The data and safety monitoring board has become the instrument most sensiti ve to being able to receive adverse event data and other information about the t rial from all of the sources, evaluate those adverse events and other informatio n with the help of professional statisticians; and thus, to get an overview of t he trial that is literally impossible to get at any single center or any single institution.

So we're faced with something of an anomaly, that the data and safety monit oring boards that are not required by regulation and exist in perhaps something less than half of the multi-centered trials that are conducted in the country, a re the bodies that have the best information and the most careful analysis of th e data. But the IRBs are the ones who, according to regulation, have the obligat ion of passing on whether the trial should be stopped, modified or continued. And consequently, we have the knowledge in one committee, and we have the r esponsibility in another committee; and at least it seems to me that we can make a very constructive kind of change in the regulations so that the data and safe ty monitoring boards communicate their data back to the IRBs. And that will, one , take some work off the IRBs and address the workload problem in the inspector general's report, and secondly, it will improve the quality of the information o n which the IRB makes its decision to continue, modify or discontinue.

So it seems to me that the time has come, and all of the kinds of incidents you've addressed today in your hearing seem to me to indicate this is the time to start afresh, modify the regulations so that the data in data and safety moni toring boards can be made available to the IRBs, and the best possible decisions concerning the continuation and oversight of trials can be made.

Typically, as we already heard testified earlier from the inspector general , the IRBs receive data, but it is raw data. They don't know which arm of the st udy the adverse event occurred on. They don't know whether it was in an elderly subject or a young subject.

They don't want the complications of disease of the subject were that accom panied the adverse event. And consequently, they cannot tell whether it was caus ed by the research, by the underlying disease condition or by some inherent cond ition that pertains to the subject himself or herself.

Data and safety monitoring boards break out the data in a number of differe nt ways, according to age, gender, race, ethnicity and a whole variety of other topics so that they can evaluate those adverse events, tell which ones are very serious, which ones are likely to associated with the research intervention, whi ch might have occurred anyway because of underling disease conditions; and thus, they are able to give the kind of analysis that will refine the judgments about the quality of the research and whether it

should continue.

So my recommendation to you and to the rest of the committee today is simpl y that, one of the ways the inspector general's report could be used or it could be capitalized upon would be simply to examine the regulations and put some kin d of a link, regulatory link, requiring data and safety monitoring boards under certain conditions; and secondly, making sure that the data that they gather and analyze is carefully and thoroughly shared with the IRBs, so the IRBs then can carry out with less work and with greater accuracy the responsibilities that are assigned to them.

This will not, in my judgment, decrease costs because the data and safety m onitoring boards have full-time statisticians working for them. They have expert s. I was at a data and safety monitoring board meeting yesterday. There was an e xpert from Germany, one from England, three from the United States and myself. Obviously, to have a meeting of that kind is very costly. They generated on one study about 300 pages of data, and we spent the best part of the day evalua ting that data to determine whether the study should go on. That's a very costly process, but I can assure you that the subjects in that study received the very best safety efforts that are humanly possible. I cannot guarantee mistakes will not be made, but I think when the data is processed in that way, the chances of mistakes become exceedingly small. And I think that's what we owe to our resear ch subjects, even though the costs may be raised.

On the other hand, the cost to the local IRBs will be reduced because their workload of analyzing large quantities of adverse data will already be done for them by statistical experts, and they will be able to make a much more enlighte ned decision as to the research in their institution.

And I'll be glad, Mr. Chairman, to answer any questions that you may have c oncerning this issue or any others.

REP. MICA: Thank you. And what we'll do is suspend questioning until we've heard from our final witness--he's also very patient--Dr. Robert Amdur, and he i s an associate professor and associate chair of Clinical Affairs, the Department of Radiology and Oncology at the Universit y of Florida.

Welcome, and you're recognized, sir.

DR. ROBERT AMDUR: Thank you. Good afternoon, Mr. Chairman and other committ ee members.

As you mentioned, my name is Robert Amdur. I'm a physician at the Universit y of Florida. My qualifications to speak to you today about the

protection of hu man research subjects are that I am a medical researcher who frequently enrolls patients in research studies, and for the past 10 years I've played a leadership role in defining and implementing ethical standards for research through my par ticipation in the institutional review board and related national organizations. I'm here today representing a national nonprofit organization called PRIMR, which stands for Public Responsibility in Medicine and Research. For over 25 ye ars, the primary mission of PRIMR has been to bring researchers, ethicists and r esearch regulators together to improve our system for protecting the rights and welfare of human research subjects.

Since 1974, PRIMR has sponsored over 100 educational conferences, published hundreds of documents, set up on-site workshops for institutions with special n eeds and many other important activities that meaningfully improve the way resea rch is done in this country.

I've submitted a written statement which goes into detail about the challen ges that currently stress our system of protecting human research subjects and P RIMR's plans for helping the research community respond to these challenges.

At this time I'd like formally request that a written copy of my testimony be included for the record.

REP. MICA: Without objection, so ordered. Proceed.

DR. AMDUR: In the next few minutes, I'd like to emphasize three requests th at I hope you will focus on as you decide on new federal initiatives related to research protections.

Request number one is to pass federal legislation that requires that all re search in the United States comply with the same high level of ethical standards regardless of funding source. The ethical standards that should be met when con ducting research involving human subjects are described in the Department of Hea lth and Human Services regulations that are often referred to as the "common rul e."

A problem with our current situation is that the authority of the common ru le does not extend to some situations where research is sponsored by private ind ustry. It makes no sense to have different ethical standards for research depend ing on funding source. All Americans should be afforded the same high level of p rotection of oversight. Medical progress will not be compromised by a more compr ehensive regulatory structure, and PRIMR urges you to support legislation that e liminates the two-class system of research protection that we currently have in this country.

Request number two is to pass legislation that consolidates the multiple di fferent sets of federal research regulations that currently exist into a single regulatory reference.

The Department of Health and Human Services currently has one set of regula tions, the FDA has another, the Department of Education has its own rules, and s o on.

In many cases, the regulations from these different federal agencies are co ngruent but in other situations they're not and in still others it's unclear wha t they are. As a result, researchers, industrial sponsors, IRB members, institut ional officials spend a tremendous amount of time and energy trying to figure ou t what hoops to jump through when different federal agencies are involved as is the common situation in both industry-sponsored and federally-funded research st udies.

The situation is ridiculous. There's no reason that we should not have a si ngle set of regulations that applies to all research involving human subjects re gardless of the federal agency that is involved or the funding source.

Request number three is to ask you to support PRIMR's efforts to create a f ormal program for accrediting each institution's system for protecting human res earch subjects. Protecting human subjects requires much more than an accounting type of checklist or audit of IRB paperwork.

It requires on-site evaluation by trained professionals of objective and su bjective endpoints, such as the level of institutional support for the IRB, the knowledge of research investigators about ethical standards, the commitment of i nstitutional officials to shielding research regulators from financial conflicts of interest and other pressures, and eventually to documenting objective endpoi nts of ethical behavior, such as the quality of informed consent for the subject s that have been enrolled in research studies.

To a set up a system for accrediting an institutional program for protectin g research subjects, PRIMR has recently formed an affiliated, not-for-profit cor poration called the Association for the Accreditation of Human Research Protecti on Programs. The acronym for this is AHRP.

The current plan is to make the AHRP accreditation program voluntary, and w e believe that most institutions will actively seek AHRP accreditation as a way of improving the integrity of their research programs. Time does not permit me t o describe the details of the AHRP accreditation process; this information is pr ovided in my written statement, and I'm happy to explain anything related to thi s in the questions session.

I'd like to conclude my remarks by reminding you that this is not about a b

unch of paperwork that enhances the power or budget or some federal agency or a special interest group. Modern society is stuck between a rock and a hard place. We must conduct complex and often dangerous research with human subjects if we are to improve the condition of life on this planet.

There is often a tension between the ethical standards that we need to work within and scientific agenda. We can create an environment where we promote mea ningful research in a way that does not exploit in any way the rights and welfar e of research subjects, but we need the strong arm of the federal government to make this happen, and we need federal support to be applied correctly.

Our current IRB system is a good one. It is a result of the Nuremberg's war crimes trial that exposed the shameful and ethical research that was conducted by Nazi physicians in the name of medical science during World War II. Earlier t his week, the world observed Holocaust Remembrance Day in honor of those who suf fered during the awful period in human history.

In one remembered ceremony, the Nobel laureate Eli Wiesel said, "Without it s ethical dimension, civilization is vulnerable." PRIMR and many other members o f the research community hope you will act swiftly and decisively to improve the system of protecting human research subjects in this country. The AHRP accredit ation program and the other changes that I've mentioned are steps in the right d irection.

On behalf of PRIMR, I thank you for inviting me, and I'm happy to provide a ny other information that would be useful. Thank you.

REP. MICA: Thank you and each of our witnesses in this panel for your testi mony. I apologize again for the delay in the hearing, but we had floor votes, an d then we had the required participation in the committee hearing.

If I can, I'd like to proceed with some questions. First, maybe to Mr. Curt in.

You have all basically criticized some of the current functioning and opera tion of the IRBs. Mr. McCarthy didn't get into too much of that; he spoke mostly on the DSMBs. But apparently, the current system appears to be somewhat flawed. I guess if we started out maybe with informed consent. Do you think it migh t be possible to have a basic standard, a informed consent procedure that would be good for all of human research testing.

Mr. Curtin?

MR. CURTIN: That seems very bureaucratic to me, very inflexible. I would ho pe that we'd be able to rely upon individual researches and IRBs to develop the informed consent that most fits the research project that they're looking at. Ma ybe that's too theoretical and maybe it can't be done.

REP. MICA: You've had some criticism--I don't know if your daughter was aff orded informed consent. Was she?

MR. CURTIN: Absolutely not.

REP. MICA: Absolutely not.

MR. CURTIN: No.

REP. MICA: So first of all, there wasn't any in place?

MR. CURTIN: For her, it was, if she answered--but for the other family memb ers, no informed consent.

REP. MICA: But like for her, she did have informed consent?

MR. CURTIN: Yes, sure.

REP. MICA: Were you satisfied with that? Your protest goes beyond her situa tion and her giving informed consent. And I understand your concern about your p rivacy, her disclosure of your medical, but were you satisfied with the informed consent that she was provided?

MR. CURTIN: The informed consent really was if she responded to it. That wo uld be considered the informed consent. Then she would have voluntarily particip ated if she had filled out the questions, and put it in the return envelope-- REP. MICA: Well, maybe we'll step back.

First, does everybody believe that there should be a requirement for inform ed consent? We haven't talked about-- MR. CURTIN: I think there should have been a statement in the instructions saying, if you're going to answer for your other family members, you might want to tell them that-- REP. MICA: No, I haven't gotten to that point. We haven't gotten to the fam ily yet. We're talking about an individual who is going to participate or someon e who's a guardian or legally responsible for that individual, there should be a n informed consent. Everybody agrees on that?

DR. AMDUR: There are situations where it is appropriate and necessary to co nduct research without informed consent, and those situations are described and provided for in current HHS regulations. A typical example would be emergency si tuations where it is not possible to conduct research

with there being informed consent. There are other situations, such as health services research involving access to medical records, where risk is minimal and it is not possible or pract icable to conduct research with a requirement for informed consent. And the fund amental ethical standards that we use when we think about these and analyze them and say, what's appropriate, what's not, what rights and welfare are important to maintain need not be violated in certain circumstances without getting inform ed consent.

REP. MICA: Dr. Amdur, you were the one I thought that had come forward, pas s federal law or regulation and set standards. And that's what I'm trying to get at.

Now, I had sitting where Mr. McCarthy is the representative of HHS, and he said they had all the authority they needed to deal with these situations. It so unded like he didn't have any recommendations for legislative changes. And you'v e come forward and recommended-- Maybe you could elaborate on what you envision that we should be doing as a federal government, again, to provide that there's adequate informed consent in human patient testing--the operation of an IRB. Right now they can't even tell me how many IRBs there are. And then the operation of an IRB, should we be more involved in making certain there aren't conflicts of interest.

And you heard this explosion and expansion of human research and just the w hole biotech industry, genetic--all of the breakthroughs in medicine has just dr amatically exploded. We hear something new everyday. We as government don't want to stand in the way of research, but you have some basic protection that should be in place.

Now, HHS said that they have adequate authority. You're saying that we shou ld pass federal regulations or laws and set some standards. Maybe you can elabor ate.

DR. AMDUR: Well, you've made a number of points, and to go into detail abou t each one I think would be beyond the cope of this discussion-- conflict of int erest, et cetera. My response would be that the request that I listed were speci fic regulatory changes that will make this current system work better.

REP. MICA: Now, HHS has the ability to institute regulations. So it's not a matter of changing the law or is it? Are you aware of where we need to change t he law?

DR. AMDUR: I may be on mistake in terms of exactly who initiates the law -- REP. MICA: We initiate the laws. What we do is we sort of-- because these t hings have the need to be changed from time to time, we defer some of it to HHS and the agencies.

DR. AMDUR: Well, I don't know any delicate way to say this. The point is HH S could have made these changes, should have made these changes. PRIMR sponsors two national meetings a year. The IRB world knows many changes that need to be m ade to make the system work better, which is a good system; and they have not be en made because of federal bureaucratic inertia, turf wars, whatever.

So that's the reason that I'm saying to you, I don't know what the problem is.

REP. MICA: I was trying to see if you had a recommendation in a legislative context. Most of it appears to be regulatory in nature and the barrier of HHS t o institute even the recommendations your group has made, we have the same probl em. We have the IG sitting next to HHS and telling us that even basic things tha t were recommended back in '98 still haven't been instituted.

So we're looking first at the statutory and the larger picture-- our respon sibility. And we do have the oversight and investigative responsibility, which w e're conducting today through this hearing, asking, again, HHS why they aren't f ollowing through with the recommendation. There's two ways they can do that; one within existing authority or if they need additional resources to make sure the se things are in place.

Now, Mr. Curtin has talked about another issue which extends beyond the inf ormed consent, but may need some type of tweaking and our laws as far as privacy or disclosure. And that's, of course, the subject of big discussions now with t he tremendous amount of raw information that's coming out about folks. And he ra ises a certain concern--we've heard an abuse here--that we need to address throu gh regulation or through legislation.

DR. AMDUR: The IRB system failed to do what it should have done in his case ; there's no question about that. We don't need a new system, we just need the I RB at MCV to have functioned the way it should have functioned.

REP. MICA: But many of the IRBs are sort of a self-regulating, without a lo t of protections. And in earlier testimony--and we're going to submit to Dr. Ell is and some other instances. Mostly, we're reading about in media accounts, of c onflicts of interest or problems, ranging from ethical to having some self inter est and proceeding with the human testing.

Again, you're dealing with boards that are basically also have some interes t in participating and moving forward, taking federal funds for that activity as opposed to closing it down or not proceeding and not receiving the funds.

And then the other problem we have is the huge explosion of all this. There were just a few doing the testing some time ago, and now we're probably looking at thousands and thousands. But the commercial and private side where you don't have federal funds, we have some loopholes in that regard.

What about a mandatory registration of IRBs?

DR. AMDUR: We need that, and that is part of the request of extending the r egulations of the common rule to all research. The reason that you don't know--o r nobody knows--how many IRBs there are in the country is because the only recor d of an IRB is if they conduct FDA regulated research of HHS funded research; an d we need to just simply fix that problem. And I don't know that HHS can do that . I think it requires a higher level of mandate to pass a federal law. I don't k now that, but the point is we need to extend the system of protection, and part of that would be a formally certified IRB according to the common rule regulatio ns. Then we would not only know how many IRBs there are but have some common sys tem that they work under.

REP. MICA: Let me ask Mr. McCarthy. You've looked at the data safety monito ring boards. Do you feel there should be some accreditation regulation, addition al regulation mandatory?

MR. MCCARTHY: Yes, I would like to see some criteria established and requir ed to be implemented under what circumstances the data and safety monitoring boa rd should be established, what its authorities and responsibilities should be an d it's relationship to the local IRB in the centers where research over which it has oversight is being carried out.

I do not know whether that can be carried out under present legislation or whether it would require a new legislative authority, but I think it would be ve ry important and a major step forward if that could occur.

I agree with Mr. Curtin that a kind of cookie-cutter approach to informed c onsent is just what we don't need because anything that routinizes informed cons ent--as a matter of fact, makes it the same for everyone--tends to rob it of its important meaning.

And so what I would like to see done with respect to informed consent is th e department spending some money to do research in how to communicate risks and benefits associated with research. We have a whole new generation of young peopl e coming along who operate much more out of visual cues than out of written cues . And to hand people a written, fairly complex document may not actually inform them of very much; whereas a videotape of the same information might be much mor e effective.

In order to develop that kind of technology, somebody needs to sponsor some imaginative research into how to better inform subjects so that they know and c an understand the consequences of their decisions to participate or not particip ate in research.

Again, I don't know if you need a legislative mandate to carry that out or whether you simply need additional budget to carry that out, but I certainly thi nk that ought to be a major function of the new office that's being created in H HS. And if it can be done without new legislation--it certainly cannot be done w ithout additional money.

And so I would encourage that the Congress bite the bullet and provide the monies so that imaginative new ways of communicating with research subjects can be developed and employed, and so that IRBs have a range of ways of communicatin g the risks and benefits of research to their subjects in meaningful ways; and t hus, I think would respect their dignity a whole lot more than we do at the pres ent time with rather complex, long-written consent documents that may not do wha t they're intended to do.

REP. MICA: Mr. Curtin obviously had a negative experience with the OPRR pro cess, and I think he recommended some solution for correction.

Maybe you could give us those again?

MR. CURTIN: Yes, sir. Now, I did not have a negative experience with OPRR. The only thing that even could be remotely called negative about it was that it took them almost a year to get around to doing anything with my complaint.

REP. MICA: That I would interpret as a problem.

MR. CURTIN: That is, yes. But once they got on it, they were great. I mean, they kept me informed.

REP. MICA: They did?

MR. CURTIN: They did. They took some very severe action. They closed 1,100 research projects at Virginia Commonwealth-- REP. MICA: But your experience was getting attention in the beginning?

MR. CURTIN: Right. But they explained that to me right off the bat. They sa id, it's going to be a year before we can get around to doing this, and a year l ater I heard from them. I would have liked it to have been sooner, but I underst and those kinds of things.

REP. MICA: And with the IRB process, you also were critical of the

response you got there.

MR. CURTIN: From the chairman, yes.

MR. MCCARTHY: Mr. Chairman, just to fill in that story because maybe even M r. Curtin doesn't know this. But after OPRR took its action, then Virginia Commo nwealth University hired me, and I have been working about 40 or 50 hours a week since January to educate investigators about their obligations on informed cons ent and to instruct potential new members of the IRBs. So they're taking the cri ticism very seriously, and I expect that within a year they will have a system t hat will be as good as any in the country.

REP. MICA: But it did take a year to get action. What did they say; they co uldn't get to it?

MR. CURTIN: They were overworked, backlogged.

MR. MCCARTHY: As a former director of OPRR, I can say that's a perennial pr oblem. I think the office has always been understaffed and underfunded.

REP. MICA: Yes. Well, and I'm also trying to find out what their recommenda tions were to us. They have to come to Congress to ask for additional funding th rough the appropriations process. If we have a deficit there and we have a large r scope of responsibility, we need to see that that's met. Maybe these 1,100 ope rations should have been closed down after the complaint was made, not a year la ter.

Again, we're just trying to look at where the problems are and what's going wrong and then how we correct them. It's a pretty simple process, except I have to get 534 other people to agree on how to fix it.

MR. CURTIN: If I might add, sir. The IRB there, they just did not take me s eriously; it's simple as that. They thought they'd write me a letter, and I'd go away.

REP. MICA: All right. It sounds like we have at least Mr. McCarthy and Dr. Amdur's wealth of experience with us, and recommendations. You have a personal e xperience.

I think Dr. Amdur testified--I believe these are your comments. I didn't ma ke good notes on who said what. But you said consolidate sets of regulations. Yo u cited HHS, FDA, education and some standards. And my staff just gave me, the D epartment of Veterans Affairs raised the standard for protecting human research participants.

Did you mean in context, again, of protection, of some standards out of pro tections for human research participants, no matter what federal agency?

DR. AMDUR: Yes, exactly. What I meant was not an abstract thing; what I mea nt was an administrative thing, meaning that if you look in the Code of Federal Regulations at 45 CFR 46, you will see HHS regulations. If you look at 21 CFR 52 , I guess it is, you'll see FDA. And most of it, 90 percent of it, are the exact same words; they're just copied. But then in the remaining 10 percent of this s ituation, the regulations are different or they are silent on certain situations . And there are many examples of that. The Department of Defense has certain req uirements, and they sign on to the common rules.

The point is that, for example, this adverse event reporting which you've h eard so much about, this is the number one workload problem for IRBs. It is the most ridiculous thing. There are boxes and boxes coming in to the University of Florida's IRB, every week, or irrelevant reports that the IRB cannot possibly ma ke any meaningful determination of. It may be a horrible adverse event that is c ritically important, but because of the things Dr. McCarthy said, the nature of what you need--you need a data safety and monitoring board.

But the point is, the IRB should not be looking at those. Well, does the IR B need to? Do the regulations say they need to? HHS regulations say certain thin gs that can be interpreted certain ways. FDA regulations say very different thin gs that likewise are interpreted very differently.

So what I do on the IRB is sit around every week--as chair of an IRB before coming to the University of Florida--and try and say, how do we interpret this? Every year we have major discussion sessions at the national meetings. "Well, h ow do we interpret this?" And we scared to turn away these things if there's any question that we need to be stamping them because we're scared of the regulator y consequences.

So the point is, what should be done is to say, we're only going to have on e set of regulations, and it would be very simple. There are people that sit aro und--and this is all we've thought about and discussed and write papers about--t hat can suggest and hammer out revised regulations where necessary that make the m congruent, just like any revised regulatory process goes.

But the thing we need is to say, we're only going to have one set of regula tions. And it doesn't matter what agency sponsors the research. And I would say we need to extend it to it doesn't matter if it's privately funded. And I think we'd need a law for that, not a federal regulation. But the point is, we only ne ed to have one set of regulations. That's what I mean when I say

standards, regu lations that describe the standards, and say, you need to go through an IRB, you need to have informed consent under these situations, here's the form of inform ed consent-- that situation.

We need just one of those, and the common rule does need a little polishing here and there, but it's basically what we would all come up with if we spent a long time thinking of standards in and a regulatory system. It's a good system. REP. MICA: Are you aware of any formalized document or anything that's been prepared that proposes that and has language that will be acceptable to the vas t majority of those who participate?

DR. AMDUR: When you say vast majority--the people who are objecting to cons olidation of the-- REP. MICA: You're never going to get everyone to agree.

DR. AMDUR: Right. But the people who are objecting are the people in the ag encies that want to keep their own regulations.

Certainly, industry sponsors, they just want a simple one. They want to fig ure out what do I need to do; they don't care what it is. It's so much better if they can just figure out what it is.

And the International Council on Harmonization would be the closest thing t o the answer to your question in that there is now, in order to make it so that pharmaceutical companies can do business in all different countries, a body that has done exactly what you've said, which is establish we're going to have one u niform requirement; and if you want to do business within this group, we're just going to say, everybody has to comply with these regulations. We're not interes ted in your HHS or whatever. If HHS is the exact same, that's fine. All we know is, here's one set. And I think that comes very close to what you're saying.

It would not be very difficult to come up with the one set. I think what's needed is some mandate at a higher level to say, come up with one set.

REP. MICA: Mr. McCarthy, you wanted to respond?

DR. MCCARTHY: I had some years experience in OPRR, and of course we tried t o do exactly what Dr. Amdur is suggesting, to come as close as humanly possible to a single set of regulations that would apply to all research whether FDA regu lated, federally funded, and we had no authority to reach out to that which was neither FDA regulated nor federally funded. So that problem I think is one that requires some congressional action to extend the authority of these offices.

But I think the problem is more complex than you heard. Each agency has its

own authorizing legislation, and it's that authorizing legislation allows it to issue regulations, and that legislation differs dramatically from FDA to Depart ment of Defense to HHS to Department of Education. Different congressional commi ttees handle that legislation drafted and so when you try to write a common set of rules that comply with a vast variety of laws it is not a simple matter to wr ite a single rule that complies with all of the authorizing legislation of all o f the federal agencies.

We did the best we could, and I would disagree. I think between HHS and FDA the congruency is about 97 percent. What I would point out however is that FDA has authority for implementing its rules, and that means different people are do ing it and sometimes they interpret the rules a little differently. That's why I would like to see this new office become at least an HHS-wide office, and I wou ld like the new office to have enough authority so it can be the lead agency to bring the other departments and agencies that do less research but still a lot o f research in line so far as possible, given the plethora of laws that are out t here.

I think much more can be done, and so I'm agreeing with Dr. Amdur's point, but I think it is not a simple one. And this is the place where I think the Cong ress itself by placing certain kinds of constrictions or at least goals for the new office in giving it authority and money to accomplish those goals could go a long way toward accomplishing what he wants. I doubt it if it can ever be perfe ct, but we can do lots better.

REP. MICA: Dr. Amdur wanted to respond?

DR. AMDUR: You know, Dr. McCarthy has worked in the government too long bec ause now he's making excuses for it. And you know, our role here is simply to sa y what needs to be done and for you to figure out how to do that. We need a comm on set of rules, and we do have plenty of models for that in the research world. For example, in 1996 Congress passed the Health Insurance Portability Act. As p art of that, it required legislation to be passed that set standards for the pro tection of privacy of access to the medical record.

Federal law said, this has to be done. It didn't say, unless FDA objects to it or unless it conflicts with FDA's view. It just said, that's it. You're Amer ica, this is the way it's going to be done. A federal law passed.

And so we are about to see a law go into effect that supersedes all of our other research baloney of interpretation of, you know, well, how do we interpret HHS? It's going to be a problem of course to implement it because there are pro blems with the way that law is written, but the point is that mechanism is there to say, well, research-- this is the way it's going to be done regardless of on e federal agency's policy or another's.

So I think that we can solve this problem.

REP. MICA: Well, I'm probably somewhere in between the two of you because I think -- DR. MCCARTHY: And we're not very far apart.

REP. MICA: Mr. McCarthy has described a situation, the political situation, congressional authorization, and there's not just agency turf jealousy. We also have the committee authorizing jealousy. And to get them to all agree on anythi ng is very difficult.

I see your point though, and we have as you pointed out in other legislatio n required some standards. I think everybody agrees that there should be informe d consent. I think everybody's agreeing now there should be some registration of at least the IRBs, right? And then we get into some other areas. We haven't rea lly talked about accreditation or certification or IRBs or DSMBs. Dr. McCarthy, what do you think about some accreditation or certification standard?

DR. MCCARTHY: I strongly endorse this effort. As a matter of fact I've been selected to serve on the board of the new organization that Dr. Amdur cited. An d I am dedicated to trying to bring this about as best we can.

REP. MICA: Should that be voluntary or mandatory?

DR. MCCARTHY: I think that it ought to be voluntary and supplemental to the kind of oversight exercised by the government, and I think we have an excellent model in the American Association for Accreditation of Laboratory Animal Resour ces, and I think it has worked for many years as a supplement to government effo rts.

REP. MICA: How long has that been in place?

DR. MCCARTHY: At least since 1970, and if memory serves about 1965, but a v ery long time. It has worked exceedingly well, and one of the people serving on the new AHRP board is the director of ALAC, so that we are able to profit from h is experience and his guidance. I think the one thing holding up accreditation i s funding, and we are now seeking some funding sources in order to get this corp oration off the ground. We think it will be self-sustaining because it will be i n the best interests of the institutions to be accredited, to get a Good Houseke eping seal of approval on their programs before OPRR or FDA or some other agent comes in and shuts them down.

So this way we think we can make a supplemental contribution to what the go vernment is doing. In no way would I weaken the government's authority or the ex tent of its oversight, but I think human subjects are so important

that we can s upplement what government can do and head off many problems before they occur. REP. MICA: Dr. Amdur, what about the certification or accreditation?

DR. AMDUR: I think that it needs to-- REP. MICA: Give me your ideas on how that should be accomplished.

DR. AMDUR: The program that will work very well for this purpose is not in the planning stages. It is in the very end stages of the planning and about to b e implemented by primer. And this is the AHRP program, and there are in three pa ges in the written testimony we explain the mechanics of it.

And very briefly what you do first is, and this is about to be completed, y ou organize a group of experts that then write down basic best practice guidelin es for the fundamental aspects of a system of protecting human subjects, the ins titution, the IRB, education and investigators, management of adverse events, et cetera. You start there, and that has been done.

Then you have a written phase where the institution responds to their curre nt status related to those.

Then you have an on-site investigation where usually two or three experts g o to the institution and have to interact with all the key components of the sys tem and see how it is really working according to objective, and there are some subjective aspects of it-- and issue a grade if you will of the institution rela ted to a whole checklist of things.

And if the institution meets certain standards which are outlined in the pr ogram, then they get the accreditation for three years is the proposal. So you k now, PRIMRs are working very hard to indeed hammer out the details. It's not per fect yet. It hasn't been tried in the field yet, and like any system it will obv iously iterate and evolve and change and be polished as its used. And the more s upport it gets the quicker it can get on-line, but it's ready to go.

And I would strongly support, you know, a model that's that far along alrea dy to get out into the field and get going. I mean, we have to accredit everythi ng we do. You go and get a gas tank for your gas grill, the people that fill the gas have to have a certification. You know, we need an accreditation process fo r the protection of human subjects. It's something that's really long overdue. A nd institutions will not balk at this. They will embrace it. They want to know w hat do I need to do to be doing things correctly? And they will embrace it if it 's a credible system it had to meaningful evaluations. If it's just an audit sys tem of a bunch of accountants going and checking and looking for pieces of paper that say certain things and the date matches this date, they'll do it if they h ave to because the

experts on protecting human subjects are the investigators in most cases. They know if the IRB is asking them meaningful questions. They know if the institution is providing the right environment to support them and be ab le to resist conflicts of interest.

And so as long as it's a meaningful, credible process done by people that k now what they're doing, the institutions will embrace it, but it needs to be sup ported as widely as possible.

REP. MICA: Thank you, and I guess you lean towards the mandatory versus vol untary?

DR. AMDUR: Well, you know, I think that, I'm scared to say yes mandatory, b ecause we should always have as little required regulation as possible. And I ju st need to see the exact format of how that requirement would be because, you kn ow, when we actually write it down and then see how it's implemented I'm concern ed. But I don't, I think that it will be enormously effective even if it's volun tary and if the regulations required-- I don't, I personally right now today thi s second I don't think it has to be a mandatory required system. And I think HHH regulations and authority already have the authority to put the pressure as the y're trying to do on institutions to do things correctly.

And the institution will seek out ways to find out what is correct and impr ove their system on their own if they are indeed under a regulatory system that evaluates the endpoint. And so I think they will seek the accreditation process on their own and there will be other forces that end up requiring it. Like indus try will require it. Once there's any meaningful system in place, industry spons ors will require it. They will say, we're not dealing with you unless you're an AHRP accredited institution.

And so I don't think that it has to be mandated at the federal level.

REP. MICA: I have additional questions. We may submit some to you and some of our other witnesses today. But I think we just passed the 6:00 hour. I do wan t to thank each of you for participating, for being with us this afternoon, for your contribution in helping us improve this entire process and also the federal agencies that are responsible for implementing law and federal policy. There be ing no further business to come before the subcommittee, again I want to thank y ou for your participation and willingness to provide us with your personal exper ience and your expertise on this important issue. This hearing is adjourned.

END.

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